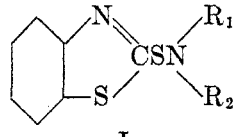
[CONTRIBUTION FROM THE CHEMICAL AND PHYSICAL RESEARCH LABORATORIES OF THE FIRESTONE TIRE AND RUBBER COMPANY]

THIAZOLESULFENAMIDES[1]

EDWARD L. CARR, GEORGE E. P. SMITH, JR., AND GLEN ALLIGER

Received January 2, 1948

The discovery that benzothiazole-2-thiol is an excellent and inexpensive accelerator for the sulfur vulcanization of rubber (1) has stimulated the study of many types of 1-thiazole-2-thiol derivatives. Among these, some benzothiazolesulfenamides, I, (R_1 and R_2 = hydrogen or hydrocarbon radicals) have been shown to be of outstanding value (2) as delayed-action, self-activating accelerators in both natural and synthetic rubbers.



I

One of these compounds was developed in Germany just before the war as "Vulkacit AZ" (R_1 = R_2 = ethyl). A parallel but independent development in this country resulted in the large scale production and use of "Santocure" (R_1 = hydrogen and R_2 = cyclohexyl).

This paper reports the synthesis of thiazolesulfenamides by an improved method which has been developed and extended to include the preparation of many new thiazolesulfenamides of possible interest to the rubber and other industries. A recent review covers the field of the known sulfenic acids and sulfenic acid derivatives very completely (3). The synthesis of sulfenamides from the corresponding sulfenic acids has been impractical because, with few exceptions, these acids are either unknown or very unstable.

Many sulfenyl chlorides and other halides are stable compounds which react with amines as well as sulfenyl thiocyanates to form sulfenamides (5, 6, 7, 8).

$$RSX + R_1R_2NH \rightarrow RSNR_1R_2 + HX$$

Trichloromethylsulfenyl chloride was the first sulfenyl halide to be prepared (4), but others of the aliphatic series have been difficult to obtain with the exception of the triphenylmethyl (5) and the *tert*-butyl (6) sulfenyl halides. The aromatic sulfenyl chlorides, especially the nitrophenyl derivatives are more stable and most sulfenamides have been prepared from these.

Similarly, thiazolesulfenyl halides should react readily to yield the corresponding sulfenamides. This reaction has been reported for a benzothiazolesulfenyl chloride (9), but the product of its reaction with a primary aliphatic amine is a *bis*-benzothiazolesulfenimide, rather than the expected N-monosubstituted benzothiazolesulfenamide.

$$2\,RSX + R_1NH_2 \rightarrow (RS)_2NR_1 + 2HX$$

[1] Presented before the Division of Organic Chemistry at the 109th meeting of the American Chemical Society, Atlantic City, N. J., April, 1946.

Certain thiazolesulfenamides have been prepared by the reaction of metallic thiazolyl mercaptides with the N-chloro derivatives of secondary amines (10).

$$RSM + R_1R_2NX \rightarrow RSNR_1R_2 + MX$$

However, this method of preparation has not been very convenient, especially for industrial use, because of the difficulties involved in the preparation and handling of the N-monochloro derivatives of the more common amines.

Another method available for the preparation of thiazolesulfenamides is the reaction of the corresponding thiazolyl disulfide with ammonia and amines (10, 11).

$$RSSR + 2\ R_1R_2NH \rightarrow RSNR_1R_2 + RSNH_2R_1\ R_2$$

This method is claimed to be of general application. However, although fair yields of thiazolesulfenamides are obtained, only half of the thiazolyl disulfide molecule is utilized in the formation of the corresponding sulfenamide. Furthermore, the sulfenamide must be separated from the substituted ammonium thiazolyl mercaptide also formed in the reaction mixture. This process may be improved by the simultaneous use of an oxidizing agent, and this improvement led to the third and most useful method for the preparation of thiazolesulfenamides.

The new process consists of the direct oxidative condensation of an amine and a metallic thiazolyl mercaptide in aqueous solution (12).

$$RSM + R_1R_2NH + (O) \rightarrow RSNR_1R_2 + MOH$$

The best oxidizing agents from the standpoints of both effectiveness and cost are chlorine and sodium hypochlorite. The other halogens are equally effective and are sometimes more suitable for laboratory preparations. Using chlorine, sodium hypochlorite or iodine as oxidizing agents, suitable reaction conditions have been determined which will give satisfactory yields of thiazolesulfenamides from the joint oxidation of most aliphatic or alicyclic primary or secondary amines with thiazolyl mercaptides.

The usual process utilizes an excess of amine in an aqueous solution containing the sodium salt of the mercaptothiazole together with some additional alkali. The reaction mixture is then stirred during the slow addition of oxidizing agent.

The exact conditions necessary to obtain the highest yield and the purest product from any given amine and thiazolyl mercaptide require a balance between (1) the relative concentrations of the reactants, especially that of the amine, (2) the *p*H of the solution, and (3) the temperature. The effects of these factors may be summarized as follows:

1. *Amine/mercaptide ratio.* An excess of 0.10 to 3 moles of amine above the theoretical quantity is required in order to produce thiazolesulfenamides from thiazolyl mercaptides. Additional amine over the theoretical increases the yield by a mass-action effect, but above a ratio of 3–4 moles of amine to one of mercaptide, this effect becomes negligible.

2. *Alkalinity* (*p*H). The optimum *p*H for the formation of the thiazolesulfen-

amides as determined in the preparation of the N-cyclohexyl- and N-isopropyl-benzothiazole-2-sulfenamides is 12.0–12.5 as measured with a Beckman "Type E" lithium-glass electrode and a Beckman *p*H meter. At *p*H values lower than 12.2, 2-benzothiazolyl disulfide is invariably found as an impurity in the product. At *p*H values above 12.5, a pure sulfenamide product is formed but in somewhat lowered yield. In this case, the 2-benzothiazolyl mercaptide is used up in a side reaction forming a soluble product. The most probable side reaction is the oxidation of mercaptide to the water-soluble sodium benzothiazole-2-sulfonate (13), a known reaction in more concentrated solutions at higher temperatures.

The use of sodium hypochlorite as an oxidizing agent produces an increase in the *p*H of the mixture during the course of the reaction, hence acid must be added to control the *p*H within the desirable limits or a lowered yield will result. On the other hand, if a halogen, such as chlorine or iodine is used, the *p*H is lowered during the reaction, and alkali must be added in order to keep the *p*H above the minimum of 12.0. However, it was found possible, when using free halogens as oxidizing agents, to start the reaction with a somewhat higher *p*H (13.0–13.5) without loss in yield or quality of product, providing that the *p*H of the final reaction mixture remained slightly above 12.0. Similarly, using hypochlorite a slightly lower starting *p*H is allowable if the final reaction mixture falls within the most desirable range.

3. *Temperature.* A temperature range of 5–30° generally was found to be satisfactory. Higher temperatures tend to favor the oxidation of mercaptide to sulfonate mentioned above, decreasing the yield of sulfenamide. On the other hand, very low temperatures tend to favor the formation of disulfide impurities in the sulfenamide product.

The balance between these factors lies in using an excess of amine and employing a temperature, *p*H, and amine/mercaptide ratio just above that necessary to keep the disulfide from precipitating.

As an example of the effect of the balance of the factors just discussed, a 96.5% yield of N-cyclohexyl-2-benzothiazolesulfenamide was obtained at room temperatures using either (a), an excess of 0.25 mole of cyclohexylamine while controlling the *p*H at 12.3, or (b), an excess of 3 moles of amine starting with an initial *p*H of 13.1 and allowing the *p*H to fall to 12.5 during the reaction. Chlorine was used as the oxidizing agent in both of these experiments. In general, it was found that 70–95% yields of most thiazolesulfenamides could be obtained by starting with 3–5 moles of amine and 1–1.5 moles of sodium hydroxide per mole of sodium thiazolyl mercaptide, followed by the addition of the oxidizing agent slowly with stirring at 10–20°.

The process is limited to some extent by the insolubility in water and by the ease of oxidation of certain amines. Thus it has been impossible to prepare thiazolesulfenamides from ordinary aromatic amines by this method. However, mercaptides of other sulfhydryl compounds, such as the mercaptothiazolines, thio-*p*-cresol, etc., may be employed in the process as well as the thiazolyl mercaptides.

The so-called "oxidative condensation process" described above, which is

carried out by the addition of oxidizing agent to a mixture of thiazolyl mercaptide and amine, is believed to take place in steps, with the intermediate formation of the thiazolyl disulfide. The probable reactions, starting with a primary alkylamine and oxidizing with either hypochlorite or chlorine are as follows:

1. $RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$
2. (a) $2\,R_1S^- + Cl_2 \rightarrow R_1SSR_1 \downarrow + 2\,Cl^-$
   (b) $2\,R_1S^- + OCl^- + H_2O \rightarrow R_1SSR_1 \downarrow + Cl^- + 2\,OH^-$
3. $R_1SSR_1 + RNH_3^+ + 2\,OH^- \rightarrow R_1SNHR \downarrow + R_1S^- + 2\,H_2O$

over-all reaction

1. + 2. + 3. (a) $R_1S^- + RNH_2 + Cl_2 + OH^- \rightarrow R_1SNHR \downarrow + 2\,Cl^- + H_2O$
   (b) $R_1S^- + RNH_2 + OCl^- \rightarrow R_1SNHR \downarrow + Cl^- + OH^-$

Reactions 1 and 2 proceed very rapidly. As oxidizing agent is added to the reaction mixture, an initial precipitation or cloudiness is observed. If conditions of concentration, *p*H, and temperature are correct, this initial precipitate disappears as rapidly as formed, and the sulfenamide is produced, first in solution and later with precipitation. However, if the concentrations of amine and mercaptide, *p*H, or the temperature, individually or collectively, are too low, the thiazolyl disulfide first formed remains as an undesired product from the first of the reaction. This insoluble disulfide will react with excess of the amine in solution (if any) according to the conditions and time of contact. If the conditions are such that this reaction is slow, an undue amount of time may be involved, and the amount of disulfide left at any given time will lower the yield of sulfenamide and necessitate purification of the latter. The reaction of amine with disulfide, reaction 3, appears to be the rate-controlling reaction for the process.

The summation of the three steps [1 + 2 + 3], (a) and (b) indicates the stoichiometry of the over-all process, and shows that alkali will be used up in the process when chlorine is the oxidizing agent, but alkali is formed in the process when hypochlorite is used. This is what actually happens in practice, and the corresponding changes in *p*H should be taken into account during the reacting period.

In several instances, especially for those reactions involving ammonia and ethylenediamine, it was found advantageous to change the order of addition of the reactants in order to obtain better yields of the desired products. In these reactions, the oxidizing agent, sodium hypochlorite, was added to a concentrated solution of ammonia or amine. To the resulting solution or slurry of chloramine (14) was then added a solution of sodium thiazolyl mercaptide, resulting in the precipitation of the sulfenamide. The mercaptide solution could be added simultaneously with the hypochlorite solution, with good results as long as the hypochlorite addition was kept in advance of the mercaptide.

This "chloroamine process" also proceeds in steps, which may be represented as follows, starting with a primary amine and oxidizing with a hypochlorite solution:

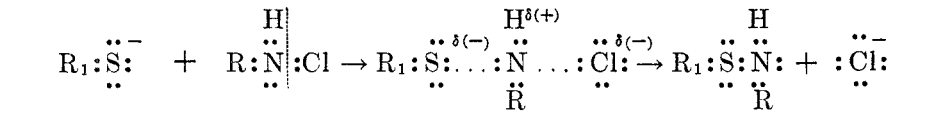
4. $RNH_2 + H_2O \rightarrow RNH_3^+ + OH^-$
5. $RNH_3^+ + OCl^- \rightarrow RNHCl \downarrow + H_2O$
6. $R_1S^- + RNHCl \rightarrow R_1SNHR \downarrow + Cl^-$

Over-all reaction, 4. + 5. + 6.

$$R_1S^- + RNH_2 + OCl^- \rightarrow R_1SNHR + Cl^- + OH^-$$

It is seen that the sum of reactions 4, 5, and 6 is identical to the sum of the steps in the oxidative condensation process 1, 2b, and 3, although the course of the reactions, and the intermediates are quite different. As would be expected, the optimum conditions for the chloroamine process are different from those for the oxidative condensation process, requiring higher concentrations of reactants, lower temperatures, and a higher *p*H, which is automatically controlled to a certain extent by the optimum conditions for the formation of the chloroamine. These conditions are further compared and discussed in connection with the preparation of thiocarbamylsulfenamide in another communication from this laboratory (15).

The reaction of the chloroamine involves splitting the nitrogen-chlorine bond during the nucleophilic displacement reaction (6) so that the electron pair is retained by the chlorine atom to form chloride ion:



As the chloride ion separates, the electron-deficient nitrogen atoms are satisfied simultaneously, in this case, by sharing with mercaptide ions, $R_1:\ddot{S}:^-$, which are abundant in the concentrated mercaptide solution, thus forming the sulfenamide.

In the oxidative condensation process, the disulfide is split unsymmetrically, reaction 3, one sulfur atom retaining the electron pair bond, $R_1:\ddot{S}|\ddot{S}:R_1$, to form a mercaptide ion, $R_1:\ddot{S}:^-$, and an electron-deficient sulfur, $R_1:\ddot{S}^+$, which is satisfied immediately by sharing with ammonium ions, $R:\ddot{N}(H):H^+$ this process requiring that the amine must be in abundant supply, thus forming the sulfenamide. This reaction is exactly analogous to the splitting of disulfides with aqueous caustic, which is believed to proceed according to the following steps:

7. $$2\,R_1:\ddot{S}:\ddot{S}:R_1 + 4\,OH^- \rightarrow 2\,R_1:\ddot{S}:\ddot{O}:^- + 2\,R_1:\ddot{S}:^- + 2\,H_2O$$

8. $$2\,R_1:\ddot{S}(:\ddot{O}:)\ddot{O}:^- \rightarrow R_1:\ddot{S}(:\ddot{O}:)\ddot{O}:^- + R_1:\ddot{S}:^-$$

7. + 8. $$2\,R_1:\ddot{S}:\ddot{S}:R_1 + 4\,OH^- \rightarrow R_1:\ddot{S}(:\ddot{O}:)\ddot{O}:^- + 3\,R_1:\ddot{S}:^- + 2\,H_2O$$

The sulfenic acid originally formed (7) is believed to rearrange to form mercaptide and sulfenic acid according to reaction 8. The amount of recoverable mercaptide should be 75.5% of the original disulfide, which is the experimental fact in the case of 2-benzothiazolyl disulfide.[2]

At higher temperatures this reaction probably competes with the formation of sulfenamides in the oxidative condensation process, but at lower temperature (0–50°), the electron-deficient sulfur apparently prefers to share with nitrogen rather than with oxygen and forms the sulfenamide exclusively.

The thiazolesulfenamides are in general rather unstable compounds, decomposing spontaneously even when dry, in times varying from a few minutes to several months or years. The decomposition products identified in each case are the disulfide (RSSR) and the substituted ammonium thiazolyl mercaptide. Light and heat accelerate the rate of decomposition. The presence of free alkali also catalyzes the reaction, thus making it necessary to free the products entirely from the alkali of the reaction mixture.

The thiazolesulfenamides are, however, fairly resistant to the action of alkalis as compared with their reactivity toward strong acids. Acidic substances decompose the sulfenamides quickly in aqueous solution or in dry ether with the formation of disulfides and the amine salts of the acids used. Probable intermediates in this reaction are the thiazolesulfenyl chlorides. In several experiments using N-cyclohexylbenzothiazolesulfenamide with hydrogen chloride in dry ether, a small amount of ether-soluble yellow oil was obtained, possibly 2-benzothiazolesulfenyl chloride, which decomposed rapidly at ordinary temperatures forming solid 2-benzothiazolyl disulfide.

The stability of a 2-benzothiazolesulfenamide was found to depend upon the nature of the amine from which it was derived. Primary alkylcarbinamines, RCH_2NH_2, gave low-melting solid, or liquid compounds which decomposed rather rapidly (in a few weeks) under ordinary conditions. The secondary alkylcarbinamines, R_2CHNH_2, gave thiazolesulfenamides which melted higher for compounds of equal molecular weights than those from the primary carbinamines, and they were more stable under ordinary conditions. In the one instance tried, a tertiary carbinamine, R_3CNH_2 (*tert*-amylamine) yielded a sulfenamide of higher melting point and greater stability than the corresponding secondary and primary compounds. Unsaturation or branching of the chain beyond the α-carbon atom appeared to make little difference in the stability. Substitution with a phenyl group, (*e.g.* the sulfenamide from benzylamine), or other negative substituents, (*e.g.* hydroxyl) appeared to stabilize the resulting sulfenamide.

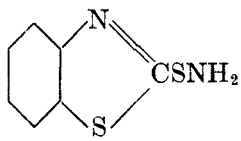
Secondary alkyl amines gave liquid sulfenamides whose stability was inter-

[2] Unpublished results obtained by Dr. B. J. Humphrey of this laboratory. Dr. Humphrey utilized a new method for the determination of benzothiazole-2-thiol, which is to be published. In the development of this method it was found that the use of barium hydroxide gave more consistent and reliable results than sodium hydroxide in dissolving the sample. The results here referred to were obtained by treatment of benzothiazolyl disulfide with barium hydroxide, followed by determination of the benzothiazole-2-thiol in the solution.

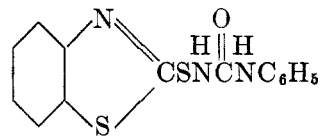
mediate between the primary and the tertiary carbinamine compounds. The corresponding sulfenamides prepared from cyclohexylamine and from heterocyclic amines such as piperidine, piperazine, and morpholine, had higher melting points and better stability than the groups of compounds from both secondary carbinamines and secondary alkylamines. The *bis*-substituted thiazolesulfenamides from piperazine and ethylenediamine were both relatively high-melting and stable.

The sulfenamides from the alkylthiazole-2-thiols were less stable than those from the benzothiazole-2-thiols and the thiazoline-2-sulfenamides were still less stable.

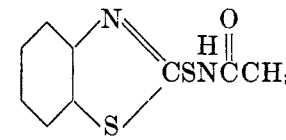
Benzothiazole-2-sulfenamide, II, reacted readily with phenylisocyanate forming N-phenylcarbamylbenzothiazole-2-sulfenamide, III. Reaction of the N-cyclohexylbenzothiazole-2-sulfenamide with phenyl isocyanate produced only N-phenyl-N′-cyclohexylurea. Furthermore, 2-benzothiazolyl disulfide was the product of the reaction of isothiocyanates with 2-benzothiazolesulfenamide. An acetyl derivative, IV, of the benzothiazolesulfenamide was formed, together with some disulfide, by the action of acetic anhydride in the presence of sodium



II



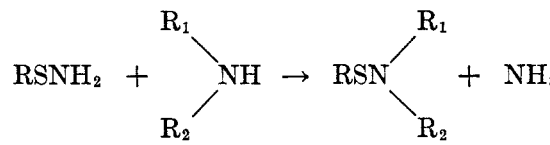
III



IV

acetate. Acid chlorides (acetyl, benzoyl, *p*-nitrobenzoyl) and 2,4-dinitrochlorobenzene yielded only the disulfide. Phthalyl chloride yielded phthalimide and disulfide.

Both thiazoline-2-sulfenamide and benzothiazole-2-sulfenamide reacted with amines to form substituted sulfenamides. In fact this reaction was used to es-

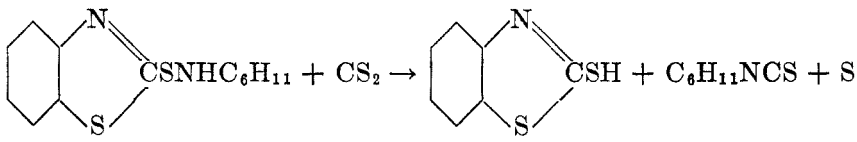


tablish the identity of thiazoline-2-sulfenamide which was too unstable to retain in a pure state for analysis. These amine exchange reactions are convenient for the preparation of sulfenamides otherwise difficult to prepare, *e.g.*, from long chain and other water-insoluble amines, such as dodecyl- and hexadecenylamine. Similar reactions have been described by Howland (16).

Benzaldehyde and formaldehyde reacted with benzothiazole-2-sulfenamide II. Acetone did not react with II, but did react with N-cyclohexylbenzothiazole-2-sulfenamide. The products were not identified.

Carbon disulfide was without effect on 2-benzothiazolesulfenamide, but

reacted with the N-cyclohexyl derivative with the formation of benzothiazole-2-thiol and cyclohexyl isothiocyanate.



This reaction offers a unique and convenient new method for the preparation of aliphatic and substituted aliphatic isothiocyanates.

The sulfenamides were readily reduced by strong reducing agents such as sodium dithionite (hyposulfite) solution to the corresponding thiazolyl mercaptan and amine.

EXPERIMENTAL

PREPARATION OF SULFENAMIDES

Four different modifications which were used in the preparation of the sulfenamides have been identified in Table I by the use of Roman numerals I through IV inclusive. Some of the compounds were prepared by several different modifications. However, only the conditions of the particular modification which gave the best results are recorded in Table I. In most of the preparations considerable excesses of amine (3–20 moles) were used. The use of excess amine ensured that the desired sulfenamide would be obtained, but this excess probably would not be necessary if optimum conditions of temperature, concentration, etc., were determined. These optimum conditions have been worked out in a few cases and in each case it was found that only a very small excess of amine was necessary under the best conditions of preparation.

In general, the compounds were purified for analysis by recrystallization several times from petroleum ether. In a few instances, ether or mixtures of ether with other solvents were used. The compounds were found to be soluble in all of the ordinary organic solvents, and they were much more soluble than the dibenzothiazolyl disulfide which was frequently the chief impurity from which they were separated.

The ordinary Kjeldahl procedure for nitrogen analysis is not applicable to this type of compound. For the nitrogen analyses reported, a convenient modification of the Friedrich micro-Kjeldahl procedure (17) was used.

It is interesting to note that in the preparation of the compounds from ethylenediamine and from piperazine, there was the possibility for the formation of both mono- and di-substituted compounds. In both cases the disubstituted (*bis*) compounds were separated. In certain preparations of these compounds there was evidence for the formation of some monosubstituted compound, but this was not separated and identified. There was only one possibility, of course, in the preparation from morpholine.

An example of each of the four identified procedures employed is given below:

I. *Simultaneous addition of oxidizing agent and alkali mercaptide to an aqueous solution of amine. Preparation of benzothiazole-2-sulfenamide.* A clear solution was prepared by dissolving 16.7 g. (0.1 mole) of purified benzothiazole-2-thiol in 75 cc. of water containing 4.0 g. (0.1 mole) of sodium hydroxide. This solution and 75 cc. of a 10% sodium hypochlorite solution were dropped slowly at equal rates into 300 cc. of conc'd ammonium hydroxide (28%, sp. gr., 0.90). The mixture was cooled in an ice-bath (5–10°) and strongly stirred throughout the addition. The sulfenamide formed as a white bulky solid which occupied considerable volume and made the stirring less effective. The precipitate was washed with cold water until free from alkali. The product was completely soluble in ether but after drying four days at room temperature, it contained a very small ether-insoluble fraction of 2-benzothiazolyl disulfide; yield, 17 g., (93.5%). The product was crystallized from a

chloroform-petroleum ether mixture, m.p. 127–128°, forming a red liquid which decomposed at slightly higher temperatures.

II. *Oxidative condensation. Use of iodine in aqueous potassium iodide solution as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A clear aqueous solution was prepared containing 10.0 g. (0.06 mole) of benzothiazole-2-thiol, 4.8 g. (0.12 mole) of sodium hydroxide, and 18 g. (0.18 mole) of cyclohexylamine in a total volume of 250 cc. To this solution at room temperature was added, drop by drop with stirring over a period of one hour, 15.3 g. (0.12 mole) of iodine dissolved in 200 cc. of water containing 16.5 g. of potassium iodide. As the iodine solution made contact with the clear reaction mixture at first, a region of turbidity appeared and then vanished. After about one-tenth of the iodine solution had been added, the sulfenamide began to separate in the form of white crystal plates. The product was washed with water until free from alkali, and air-dried at a temperature not exceeding 50°; yield 15.2 g. (96%). It was completely soluble in ether, petroleum ether, and alcohol, indicating the absence of disulfide. It was crystallized from ether or petroleum ether, m.p. 102°.

III. *Oxidative condensation. use of chlorine (air-diluted) as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A solution was prepared containing 167 g. (1.0 mole) of benzothiazole-2-thiol, 100 g. (2.5 moles) of sodium hydroxide, and 245 g. (2.5 moles) of cyclohexylamine in a volume of 5000 cc. A mixture of chlorine with air, (about 6–8 parts of air to one of chlorine), was introduced into the mixture through four small-bore glass nozzles arranged in parallel. Rapid stirring was used throughout the reaction. The temperature varied from 25° to 32° and the *p*H was lowered from 13.1 to 12.5 during the reaction, which was run to completion, that is, until no benzothiazole-2-thiol was precipitated from a filtered test sample on acidification. The time required was 4–5 hours. The first product redissolved in the reaction mixture. After about fifteen minutes, glistening white crystals of the sulfenamide began to separate. Towards the end of the reaction, the precipitate became more granular and a light tan in color. The product was washed free of alkali with cold water and dried at temperatures below 50°; yield, 254 g. (96.5%). The product contained about 0.5% of ether-insoluble material. One crystallization from ether or petroleum ether yielded pure white crystals, m.p. 102°.

Exactly the same results were obtained by using less initial sodium hydroxide and controlling the *p*H of the solution between 12.3–12.5 by addition of sodium hydroxide solution from a burette, drop by drop, during the reaction. The yield of light tan product was 255 g. (96.5%). In both experiments, the initial moist material was completely soluble in ether but developed about 0.5–0.6% ether-insoluble material during the drying. Crystallized as above, m.p. 102°.

IV. *Oxidative condensation. Use of sodium hypochlorite as an oxidizing agent. Preparation of N-cyclohexylbenzothiazole-2-sulfenamide.* A solution of 16.7 g. (0.1 mole) of benzothiazole-2-thiol and 4.0 g. (0.1 mole) of sodium hydroxide was made in about 100 cc. of water. To this was added 12.4 g. (0.125 mole) of cyclohexylamine, and the whole solution was diluted to 250 cc. The initial *p*H of this solution was 12.4. It was cooled to 10°, causing the formation of some crystals, presumably the cyclohexylammonium salt of benzothiazole-2-thiol. Solutions of about 10% sodium hypochloride and about 4.1 *N* sulfuric acid were added, drop by drop, simultaneously from two burettes at such rates that the *p*H of the solution was kept between 12.2–12.5 throughout the reaction. The mixture was stirred vigorously and kept at 9.5–10.5°. Addition was continued until there was no free benzothiazole-2-thiol left in solution, as found by acidification of a small amount of filtrate. The pure white crystalline precipitate was filtered, washed thoroughly with water and dried; yield, 22.1 g. (83.8%). Before drying, the product was entirely ether-soluble, but it developed 2.25% insoluble disulfide during drying; m.p. 98–102°.

In another experiment, similar results were obtained by using more amine (0.35 mole) and adding the sodium hypochlorite very slowly with stirring at room temperature (25°). No attempt was made to control the *p*H in this experiment. The product was dried at room temperature; m.p. 100–102° without further purification, yield, 82.5%.

TABLE I

THIAZOLE-2-SULFENAMIDES

	PREP. METHOD	YIELD, %	MOLE RATIO AMINE TO THIAZOLE	REACTION TEMP., °C.	M.P., °C.	ANALYSIS			
						S		N	
						Calc'd	Found	Calc'd	Found
I. THIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	I	—	5:1	25–30	52–53	29.9	29.7	13.1	13.1
II. BENZOTHIAZOLE-2-SULFENAMIDE									
Unsubstituted	I	94	—	5–10	127–128	35.18	35.25	—	—
N-Methyl-	III	68	5:1	Room T.	Liq.	—	—	—	—
N,N-Dimethyl-	II	39	5:1	0–20	Liq.	—	—	—	—
N-Ethyl-	II	79	20:1	Room T.	55–57	30.49	30.80	13.32	12.97
N,N-Diethyl-	III	55	4:1	Room T.	Liq.	—	—	—	—
N-*n*-Propyl-	II	77	5:1	Room T.	32–33	28.58	28.47	12.49	12.35
N-Isopropyl-	III	82	3:1	Room T.	93–94	28.58	28.54	12.49	12.46
N-*n*-Butyl-	II	64	10:1	Room T.	35–37	11.75	11.15	—	—
N,N-Di-*n*-butyl-[a]	II	—	4:1	Room T.	Liq.	—	—	—	—
N-(1-Methylpropyl)-	II	70	5:1	Room T.	49–50	26.90	27.04	11.75	11.68
N-(1-Methylbutyl)-	II	96	5:1	8–11	58–60	25.41	25.38	11.10	11.19
N-(2,2-Dimethylpropyl)-	II	—	5:1	Room T.	80–82	25.41	25.60	11.10	11.50
N-(1,3-Dimethylbutyl)-	II	71	5:1	5–6	52–54	24.07	24.15	10.52	10.31
N,N-Di-*n*-amyl-[b]	II	37	4:1	0–20	Liq.	—	—	—	—
N-(2-Hydroxyethyl)-	II	—	10:1	Room T.	94–95	—	—	12.10	11.90
N-Methallyl-	II	76	12:1	Room T.	64–66	27.13	26.97	11.85	11.76
N-Cyclohexyl-	II	96	2.5:1	25–32	102	24.25	24.55	—	—
N-Benzyl-	II	95	4:1	Room T.	117	23.54	23.90	10.29	10.00
N,N′-Ethylene-*bis*-	IV	26.5	4:1	—	125–126	—	—	—	—
N-Cyclopentamethylene-	III	60	6:1	Room T.	80	—	—	—	—
N-Oxadiethylene-(from morpholine)	II	86	10:1	Room T.	85–86	25.41	25.65	11.10	10.65
N,N′-Diethylene-*bis*-(from piperazine)	II	96	5:1	0–20	190–192	30.78	30.65	13.45	13.42
N-Furfuryl-	(IV)	52	1.25:1	0–10	103–104	24.1	24.1	10.7	10.6
N-Thenyl-	(IV)	—	1.25:1	0–10	105–106	—	—	10.1	9.8
N-(2-Methyl-2-hydroxypropyl)-	(IV)	16	1.25:1	0–10	108–109	11.0	10.7	25.1	24.7

III. 6-NITROBENZOTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	—	—	—	119	20.72	20.90	13.58	13.50
IV. 4-METHYLTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	73	3.5:1	8–10	49–50	—	—	—	—
V. 4-ETHYLTHIAZOLE-2-SULFENAMIDE									
N-Cyclohexyl-	II	77	3:1	0–20	65–68	—	—	—	—
VI. 4,5-DIMETHYLTHIAZOLE-2-SULFENAMIDE									
N-Isopropyl	II	80	10:1	8–10	62–63	—	—	—	—
N-(1-Methylpropyl)-	II	72	5:1	Room T.	51–52	—	—	—	—
N-(1-Methylbutyl)-	II	56	5:1	Room T.	40–42	—	—	—	—
N-(1,3-Dimethylbutyl)-	II	51	5:1	5–7	Liq.	—	—	—	—
N-Cyclohexyl-	II	95	4:1	Room T.	92–94	—	—	—	—
N,N′-Diethylene-*bis*-(from piperazine)	II	—	7.5:1	Room T.	154	34.42	34.70	15.04	15.43
VII. TETRAHYDROBENZOTHIAZOLE-2-SULFENAMIDE									
N-Isopropyl-	II	53	10:1	Room T.	Liq.	—	—	—	—
N-(1-Methylbutyl)-	II	—	5:1	Room T.	Liq.	—	—	10.9	10.7
N-Cyclohexyl-	II	—	3:1	5–10	100–103	—	—	—	—
N-Benzyl-	II	—	5:1	Room T.	Liq.	—	—	10.1	9.9
VIII. THIAZOLINE-2-SULFENAMIDE									
Unsubstituted[c]	I	—	6:1	0	49–51	—	—	—	—
N-Isopropyl-	III	47	1.25:1	0	28–28.5	36.38	36.52	15.89	15.92
N-(1-Methylbutyl)-	III	70	1.25:1	0	Liq.	—	—	—	—
N-Cyclohexyl-	II	83	3:1	Room T.		29.64	29.60	12.95	13.00

[a] A dioxane-water mixture was used as a reaction medium instead of water because of the water insolubility of di-*n*-butylamine. [b] In this case alcohol was used as an auxiliary solvent because of the low water solubility of di-*n*-amylamine. [c] The identity of thiazoline-2-sulfenamide was proven by reaction with cyclohexylamine which formed the N-cyclohexyl derivative.

N-Phenylcarbamylbenzothiazole-2-sulfenamide. III. To 5.0 g. (0.0275 mole) of benzothiazole-2-sulfenamide was added 10.0 g. (0.084 mole) of phenyl isocyanate. The mixture was warmed gently to start the reaction which then took place rapidly, and cooling was necessary to prevent it from becoming too violent. The reaction product was washed with ether, extracted with benzene to remove 2-benzothiazolyl disulfide, and the residue was crystallized several times from boiling alcohol. Pink crystalline plates; m.p., 208–209°, yield, 39%.

Anal. Calc'd for $C_{14}H_{11}N_3OS_2$: N, 13.94; S, 21.28.

Found: N, 13.60, 13.75; S, 21.13.

N-Acetylbenzothiazole-2-sulfenamide. IV. To 20.0 g. (0.196 mole) of acetic anhydride was added 2.0 g. (0.0242 mole) of fused sodium acetate and 4.0 g. (0.022 mole) of benzothiazole-2-sulfenamide. The mixture was allowed to stand about fifteen hours at 30°. A small amount of water was added to hydrolyze the acetic anhydride, and the 2-benzothiazolyl disulfide was then filtered off. Further dilution of the filtrate with water precipitated a low-melting solid, which, after several recrystallizations from ether yielded the pure acetyl derivative, m.p. 135–136°, yield, 30%.

Anal. Calc'd for $C_9H_8N_2OS_2$: N, 12.49; S, 28.59.

Found: N, 12.48, 12.53; S, 28.57, 28.73.

Reaction of N-cyclohexylbenzothiazole-2-sulfenamide with phenyl isocyanate. To an ether solution of 10.0 g. (0.038 mole) of N-cyclohexyl-2-benzothiazolesulfenamide was added 9.0 g. (0.075 mole) of phenyl isocyanate. There was no evidence of immediate reaction, but on standing fifteen hours at 35–40°, the reaction mixture solidified. The product was washed with ether, and crystallized from benzene and then from toluene. The white crystals, m.p. 181–182°, proved to be N-phenyl-N′-cyclohexylurea. A mixture melting point determination with an authentic sample (m.p. 179–181°) prepared from phenyl isocyanate and cyclohexylamine was 179–181°. Yield, 42.7%. An additional 24% yield of crude material was recovered from the ether filtrate.

Anal. Calc'd for $C_{20}H_{21}N_3OS_2$: N, 12.85. Found: N, 12.40.

Action of carbon disulfide on N-cyclohexylbenzothiazole-2-sulfenamide. Five grams of the N-cyclohexylbenzothiazole-2-sulfenamide was mixed with 50 cc. of carbon disulfide. Solution was practically immediate, and for ten minutes there was no evidence of reaction. A crystalline product, 2 g., then precipitated with a slight evolution of heat. The product, m.p. 179°, was soluble in alkali and when mixed with pure benzothiazole-2-thiol the melting point was not depressed. Evaporation of the solvent left a liquid with a strong odor, and a small amount of solid. The liquid reacted with cyclohexylamine to give N,N′-dicyclohexylthiourea which was identified by the melting point, 179°, and mixture melting point. The liquid product was, therefore, cyclohexyl isothiocyanate. Free sulfur probably was formed but was not identified. A sample of the liquid from another similar preparation was distilled; b.p. 81–83°/3, n_D^{20} 1.5384.

The reaction of amines with thiazole- and thiazoline-sulfenamides. A small amount of benzothiazole-2-sulfenamide was dissolved in isopropylamine and the solution allowed to stand for three hours. The solid residue had m.p. 92–93°. A mixture melting point with a sample of N-isopropylbenzothiazole-2-sulfenamide showed no depression.

A similar experiment involving thiazoline-2-sulfenamide and cyclohexylamine yielded a product which was identified by melting point, and mixture melting point as N-cyclohexylthiazoline-2-sulfenamide. In this case the reaction was taken as proof of the identity of the very unstable thiazoline-2-sulfenamide.

ACKNOWLEDGMENT

The writers wish to thank Dr. R. F. Dunbrook and Dr. F. W. Stavely for their interest and encouragement in this work, and the management of the Firestone Tire & Rubber Company for permission to publish this report. They

take this opportunity, also, to express their appreciation for the valuable help and many suggestions received from Dr. B. J. Humphrey during the early phases of this project and for the elementary microanalyses, including the application of the Friedrich micro-Kjeldahl nitrogen method to this type of compound, which was the work of Dr. G. P. Rowland of the Firestone Laboratories.

SUMMARY

A general method has been developed for the preparation of thiazolesulfenamides by the oxidation of 2-mercaptothiazoles in the presence of amines with halogen oxidizing agents. This method has been extended to the preparation of N-substituted sulfenamides from ammonia; primary, secondary, and heterocyclic amines; and from 2-mercaptothiazoline and 2-mercaptoalkylthiazoles as well as from 2-mercaptobenzothiazoles. Some of the chemical reactions and the factors affecting the stability of the thiazole sulfenamides have been discussed briefly.

AKRON 17, OHIO

REFERENCES

(1) BEDFORD AND SEBRELL, *Ind. Eng. Chem.*, **13**, 1034 (1931); *Ind. Eng. Chem.*, **14**, 25 (1922); *Ind. Eng. Chem.*, **16**, 792 (1924); SEBRELL AND BEDFORD, U. S. Patent 1,544,687 (1924); SEBRELL AND BOORD, *Ind. Eng. Chem.*, **15**, 1009 (1923).

(2) (a) HARMAN, *Ind. Eng. Chem.*, **29**, 205 (1937); U. S. Patent 2,191,656 (1940); (b) ZAUCKER, U. S. Patent Reissue 19,286 (1934).

(3) KHARASCH, POTEMPA, AND WEHRMEISTER, *Chem. Revs.*, **39**, 269 (1946).

(4) RATHKE, *Ann.*, **167**, 195 (1873).

(5) VORLANDER AND MITTAG, *Ber.*, **52**, 413 (1919).

(6) (a) RHEINBOLDT AND MOTZKUS, *Ber.*, **72**, 657 (1939); RHEINBOLDT AND MOTT, *Ber.*, **72**, 668 (1939); (b) SCHULZE, U. S. Patent 2,123,082 (1938).

(7) (a) ZINCKE, *Ber.*, **44**, 769 (1911); ZINCKE AND DAHM, *Ber.*, **45**, 3457 (1912); ZINCKE AND KRUGER, *Ber.*, **45**, 3468 (1912); ZINCKE AND EISMAYER, *Ber.*, **51**, 751 (1918); ZINCKE, *Ann.*, **391**, 55, (1912); ZINCKE AND FARR, *Ann.*, **391**, 57, (1912); ZINCKE, *Ann.*, **400**, 1 (1913); ZINCKE AND LENHARDT, *Ann.*, **400**, 2 (1913); ZINCKE AND ROSE, *Ann.*, **406**, 103 (1914); ZINCKE AND BAEUMER, *Ann.*, **416**, 86 (1918); (b) FRIES, *Ber.*, **45**, 2965 (1912); FRIES AND SCHURMANN, *Ber.*, **52**, 2170, 2182 (1919); (c) LECHER AND HOLSCHNEIDER, *Ber.*, **57**, 755 (1924); LECHER, *Ber.*, **58**, 409 (1925).

(8) (a) RATHKE, *Ann.*, **167**, 211 (1873); (b) GEBAUER-FULNEGG, *Monatsh.*, **48**, 645 (1927); GEBAUER-FULNEGG AND RIESZ, *Monatsh.*, **49**, 31 (1928); *Monatsh.*, **52**, 365 (1929); GEBAUER-FULNEGG, *J. Am. Chem. Soc.*, **49**, 2270 (1927); (c) MOORE AND JOHNSON, *J. Am. Chem. Soc.*, **57**, 1517, 2234 (1935); *J. Am. Chem. Soc.*, **58**, 1091, 1960 (1936); (d) BILLMAN AND O'MAHONY, *J. Am. Chem. Soc.*, **61**, 2340 (1934); BILLMAN, GARRISON, ANDERSON, AND WOLNAK, *J. Am. Chem. Soc.*, **63**, 1920 (1941).

(9) MESSER, U. S. Patents 2,321,305 (1943), 2,321,306 (1945), and 2,370,253 (1945).

(10) ZAUCKER, U. S. Patent Reissue 19,286 (1934).

(11) (a) BUSCH, *Ber.*, **29**, 2127 (1896); BUSCH AND STERN, *Ber.*, **29**, 2148 (1896); (b) TWISS AND JONES, British Patent 413,296 (1934); (c) I. G. FARBENDUSTRIE, British Patent 377,730 (1932); (d) HARMAN, U. S. Patents, 2,100,692 (1937), 2,214,460 (1940), and 2,226,767 (1940).

(12) (a) TSCHUNKUR AND KOHLER, U. S. Patent 2,045,888 (1936); (b) HARMAN, U. S. Patent 2,191,657 (1940); (c) HANSLICK, U. S. Patent 2,261,024 (1941); (d) ASHWORTH, U. S. Patent 2,268,467 (1941); CARR, U. S. Patents 2,271,834 (1942), 2,339,552

and 2,354,427 (1944), 2,381,384 (1945), 2,393,500 and 2,393,507 (1946); SMITH, U. S. Patents 2,367,827 (1945) and 2,415,029 (1947); SMITH AND CARR, U. S. Patents 2,445,722 (1948) and 2,459,736 (1949).

(13) SCHUBERT AND HERDIECKERHOFF, U. S. Patent 2,018,813 (1935).

(14) COLEMAN AND HAUSER, *J. Am. Chem. Soc.*, **50**, 1195 (1928); COLEMAN AND FORRESTER, *J. Am. Chem. Soc.*, **58**, 27 (1936).

(15) SMITH, ALLIGER, CARR, AND YOUNG, *J. Org. Chem.*, Nov., 1949. (Thiocarbamylsulfenamides).

(16) HOWLAND, U. S. Patent 2,382,793 (1945).

(17) FRIEDRICH, KUHAAS, AND SCHNURCH, *Z. physiol. Chem.*, **216**, 68 (1933) [*Chem. Abstr.*, **27**, 2648 (1933)].