General Method for the Preparation of N-Monosubstituted 3-Isothiazole and 3-(1,2,5-Thiadiazol)amines. Preparation of a New Class of 2-Substituted 1,2,5-Thiadiazol-3(2*H*)-ones

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The preparations of N-monosubstituted 3-isothiazole and 3-(1,2,5-thiadiazol)amines and the corresponding 2-substituted compounds are described. A general method for the preparation of the previously unknown 2-substituted 1,2,5-thiadiazol-3(2*H*)-ones is presented. Mechanistic evidence is presented for the formation of the amines involving ring opening followed by recyclization.

Recently[1] we reported the discovery of a novel general method of synthesis of *N*-alkyl- and aryl-3-isothiazolamines, a previously largely unknown class of compounds. We now wish to present this work in detail together with an extension to the 1,2,5-thiadiazole system and other related work.

The chemistry of the relatively new isothiazole and 1,2,5-thiadiazole ring systems has been growing rapidly and both systems have been reviewed in recent years.[2,3] An area which has received only limited attention in both the isothiazole and 1,2,5-thiadiazole systems is the amine function in the 3 position. 3-Isothiazolamine itself was prepared by Hoffman rearrangement of the 3-carboxamide.[4] Isolated 4- or 5-substituted 3-isothiazolamines have been prepared from acylimino disulfides[5] and by oxidative cyclization of thiobenzoylacetamidine[6] or dicyanoethylene derivatives.[7] However, there does not appear to be any general method available for the preparation of N-substituted 3-isothiazolamines. 3-(1,2,5-Thiadiazol)amine has been prepared from 1,2,5-thiadiazol-3-carbonylazide[8] via a Curtius rearrangement and from 2-aminoacetamidine and sulfur monochloride,[9] but again no general synthesis of *N*-aryl- or *N*-alkyl-3-(1,2,5-thiadiazol)amines has been reported.

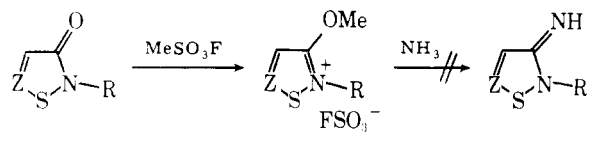
We were initially attempting to prepare 2-methylisothiazol-3(2*H*)-imine and the corresponding 1,2,5-thiadiazol-3-(2*H*)-imine by the approach in Scheme I. However, **6a** and **6g** were obtained in 80% yield. This interesting, unexpected result prompted us to investigate the mechanism and generality of the rearrangement.

Results

The required isothiazolones of type **1** (Z = CH) [**1a** (R = Me), **1c** (R = Ph), **1d** (R = CH_2Ph), **1e** (R = cyclohexyl), and **1f** (R = CH_2CH_2Cl)] were prepared by previously published methods.[10]

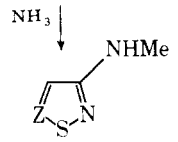
Alkylation of 3-hydroxy-1,2,5-thiadiazoles in general gives ethers rather than lactams.[9,11] However, in one series[12] using

Scheme I



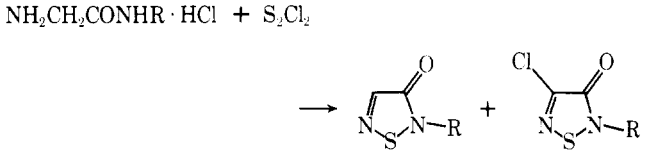
1a, Z = CH; R = Me
g, Z = N; R = Me

4a, Z = CH; R = Me
g, Z = N; R = Me



6a, Z = CH; R = Me
g, Z = N; R = Me

Scheme II



1 **2**

epichlorohydrin as the alkylating agent, a mixture of O- and N-alkylation occurred. There appears to be no report of a general synthesis of 2-aryl- or 2-alkyl-1,2,5-thiadiazol-3(2*H*)-ones in the literature.[13]

We attempted at first the direct alkylation of 3-hydroxy-1,2,5-thiadiazole under a variety of conditions. With methyl iodide a 33% yield of 2-methyl-1,2,5-thiadiazol-3(2*H*)-one was obtained. However, alkylation with ethyl iodide gave less than 5% isolated yield of the N-alkylated product. Presumably O-alkylation dominates in both cases. In view of the need for a general, specific route to 2-substituted 1,2,5-thiadiazol-3(2*H*)-ones, we investigated the reaction of appropriate 2-aminoacetamides with sulfur monochloride (Scheme II).

The 2-aminoacetamides were prepared from *N*-carbobenzyloxyglycine either via the mixed anhydride procedure[14] or via the *p*-nitrophenyl ester of glycine.[15] Only *n*-propyl-2-aminoacetamide and its CBZ derivative have not been previously reported.

The 1,2,5-thiadiazole forming reaction is carried out by adding, in portions, the aminoacetamide to a precooled solution of 3 equiv of sulfur monochloride in DMF. The product mixture is isolated by removal of precipitated sulfur by filtration, evaporation of DMF under high vacuum, and extraction with chloroform. Two compounds are formed in this reaction. The major component is the desired **1**. To a minor extent the chloro-substituted analogues, **2**, are produced. The two compounds are conveniently separated by column chromatography on silica gel, eluting with benzene/ethyl acetate; in all cases the chlorothiadiazole elutes first from the column. Combined yields are 65–81% with the nonchlorinated product dominating (40–81% yields). The relevant data are contained in Table I.

It is not certain at which stage in the reaction the chlorine atom has been introduced; however, a preliminary investigation has shown that under the conditions of the experiment (DMF, S_2Cl_2, 24 h at room temperature) compounds **1g–k** are partially transformed to the chloro analogues **2g–k**, which indicates that the chloro compounds may have been formed in the reaction mixture by reaction of excess S_2Cl_2 with the preformed **1g–k**. We also found that **2g–k** could conveniently be prepared in high yield (60–98%) by reacting **1g–k** with SO_2Cl_2 at room temperature for 1 h in DMF.

The quaternary salts **4** and **5** were made from **1** and **3**[16] as shown in Scheme III.

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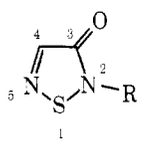
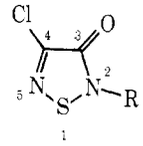
Table I. 2-Substituted and 2-Substituted 4-Chloro-1,2,5-thiadiazol-3(*H*)-ones[a]



1

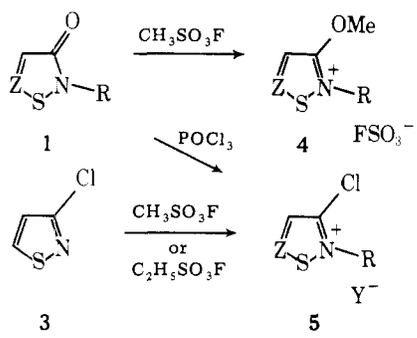


2

R		registry no.	mp, °C	yield, %		registry no.	mp, °C	yield, %[b]
Me	**1g**	67863-07-4	116–117 (EtOAc)	66	**2g**	49638-04-2	113 (EtOAc–benzene)	8 (60)
n-propyl	**1h**	67863-09-6	46–49 (ether–hexane)	40	**2h**	68876-13-1	oil	43 (80)
Ph	**1i**	67863-08-5	70–71 (benzene–ether)	53	**2i**	68876-14-2	112–113 (benzene–ether)	11 (70)
CH_2Ph	**1j**	67863-06-3	76–77 (benzene–ether)	63	**2j**	68876-15-3	48–49 (benzene–ether)	16 (78)
n-dodecyl	**1k**	67863-03-0	68–70 (hexane)	81	**2k**	68876-16-4	37–39 (petroleum ether)	0 (98)

[a] Satisfactory analytical data were obtained for all compounds. [b] The yields in parentheses are the ones resulting from the chlorination of **1** with sulfuryl chloride.

Scheme III



Compounds of type **4** were prepared in high yields by reacting the appropriate **1** with excess methyl fluorosulfonate. In some cases CH_2Cl_2 as solvent has been used to moderate the reaction. The crystalline products precipitate from the reaction mixture. The products are generally hygroscopic and some deteriorate on standing.

Treatment of **3** with methyl and ethyl fluorosulfonate gave **5a** and **5b**, respectively. Compounds **5c,d,e,f,i** are formed by mixing, and at times warming, $POCl_3$ and the appropriate 2-substituted isothiazolone or 1,2,5-thiadiazolone. For characterization purposes the compounds are isolated by precipitation with ether, or by removal of excess $POCl_3$ and trituration with ether. For optimum yields, however, the best procedure is to react the compounds with a minimum amount of $POCl_3$, then add excess ether until precipitation of a white gum, followed by decantation. The gum is pure, as judged by NMR, and perfectly suited for the next step. The crystalline **5** are hygroscopic, deteriorate on standing for long periods of time, and are often contaminated with phosphorus salts, and good analyses were not always obtained; here again, spectral data are entirely consistent with assigned structures.

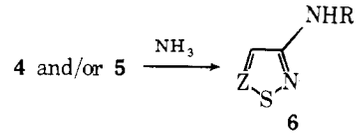
Table II contains the collected information on type **4** and **5** compounds.

When suspensions or solutions of quaternary compounds of types **4** or **5** in acetonitrile are treated with excess ammonia, an exothermic reaction takes place and good to excellent yields of the rearranged amines (**6**) are obtained (Scheme IV).

The analysis, IR, NMR, and mass spectra of **6** are consistent with the proposed structures (Table III). In compounds **6a,b,d,g,h,j,k,** one can clearly see the coupling constant with the adjacent NH, which disappears on D_2O exchange.

It should be noted that in the isothiazolium system the quaternary chloro compounds (**5a–f**) on treatment with ammonia gave, in general, much higher yields (72–95%) of **6a–f** than the 3-methoxyisothiazolium salts (**4a,c,d,e**), which under similar conditions gave only 0–40% yields of **6**. For example, **5c** gave **6c** in 95% yield, whereas **4c** failed to give a detectable

Scheme IV



amount of **6c** on treatment with ammonia. Of the 1,2,5-thiadiazolium salts only **4i** failed to give the corresponding type **6** compound. However, a 50% yield of **6i** was obtained when the chlorothiadiazolium chloride **5i** was used as the intermediate.

An interesting application of the rearrangement is illustrated by the preparation of the novel bicyclic system 2,3-dihydroimidazo[1,2-*b*]isothiazole (**9**) (Scheme V). NH_3 treatment of **5f** in acetonitrile gave the *N*-(2-chloroethyl)-3-isothiazolamine (**6f**), which with potassium *tert*-butoxide in *tert*-butyl alcohol gave 3-(*N*-aziridinyl)isothiazole (**7**).

Addition of HBr yielded **8**; cyclization in refluxing methanol for a few hours or by standing at room temperature for 2–3 days gave the bicyclic system **9a**; ion exchange chromatography yielded **9b**. Compound **6f** is much less reactive, e.g., after 2 days at 50 °C 25% conversion to **9b** was observed along with some decomposition.

We have also investigated the reaction of type **4** and **5** compounds wth primary amines. When the reaction is performed under the same conditions as with ammonia, i.e., excess amine in acetonitrile as solvent, only decomposition products are obtained. When, however, 2 equiv of the amine are used, if **5** is the starting material, or 1 equiv, if **4** is the starting material, good yields of products are isolated (Scheme VI).

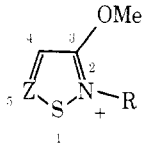
When R = R′, a single product (**10a–d,** in this case **10** = **11**) is obtained in good yield. Table IV contains the relevant information. The NMR spectra of these compounds are very informative. The chemical shifts of the alkyl groups attached to the exo- and endocyclic nitrogens are quite different (~1 ppm). Because of the positive charge on the ring nitrogen the chemical shift of the alkyl groups attached to it has been assigned the lower field absorption. This assignment is confirmed in the case of **10a** by the fact that the higher field methyl shows a coupling with the adjacent NH.

When R ≠ R′, the results are more complicated. In those cases examined in the isothiazole series, two isomers are formed in the approximate ratio of 4:1 (analyzed by NMR).[17] The single 1,2,5-thiadiazolium salt (**4g**), reacted in this way, gave a 1:1 mixture of isomers.

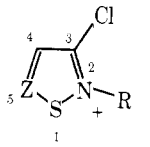
In the instance where the fluorosulfonates of **10** and **11** are obtained they are converted to the chlorides by ion exchange chromatography.

No attempts were made to separate the isomers. Attempts

Table II. 3-Chloro- and 3-Methoxyisothiazolium and 1,2,5-Thiadiazolium Salts[a]



4

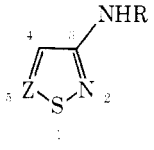


5

	registry no.	Z	R	mp, °C		registry no.	Z	R	Y	mp, °C
4a	68449-63-8	CH	Me	148–150	**5a**	68876-28-8	CH	Me	FSO_3	185 (dec)[b]
4c	68663-72-9	CH	Ph	98–100	**5b**	68876-30-2	CH	Et	FSO_3	55–60[b]
4d	68449-69-4	CH	CH_2Ph	oil	**5c**	68449-70-7	CH	Ph	Cl	168–170
4e	68449-73-0	CH	cyclohexyl	133–135	**5d**	68449-67-2	CH	CH_2Ph	Cl	145–147[b]
4g	68876-18-6	N	Me	138–139	**5e**	68449-71-8	CH	cyclohexyl	Cl	102–105[b]
4h	68876-20-0	N	*n*-propyl	oil	**5f**	68876-31-3	CH	CH_2CH_2Cl	Cl	oil
4i	68876-22-2	N	Ph	135–137 (dec)	**5i**	68876-32-4	N	Ph	Cl	110 (dec)
4j	68876-24-4	N	CH_2Ph	oil						
4k	68876-26-6	N	*n*-dodecyl	oil						

[a] Compounds **4a,c,e,g,i** and **5c,i** gave good analytical data. [b] Mp of these compounds should be looked at with reservations since they did not give good analytical data (see Results section).

Table III. Substituted 3-Isothiazol and [1,2,5-Thiadiazol]amines[a]

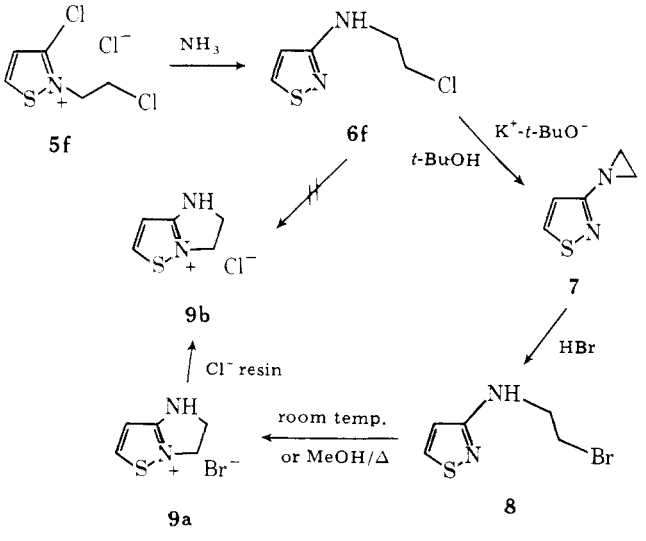


6

	registry no.	Z	R	starting material	mp, °C	yield, %[b]
6a	68449-74-1	CH	Me	**5a**	oil[c]	80
6b	68449-76-3	CH	Et	**5b**	oil[d]	72
6c	68449-79-6	CH	Ph	**5c**	156–158 (benzene)	95
6d	68449-78-5	CH	CH_2Ph	**5d**	74–76 (benzene–petroleum ether)	95
6e	68449-80-9	CH	cyclohexyl	**5e**	133–134 (ether)	95
6f	68876-33-5	CH	CH_2CH_2Cl	**5f**	37–39	78
6g	68876-34-6	N	Me	**4g**	oil[e]	80
6h	68876-35-7	N	*n*-propyl	**4h**	oil	85
6i	68876-36-8	N	Ph	**5i**	80–82 (ether–hexane)	50
6j	68876-37-9	N	CH_2Ph	**4j**	49–51 (benzene–hexane)	60
6k	68876-38-0	N	*n*-dodecyl	**4k**	48–50 (hexane)	60

[a] Satisfactory analytical data were obtained for all compounds. [b] Yields based on **1**. [c] Fluorosulfonate, mp 86–89 °C (EtOH–ether). [e] Fluorosulfonate, mp 153–155 °C (EtOH–ether). [e] Hydrobromide, mp 102–104 °C (isopropyl alcohol–ether).

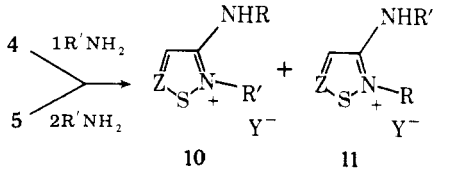
Scheme V



to generate the free base of **10** and/or **11** by base treatment yielded in all cases decomposition mixtures. This was expected since, as was mentioned above, the use of excess amine on **4** or **5** led to mixtures. These results are discussed later.

In a few cases the direct methylation of 3-isothiazolamines and 3-(1,2,5-thiadiazol)amines with methyl fluorosulfonate

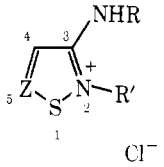
Scheme VI



10 11

starting material	amine R'	ratio of products 10–11
5d	Me	80:20
5a	CH_2Ph	85:15
5d	cyclohexyl	80:20
4g	*n*-propyl	50:50

Table IV. 2-Alkyl-3-alkylaminoisothiazolium and 1,2,5-Thiadiazolium Salts[a]



10

	registry no.	Z	R = R′	starting material	mp, °C	yield, %
10a	68876-39-1	CH	Me	**5a**	205 (dec)	84
10b	68876-40-4	CH	Et	**5b**	136–138	95
10c	68876-41-5	N	Me	**4g**	196 (dec)	73
10d	68876-42-6	N	*n*-propyl	**4h**	oil	65

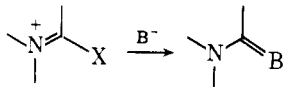
[a] Satisfactory analytical data were obtained for all compounds.

was investigated. 3-Isothiazolamine[4] itself gave 3-amino-2-methylisothiazolium fluorosulfonate (**12a**) in 95% yield. The compound is, however, better handled and stored as the chloride **12b** (34% yield), prepared by the ion exchange procedure (Scheme VII).

Similarly *N*-phenyl-3-isothiazolamine **6c** gave 2-methyl-3-anilinoisothiazolium fluorosulfonate (**13**) in 72% yield. 3-(1,2,5-Thiadiazol)amine[9] and *N*-methyl-3-(1,2,5-thiadiazol)amine, however, gave only complex mixtures with methyl fluorosulfonate. Treatment of **12** with base gave **6a** rather than the expected free base of **12**. The free base recovered was identical in all respects with **6a** derived from **5a**.

Discussion

Quaternary iminium compounds of the general type **14** are known to be very reactive toward nucleophiles.

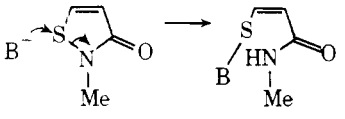


14

X = leaving group

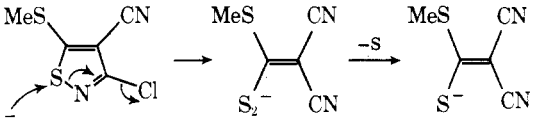
Without reviewing here the extensive literature on the subject, it is sufficient to say that these reactive species are involved in the Vilsmeier–Haack reaction and in the conversion of a cyano group to ester or amides (via HCl adduct). They are used extensively in pyridine chemistry and more generally in nitrogen heterocycles, etc.

Nucleophilic attack on the sulfur of isothiazoles has been reported in the literature. Crow and Leonard[18] have shown that good nucleophiles such as CN^- and RS^- open the isothiazole ring system to yield open chain compounds.

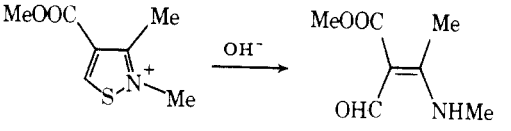


B = CN^-, RS^-

Hatchard[19] also reported a similar opening on a different system.



Lee and Volpp[20] reported the ring cleavage of an isothiazolium salt by hydroxide.

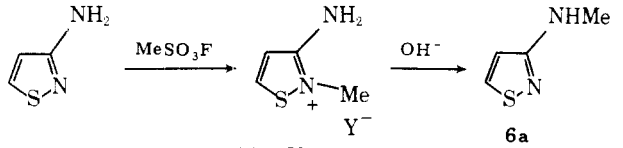


The question of the relative reactivity of an iminium carbon of type **14** and an $-SN^+=$ bond in the same molecule is largely unknown. One such example is reported in the literature[21] in the benzisothiazole series, and here instead of the expected attack on the iminium carbon, sulfur seems to be the preferred center of attack by nucleophiles.

In reactions of compounds of type **4** and **5** with ammonia we were expecting the attack to occur on the iminium carbon to yield 2-substituted 3-imino derivatives. As it turns out, however, we obtained exclusively the monosubstituted amines **6**, indicating that ring opening must have occurred. Scheme VIII shows the proposed mechanism in which attack by ammonia on **4** or **5** yields an open chain *S*-amino intermediate, **15a** or **15b**, respectively, which can cyclize easily to afford the substituted 3-amino derivatives **6**.

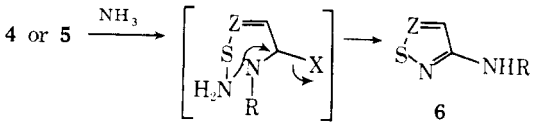
In our first attempt to react primary amines with **4** and **5** under the same experimental conditions using excess amine, only decomposition products were obtained and NMR spectra showed that the mixture contained no olefinic products. The compounds as they are formed in the reaction mixture would be of the quaternary type (**10** and **11**) and if, instead of the expected deprotonation to yield the free base, a second nucleophilic attack on sulfur occurred, we would have unstable open chain compounds, which decompose under the experimental conditions. By using equivalent amounts of the primary amines we could, in fact, isolate good yields of the alkylamino quaternary salts **10a–d.** It is also possible that the free base is unstable to the amine medium. Since we could not isolate any of the free bases of **10** and **11**, one can only specu-

Scheme VII



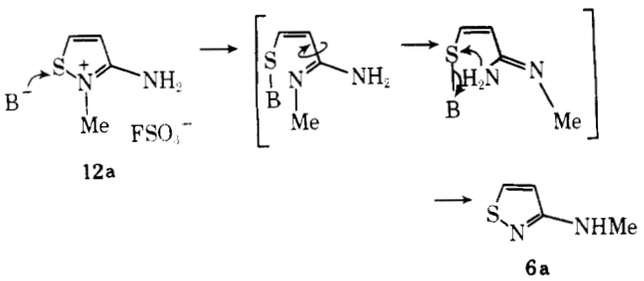
12a, Y = FSO_3
b, Y = Cl

Scheme VIII



15a, X = Cl
b, X = OMe

Scheme IX



12a 6a

late on their stability. One is tempted to argue that the free base of **10a**, for example, should be more stable to nucleophiles than **1a**; however, **1a** on treatment with CH_3NH_2 in acetonitrile for a prolonged period of time was recovered unchanged.

As was mentioned earlier, on attempted generation of the free base of **12a** or **12b** by treatment with NaOH or ammonia, only the rearranged amine **6a** could be isolated.

Here again nucleophilic attack to open the ring is occurring in preference to the expected deprotonation. Rotation around the amidine bond is followed by recyclization to yield the more favored aromatic system (Scheme IX). This process is similar to the well-known Dimroth rearrangement, in which ring N-alkylated or N-arylated imino heterocycles rearrange to the corresponding alkyl or arylamino heterocycles.[22] This is the first example we know of a Dimroth rearrangement in the isothiazole ring system.

This fact led us to investigate further the mechanism of the rearrangement proposed in Scheme VIII, since it is conceivable that attack by the ammonia molecule on the iminium carbon in **4** or **5** could occur to yield in the reaction mixture compounds of the type **16** which are then transformed to **6** by a Dimroth type rearrangement (Scheme X).

We needed then a way of evaluating the extent of attack by the ammonia (if any) on the iminium carbon.

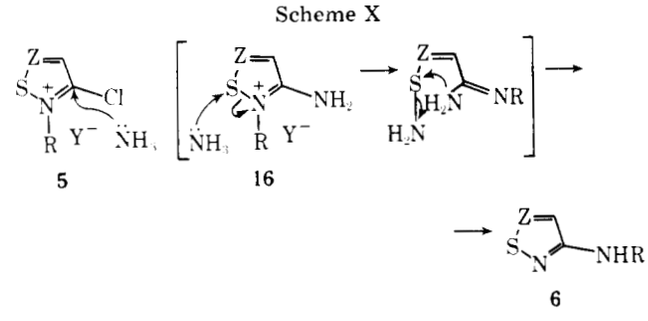
Our first idea was to use $^{15}NH_3$ as a means of differentiation between attack on sulfur or attack on carbon. However, a quick look at Scheme VIII and Scheme X shows that the ^{15}N is incorporated in the cycle by both mechanisms and would not provide an answer to the problem.

The choice of deuterated methylamine as nucleophile and labeling unit seems to be appropriate for the desired study. $CD_3NH_3^+Cl^-$ (99.0% D_3) was used and the experiments were carried out under our usual standard conditions. The results obtained with **5a** in the isothiazole series, as analyzed by NMR, are shown in Scheme XI.

These results indicate that most of the attack occurs at the sulfur but some probably occurs at the carbon and that acyclic intermediates, when involved, efficiently reclose without interception by a second molecule of amine.

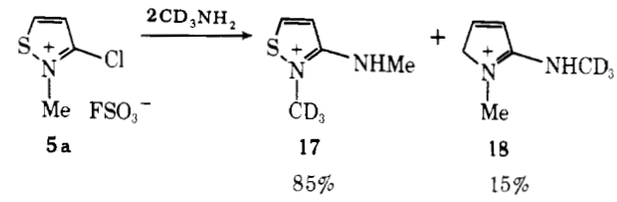
The results obtained with CD_3NH_2 are also substantiated by the data mentioned earlier (see Results and Scheme VI) using an amine with a different hydrocarbon skeleton. In the cases investigated a 4:1 ratio of isomers was obtained, the

Scheme X



5 16 6

Scheme XI



5a 17 18

85% 15%

major component being the one produced by an attack on sulfur.

The reaction with CD_3NH_2 was also performed with **4g** in the 1,2,5-thiadiazole series. An approximately 1:1 mixture of isomers was obtained, indicating that attack at the sulfur atom could be less favored than in the isothiazole system. A similar result was obtained by reacting **4g** with *n*-propylamine (see Scheme VI).

The difference in behavior between the two systems is not clear. One explanation may be that the quaternary 1,2,5-thiadiazolium compounds are intrinsically more reactive to nucleophiles than the isothiazolium analogues and attack by amines is more indiscriminate in the former case.

These results extrapolated to the ammonia case in which only one isomer is obtained indicate that our proposed mechanism (Scheme VIII), i.e. first attack on the sulfur by the ammonia molecule followed by cyclization, is the main course of the reaction in the isothiazole system. To a minor extent the attack by the ammonia on the iminium carbon could occur to yield intermediates of type **16**, which are then followed by a Dimroth type rearrangement as outlined in Scheme X. In the 1,2,5-thiadiazole system the two mechanisms seem to be equally effective.

A summary of the two mechanistic pathways leading to compound **6**, as illustrated for **5**, is shown in Scheme XII.

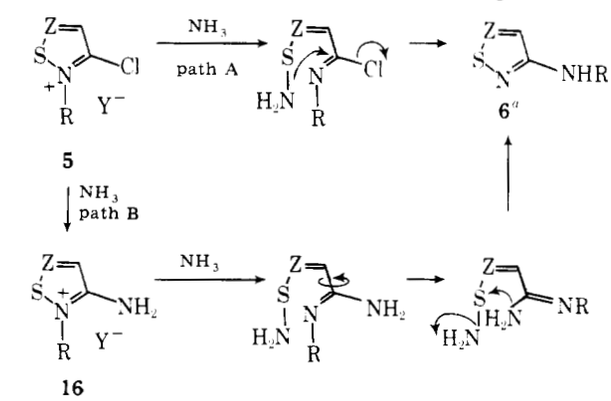
Experimental Section

Methyl fluorosulfonate and ethyl fluorosulfonate[23] were obtained from Aldrich Chemical Co. Melting points are uncorrected. NMR spectra were recorded on a Varian EM 360 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer (solid, KBr pellets; oils, thin films). Ultraviolet spectra were run on a Perkin-Elmer 202 Ultraviolet-Visible Spectrophotometer. Microanalyses were performed by C. Daessle, Montreal, and mass spectra by Morgan Schaffer, Montreal.

2-Substituted isothiazol-3(2*H*)-ones **1(a,c–f)** were prepared as previously reported.[10]

***n*-Propyl-2-aminoacetamide (22) and *n*-Dodecyl-2-aminoacetamide (23).** 2-Aminoacetamides were prepared by known methods.[14,15] Compounds **22** and **23** and the precursors *N*-(*n*-propyl)-2-(benzyloxycarbonylamino)acetamide (**24**) and *N*-(*n*-dodecyl)-2-(benzyloxycarbonylamino)acetamide (**25**) are not previously reported. Intermediate **24**, mp 100–102 °C, was prepared from the *p*-nitrophenyl ester of *N*-carbobenzyloxyglycine and propylamine: NMR ($CDCl_3$) δ 0.81 (CH_3, t), 1.43 (CH_2, m), 3.18 (CH_2, q), 3.80 (NH**CH_2**,

Scheme XII. Mechanistic Picture Leading to 6



5 16 6[a]

[a] Isothiazoles: path A ~80–85%, path B ~15–20%. 1,2,5-Thiadiazoles: path A ~50%, path B ~50%.

d), 5.08 (OCH_2, s), 5.97 (NH, br), 6.07 (NH, br), 7.31 (C_6H_5, s); IR 3330 cm^{-1} (N–H), 1692, 1645 (C=O).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.17; H, 7.55; N, 11.23.

Hydrogenation of **24** in methanol using 10% Pd/C as catalyst yields **22**. The HCl salt is hygroscopic. A maleic acid salt was prepared for analysis: mp 148–149 °C; NMR (D_2O) δ 0.85 (CH_3, t), 1.43 (CH_2, q), 3.17 (CH_2, t), 3.68 (CH_2, s).

Anal. Calcd for $C_9H_{16}N_2O_5$: C, 46.54; H, 6.94; N, 12.06. Found: C, 46.44; H, 7.18; N, 11.85.

Intermediate **25**, mp 110–112 °C, was prepared by the mixed anhydride method: NMR ($CDCl_3$) δ 0.88 (CH_3, t, distorted), 0.60–2.30 [$(CH_2)_{10}$, br], 3.23 ($NHCH_2$, q, J_{CH_2-NH} = 6 Hz, collapses to a triplet on CF_3COOD exchange), 3.80 ($COCH_2$, d, J_{CH_2-NH} = 5 Hz, collapses to a singlet on exchange), 5.10 ($C_6H_5CH_2$, s), 5.60 (NH, t, J_{CH_2-NH} = 5 Hz), 6.13 (NH, br), 7.31 (C_6H_5, s); IR 3330 cm^{-1}, 3290 (NH), 1690, 1655 (C=O).

Anal. Calcd for $C_{22}H_{36}N_2O_3$: C, 70.18; H, 9.64; N, 7.44. Found: C, 69.76; H, 9.26; N, 7.56.

Product **23**, mp > 200 °C, was prepared from **25** as described above: NMR (D_2O) δ 0.80 (CH_3, t, distorted), 0.80–2.20 [$(CH_2)_{10}$, br], 3.20 ($NHCH_2$, br), 3.84 ($CO-CH_2$, s); IR 3270 cm^{-1} (NH), 1660 (C=O).

Anal. Calcd for $C_{14}H_{31}ClN_2O$: C, 60.30; H, 11.21; N, 10.04; Cl, 12.71. Found: C, 60.49; H, 11.27; N, 10.23; Cl, 12.94.

On a large scale (10 g), **23** precipitated with the catalyst and concentrated HCl (3 mL) was added to solubilize it. The filtrate was concentrated until the appearance of crystals. The mixture was warmed until complete dissolution; ether was added to induce crystallization and the hydrochloride filtered (77% yield).

2-Substituted 1,2,5-Thiadiazol-3(2*H*)-ones (1g–k). 2-Substituted 1,2,5-thiadiazol-3(2*H*)-ones were all prepared by the same procedure, illustrated below for **1j**. *N*-Benzyl-2-aminoacetamide·HCl (15.4 g, 0.077 mol) was added in portions to a stirred ice–water cooled solution of sulfur monochloride (18.4 mL, 0.23 mol) in 50 mL of dimethyl formamide, maintaining the temperature of the reaction mixture below 40 °C. After the addition was complete, the ice–water bath was removed and the reaction stirred for 16 h. The solution was filtered to remove precipitated sulfur and evaporated under high vacuum to remove excess S_2Cl_2 and DMF. The residue was dissolved in 100 mL of chloroform, washed several times with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a large, dry silica gel column, eluting with benzene containing 2.5% ethyl acetate. A small amount of sulfur first elutes from the column, then **2j** (2.5 g), followed by **1j** (9.3 g). Table I contains relevant information.

2-Substituted 4-Chloro-1,2,5-Thiadiazol-3(2*H*)-ones (2g–k). To 2-(*n*-dodecyl)-1,2,5-thiadiazol-3(2*H*)-one (**1k**) (270 mg, 1 mmol) in dry DMF (2 mL) was added sulfuryl chloride (675 mg, 5 mmol). An exothermic reaction resulted. The mixture was stirred at room temperature for 1 h, then decomposed with water and extracted with ether affording **2k** as an oil (300 mg) which crystallized to a white solid (98% yield). Compounds **2g–j** were similarly prepared. Relevant data are reported in Table I.

3-Chloroisothiazole (3). A mixture of 150 g of 3-hydroxyisothiazole, 340 g of phosphorus pentachloride, and 37.5 mL of phosphorus oxychloride was heated gradually to 100 °C. A dark solution was formed and maintained at 100 °C for 1 h. The solution was cooled and poured slowly onto 1 kg of ice. The mixture was extracted with ether (6 × 300 mL), the combined extracts were dried (Na_2SO_4), and the ether was distilled at atmospheric pressure. The dark residue was extracted at room temperature with carbon tetrachloride and the solution separated from the dark insoluble oil. The carbon tetrachloride solution was charcoaled and the solvent was then removed under slightly reduced pressure. The brown mobile liquid was distilled: bp 62–64 °C (20 mm Hg) [lit.[16] bp 66–68 °C (20 mm Hg)]; yield 33%: NMR ($CDCl_3$) δ 7.12 (H_4), 8.72 (H_5, $J_{4,5}$ = 4 Hz); UV λ (log ϵ) 248 (3.83), 207 (3.40).

2-Substituted 3-Methoxyisothiazolium Fluorosulfonates (4a,c,d,e). 2-Substituted isothiazol-3(2*H*)-ones (**1a,c,d,e**) (1.0 g) were treated with excess methyl fluorosulfonate. Usually an immediate exothermic reaction occurred. Occasionally the reaction was initiated with warming. When crystalline the precipitated salts were filtered, washed with ether, and recrystallized from acetonitrile–ether. Compound **4d**, an oil, was recovered by evaporation of excess methyl fluorosulfonate and was characterized by NMR only. Physical data are to be found in Table II.

2-Substituted 3-Methoxy-1,2,5-thiadiazolium Fluorosulfonates (4g–k). 2-Substituted 1,2,5-thiadiazol-3(2*H*)-ones (**1g–k**) (1.0 g) were refluxed for 90 min in 10 mL of methylene chloride containing 2 equiv of methyl fluorosulfonate. Products **4g** and **4i** precipitated and were isolated by filtration. Analytical samples were obtained by recrystallization from acetonitrile–ether. Compounds **4h,j,k** were isolated by evaporation and characterized by NMR only. Physical data are summarized in Table II.

2-Methyl-3-chloroisothiazolium Fluorosulfonate (5a) and 2-Ethyl-3-chloroisothiazolium Fluorosulfonate (5b). 3-Chloroisothiazole (**3**) (10 g, 0.084 mol) was placed in a 250-mL pressure bottle and cooled in ice water and methyl fluorosulfonate (10 g, 0.088 mol) was added. The bottle was sealed and after several minutes a vigorous exothermic reaction occurred, the contents becoming solid. The reaction was cooled and the white solid was triturated with methylene chloride and filtered yielding 17.9 g (92%) of **5a**. The ethyl analogue **5b** was prepared in a similar manner from **3** and ethyl fluorosulfonate except the reaction was initiated by warming (yield 95%). Physical data are summarized in Table II.

2-Substituted 3-Chloroisothiazolium Chlorides (5c–f) and 2-Phenyl-3-chlorothiadiazolium Chloride (5i). 2-Substituted isothiazol-3(2*H*)-ones (**1c–f**) (1.0 g) were stirred at room temperature with phosphorus oxychloride (3–5 mL); the progress of the reaction was checked by TLC for disappearance of starting material. In some cases to speed up the reaction the mixture was warmed to 60 °C. Ether was added to precipitate a white gum. The residue was flushed once with ether and decanted. The material was used as such for the next step. The thiadiazolium salt **5i** was prepared in an analogous manner from **1i**. Relevant physical data are gathered in Table II.

***N*-Substituted 3-Isothiazolamines (6a–f) and *N*-Substituted 3-(1,2,5-Thiadiazol)amines (6g–k).** The appropriate **4** or **5** (1.0 g) (see Table III for the choice of best starting material) was dissolved or suspended in acetonitrile (10 mL). The suspension or solution was cooled to 0 °C in ice water and ammonia gas was bubbled into the mixture for several minutes. The reaction mixture was brought to room temperature, filtered, and evaporated to dryness. The residue was partitioned between chloroform and dilute aqueous base. The organic phase was separated and the aqueous phase extracted with one volume of chloroform. Combined organic phases were dried (Na_2SO_4) and evaporated. The crude **6c–e** did not require any further purification. Analytical samples were obtained by recrystallization. All the other compounds were chromatographed on silica gel. Physical data are reported in Table III.

3-(*N*-Aziridinyl)isothiazole (7). 3-(2-Chloroethylamino)isothiazole (**6f**) (7.3 g, 0.045 mol) was dissolved in *tert*-butyl alcohol (50 mL). Potassium *tert*-butoxide (5.3 g, 0.047 mol) was added in portions, maintaining temperature below 30 °C with the aid of an ice bath. After addition of base was completed the reaction was stirred for a further 15 min. Ethyl acetate and water were added and the organic layer separated and evaporated at low temperature to give 5.4 g (95%) of an oil which crystallized on standing. The product sublimes (20 mm, 40 °C) readily and a sample was purified for characterization in this way: mp 48–49 °C; NMR ($CDCl_3$) δ 2.28 [$(CH_2)_2$, s], 6.86 (H_4, d), 8.48 (H_5, d, $J_{4,5}$ = 5 Hz); UV λ (log ϵ) 261 (3.44), 208 (3.19).

Anal. Calcd for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.20; S, 25.41. Found: C, 47.80; H, 4.92; N, 21.84; S, 25.03.

2,3-Dihydroimidazo[1,2-*b*]isothiazolium Chloride (9b). 3-(*N*-Aziridinyl)isothiazole (**7**) (4.7 g, 0.037 mol) was dissolved in chloroform (20 mL) and cooled in an ice water bath. HBr (48%, 16 mL) was added dropwise, maintaining the reaction temperature below 30 °C. After addition was complete, the reaction was stirred for a further 15 min. An additional 30 mL of chloroform was added and the reaction mixture was neutralized with sodium bicarbonate. The chloroform layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give 6.0 g of *N*-(2-bromoethyl)-3-isothiazolamine (**8**), as an oil: NMR ($CDCl_3$) δ 3.68 [$(CH_2)_2$, m], 6.44 (H_4, d), 8.35 (H_5, d, $J_{4,5}$ = 5 Hz), 5.00 (NH, br).

The intermediate **8** converts on standing at room temperature for 2–3 days to the crystalline bicyclic product **9a**. Alternatively it can be refluxed in MeOH for 5 h. The impure product was dissolved in methanol, decolorized with charcoal, concentrated under vacuum, and reprecipitated with ether to give 5.1 g of product, which was further purified by triturating with hot isopropyl alcohol, leaving 2.8 g of pure bromide (**9a**), mp 163–165 °C. The bromide was converted in quantitative yield to the chloride **9b** by ion exchange chromatography on Bio-Rad AG1-X8 ion exchange resin (chloride form): mp 164–167 °C; NMR (D_2O) δ 4.42 [$(CH_2)_2$, s], 6.70 (H_6, d), 8.88 (H_7, d, $J_{6,7}$ = 6 Hz); UV λ (log ϵ) 302 (3.85), 222 (3.42), 205 (3.69); mass spectrum, *m/e* 126.

Anal. Calcd for $C_5H_7N_2SCl$: C, 37.00; H, 4.32; N, 17.30; S, 19.75; Cl, 21.85. Found: C, 37.16; H, 4.66; N, 16.99; S, 19.49; Cl, 21.75.

2-Methyl-3-methylaminoisothiazolium Chloride (10a) and 2-Ethyl-3-ethylaminoisothiazolium Chloride (10b). 2-Methyl-3-chloroisothiazolium fluorosulfonate (**5a**) (5.67 g, 0.024 mol) was

dissolved in acetonitrile (20 mL) and a solution of methylamine (1.51 g, 0.048 mol) in acetonitrile was added dropwise. Methylamine hydrochloride gradually crystallized from the reaction mixture. The reaction was stirred at room temperature for 1 h, filtered, and evaporated under reduced pressure. The residue was redissolved in acetonitrile (15 mL), filtered again, and evaporated. The residue (5.5 g) crystallized on cooling. The fluorosulfonate salt was passed through excess Bio-Rad AG1-X8 ion exchange resin (chloride form). The aqueous eluate was evaporated to give the crystalline chloride **10a,** which was recrystallized from isopropyl alcohol–ether; 3.2 g was recovered.

The ethyl analogue **10b** was prepared in a similar manner from **5b** and ethylamine.

2-Methyl-3-methylamino-1,2,5-thiadiazolium Chloride (10c) and 2-Propyl-3-propylamino-1,2,5-thiadiazolium Chloride (10d). Compounds **10c** and **10d** were prepared in a similar manner to **10a** from **4g** and **4h,** except in each case only 1 equiv of the appropriate primary amine was added. Table IV contains the physical data on **10a–d.**

2-Methyl-3-aminoisothiazolium Chloride (12b). Freshly distilled methyl fluorosulfonate (11.5 g, 0.1 mol) was added to an ice–water cooled solution of 3-isothiazolamine[4] (9 g, 0.09 mol) dissolved in methylene chloride (100 mL). A vigorous reaction occurred and a precipitate formed. The reaction was brought to room temperature, stirred for 1 h, and stripped to a heavy oil, leaving a quantitative yield of the fluorosulfonate salt (**12a**). The fluorosulfonate was exchanged for chloride as described above. The resulting aqueous solution of the chloride salt was charcoaled and evaporated at low pressure. The residue was redissolved in a minimum volume of isopropyl alcohol and stored at 0–5 °C for 4 days. The cream-colored crystals (3.9 g) were filtered. A second crop of 0.67 g was recovered from mother liquors: yield 34%; mp 147–151 °C; NMR (Me_2SO-d_6) δ 3.63 (CH_3, s), 6.75 (H_4, d), 8.78 (H_5, d, $J_{4,5}$ = 6 Hz), 9.00 (=NH_2^+, br, exchangeable); UV λ (log ϵ) 207 (3.43), 283 (3.97) (**12a** has an identical NMR spectrum); IR 1665 cm^{-1}, 1605 (**12a,** IR 1660 cm^{-1}, 1600).

Anal. Calcd for $C_5H_7N_2ClS$: C, 32.11; H, 4.04; N, 18.72; S, 21.43; Cl, 23.69. Found: C, 31.94; H, 4.50; N, 18.65; S, 21.27; Cl, 23.48.

Note that **6a**·fluorosulfonate has the following physical data: NMR (Me_2SO-d_6) δ 2.87 (CH_3, s), 6.57 (H_4, d), 8.72 (H_5, d, $J_{4,5}$ = 6 Hz), 9.00 (-**NH**CH_3 and NH^+, s, exchangeable); IR 1655 cm^{-1}, 1635 and a fingerprint region quite distinct from that of **12a.**

2-Methyl-3-anilinoisothiazolium fluorosulfonate (**13**) was prepared as above in 72% yield, mp 170–172 °C, from **6c.**

Anal. Calcd for $C_{10}H_{11}FN_2O_3S_2$: C, 41.37; H, 3.82; F, 6.54; N, 9.65; S, 22.09. Found: C, 41.10; H, 4.30, F, 6.64; N, 9.79; S, 22.07.

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Supplementary Material Available: Complete spectroscopic data (7 pages). Ordering information is given on any current masthead page.

Registry No.—**1a,** 2682-20-4; **1c,** 21277-98-5; **1d,** 21277-97-4; **1e,** 26542-18-7; **1f,** 33319-79-8; **3,** 14217-66-4; **6a**·fluorosulfonate, 68449-75-2; **6b**·fluorosulfonate, 68449-77-4; **6g**·HBr, 68876-43-7; **7,** 68876-44-8; **8,** 68876-45-9; **9a,** 68876-46-0; **9b,** 68876-47-a; **12a,** 68876-49-3; **12b,** 68876-50-6; **13,** 68876-52-8; **22,** 62029-81-6; **23,** 59404-81-8; **24,** 21855-74-3; **25,** 67863-11-0; *N*-benzyl-2-aminoacetamide·HCl, 20432-97-7; 3-hydroxyisothiazole, 1003-07-2; methyl fluorosulfonate, 421-20-5; methylamine, 74-89-5; ethylamine, 75-04-7; 3-isothiazolamine, 4592-62-5.

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