[Contribution from the Research Laboratories of the Goodyear Tire and Rubber Co.]

REACTIONS IN THE THIAZOLE SERIES. I. REACTIONS OF 2-CHLOROBENZOTHIAZOLES WITH THIOUREAS

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Rather extensive studies involving the addition compounds of alkyl halides with thiourea have been pursued for the purpose of elucidating the structures of thiourea, of its addition compounds, and of basic substances derived therefrom[1–6]. The formation of aliphatic mercaptans by the decomposition of addition compounds of this type indicates that the hydrocarbon group is attached to sulfur. While such reactions in the aliphatic series were observed by Claus[7] at an early date, a survey of the literature reveals that these studies have been extended to halogen compounds of the aromatic and heterocyclic series in but a few instances. Furthermore, with but one exception[8,9] no attempts have been made to determine the relative reactivities of substituted thioureas toward the various types of organic halides.

Of a number of chloropolynitrobenzenes investigated, only 1-chloro-2,4-dinitrobenzene and picryl chloride have been found reactive toward thiourea[10,11], the former yielding bis (2,4-dinitrophenyl) disulfide, and the latter dipicryl sulfide. Rosenhauer, Hoffman, and Heuser[12] have shown that thiourea and certain chloroquinolines react to form either mercaptans, sulfides, or disulfides. Their observations support the view that the primary reactions consist in the formation of definite additive compounds.

Experiments described in the following pages show that analogous reactions occur when 2-chlorobenzothiazoles and thiourea are refluxed, or are

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[1] Bernthsen and Klinger, *Ber.* **11**, 492–5 (1878); **12**, 574–6 (1879).

[2] Rathke, *ibid.*, **14**, 1774–80 (1881).

[3] Will, *ibid.*, **14**, 1489–92 (1881); **15**, 338–48 (1882).

[4] Will and Bielschowski, *ibid.*, **15**, 1309–18 (1882).

[5] Werner, *J. Chem. Soc.*, **57**, 283–304 (1890).

[6] Lecher and Heuck, *Ann.*, **438**, 169–84 (1924).

[7] Claus, *Ber.*, **7**, 235–7 (1874); **8**, 41–4 (1875); *Ann.*, **179**, 146–7 (1875).

[8] Goldschmidt and Grini, *Z. Elektrochem.*, **19**, 226–34 (1913).

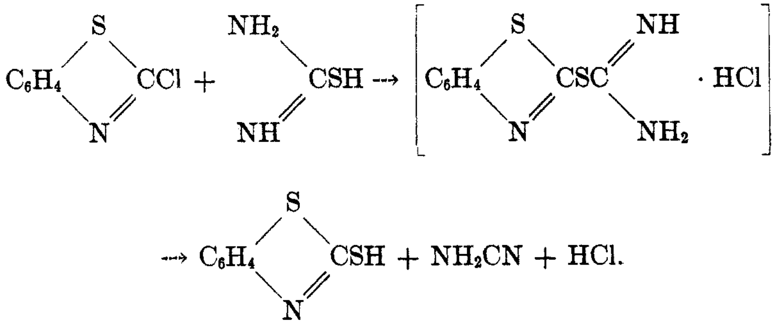
[9] Goldschmidt and Hougen, *ibid.*, **22**, 339–49 (1916).

[10] Willgerodt, *Ber.*, **10**, 1686–9 (1877); Private Communication to "Beilstein", II, Third Edition, p. 816.

[11] Taylor and Dixon, *J. Chem. Soc.*, **125**, 243–50 (1924).

[12] Rosenhauer, Hoffman, and Heuser, *Ber.*, **62B**, 2730–6 (1929).

allowed to stand for some time at room temperature, in alcoholic solution. The interaction of 2-chlorobenzothiazole and thiourea may be represented by the equations,



The instability of the intermediate addition compound is apparently such that it decomposes spontaneously, even at room temperature, resulting in the formation of 2-mercaptobenzothiazole, cyanamide, and hydrogen chloride. Both 2-mercaptobenzothiazole and cyanamide have been identified, the latter in the form of its silver salt, and the formation of hydrogen chloride is indicated by the fact that an aqueous solution of the reaction product is acid to litmus and exhibits reactions characteristic of hydrochloric acid. Similar reactions occur with monosubstituted thioureas, while the disubstituted compounds may result in the formation of mercaptans or stable addition compounds, depending upon the nature of the substituent groups and upon the lability of the halogen atom in the 2-position in the thiazole ring. In certain cases the disubstituted compounds are unreactive.

EXPERIMENTAL

With the exceptions noted below, materials used in this investigation were prepared and purified by methods ordinarily employed, or consisted of carefully purified commercial products. All analytical data presented herein were obtained by standard procedures and are averaged values.

Preparation of 2-chlorobenzothiazole.—The method employed for the preparation of 2-chlorobenzothiazole is essentially that due to Clifford[13] and is generally applicable to the preparation of 2-chlorobenzothiazoles.

One hundred fifty grams of sulfur monochloride (10% excess) was added in small portions and with stirring to 167 g. (1 mole) of commercial grade 2-mercaptobenzothiazole contained in a three liter flask provided with an air reflux condenser. When the initial exothermic reaction had subsided, the reaction mixture was heated cautiously until frothing ceased, then refluxed on the sand bath for one and one-half hours and allowed to stand overnight. The black liquid was transferred to a Claisen

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[13] CLIFFORD, *U. S. Pat.* 2,043,948, June 9, 1936.

flask and distilled; the fraction boiling at 150–70° (55–65 mm.) being collected. This material was washed thoroughly with 10% sodium carbonate solution, washed with water, separated, and dried over anhydrous sodium sulfate. Redistillation of the dried product gave a 72% yield (117 g.) of clear colorless 2-chlorobenzothiazole; b.p., 158-62°/50 mm.

Preparation of s-*dicyclohexylthiourea.*—One-half mole of *N*-methylenecyclohexylamine (55 g.) in a 500 cc. flask was melted on the steam bath. Small portions of sulfur were then added to the melt until 31.8 g. had been added. The reaction mixture darkened, heat was liberated, and there was a copious evolution of hydrogen sulfide. After heating under reflux (air condenser) for five minutes, the mixture was distilled under reduced pressure. The pale yellow oily distillate which solidified upon cooling was recrystallized from alcohol; white crystals of *s*-dicyclohexylthiourea; m. p. 179–80°. The melting point of a mixture with a specimen prepared as described by Skita and Rolfes[14] was not depressed. Yield, 22 g. or 37%.

Anal. Calc'd for $C_{13}H_{24}N_2S$: N, 11.7; S, 13.3.
Found: " 11.5; " 13.4.

Various modifications of the foregoing procedure resulted in no marked increase in yield, the maximum obtained being 44%. The crude reaction product may be distilled at atmospheric pressure without materially altering either the yield or the quality of the product. Insofar as we have been able to determine, *s*-dicyclohexylthiourea has previously been prepared only by the method of Skita and Rolfes.

Attempt to prepare s-*dipentamethylenethiourea.*—In view of the results obtained in the reaction between *N*-methylenecyclohexylamine and sulfur, it seemed probable that the preparation of *s*-dipentamethylenethiourea might be accomplished through the interaction of 1,1′-methylenebispiperidine and sulfur. It was found, however, that such interaction results in the formation of relatively low yields of piperidine pentamethylenedithiocarbamate, hydrogen sulfide, piperidine hydrosulfide, and variable amounts of tarry products.

Since the reaction was found to be a very violent one, the procedure finally adopted involved the use of xylene as the reaction medium, the following being a description of a typical case. Ninety-two grams of 1,1′-methylenebispiperidine, 36.4 g. of sulfur, and 100 cc. of xylene were placed in a three-liter flask equipped with an air condenser tube, the top section of which was bent at a forty-five degree angle and which led into a one-liter Erlenmeyer flask immersed in an ice bath. (The condenser tube should have an inside diameter of at least 1.6 cm.) The purpose of this apparatus is to obviate loss of the product during the violently exothermic reaction when much of the reaction mixture will be forced out through the condenser tube and lost if these precautions are not observed.

The reaction vessel was warmed gently until the reaction began. Cold water was then allowed to flow over the surface of the flask in order to keep the reaction under control. When vigorous boiling ceased, that portion of the reaction mixture which was trapped in the Erlenmeyer flask at the exit to the condenser tube was returned to the reaction vessel, and the whole was refluxed for 20 minutes. The system was then arranged for distillation at atmospheric pressure in the usual manner, using an air condenser. The greater portion of the reaction mixture was distilled over, including the solvent xylene, and collected in a cooled receiver. The white crystalline product was separated by filtration and recrystallized from methyl alcohol. White

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[14] SKITA AND ROLFES, *Ber.*, **53B,** 1247 (1920).

crystals of piperidine pentamethylenedithiocarbamate; m. p., 172–3°; yield, 42 g. or 34%.

Anal. Calc'd for $C_{11}H_{22}N_2S_2$: N, 11.4; S, 26.0.
Found: " 11.1; " 26.3.

The melting point of a mixture with an authentic specimen of the piperidine salt prepared from piperidine and carbon bisulfide in the usual manner showed no depression.

During refluxing, piperidine hydrosulfide condensed on the walls of the condenser assembly, and a smaller quantity volatilized in the early stages of the distillation. While our experience with this reaction is not sufficiently extensive to warrant speculation as to the mechanism of the formation of the products obtained, it is possible that the anticipated product, *s*-dipentamethylenethiourea, was formed as an intermediate in the production of the dithiocarbamate.

Reactions of 2-chlorobenzothiazole.—Seventeen grams of 2-chlorobenzothiazole and 7.6 g. of thiourea were refluxed for one hour in 100 cc. of ethyl alcohol. The clear alcoholic solution was poured into 500 cc. of ice water, whereupon a white crystalline solid separated. This material was filtered off and washed with water. The crude product, 2-mercaptobenzothiazole, weighed 16.8 g. (100% yield) and melted at 175–6°. After recrystallization from alcohol it melted at 176–7° and this melting point was not depressed when a sample was mixed with an equal weight of 2-mercaptobenzothiazole prepared by an entirely independent method.[15]

TABLE I

REACTIONS WITH 2-CHLOROBENZOTHIAZOLE

THIOUREA	YIELD, %	M. P., °C.
Thiourea	100	175–6
Allyl-	100	170–3
Phenyl-	78	170–3
o-Tolyl-	79	169–74
s-Diphenyl-	0	
s-Dicyclohexyl-	0	
N,*N*-Dimethyl-*N'*-phenyl-	0	
N,*N*-Pentamethylene-*N'*-phenyl-	0	

Anal. Calc'd for $C_7H_5NS_2$: N, 8.4; S, 38.3.
Found: " 8.3; " 38.4.

The filtrate was made distinctly alkaline with ammonium hydroxide and treated with aqueous silver nitrate. A small quantity of yellow silver cyanamide, m. p., 200° (dec.) was precipitated.

Equimolar quantities of 2-chlorobenzothiazole and thiourea in alcohol solution were allowed to stand overnight at room temperature in a tightly stoppered container. When the solvent alcohol was allowed to evaporate without application of heat, a theoretical yield of 2-mercaptobenzothiazole was obtained.

In Table I are presented yield data relative to reactions of 2-chlorobenzothiazole with a number of thioureas. The melting points of the *crude* products are included in the table since they serve as an index to the purity of 2-mercaptobenzothiazole

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[15] KELLY. *U. S. Pat.* 1,631,871, June 7, 1927.

produced in these reactions. In each case one-tenth molar quantities of 2-chlorobenzothiazole and the designated thiourea were refluxed for one hour in 100 cc. of alcohol.

Monosubstituted thioureas.—After reactions involving monosubstituted thioureas, a different method was required for the isolation of the mercaptan, due to the presence of insoluble monosubstituted cyanamides. When the alcoholic solutions were poured into ice water, there separated not definitely crystalline products such as are obtained when thiourea itself is used, but rather soft semi-solid materials which only partially solidified upon standing in the aqueous medium in the cold. When these products were purified by crystallization from organic solvents, unavoidable purification losses led to yield values appreciably lower than actually formed in the reactions. Accordingly, the crude products were filtered off, dried, and the melting points were estimated; the products were then extracted three times with 50 cc. portions of cold 10% sodium hydroxide solution. 2-Mercaptobenzothiazole was then precipitated from the combined extracts by acidification with dilute hydrochloric acid. After recrystallization from 50% alcohol, 2-mercaptobenzothiazole isolated in this manner melted at 175–7° and its identity was confirmed by mixture melting points in each case.

The residues remaining after the alkali extractions were examined in some detail and in every case were found to consist of a mixture of products. For example, in the case of the reactions with phenylthiourea, fractional crystallizations of the alkali-insoluble material from alcohol, ether, and ethyl acetate resulted in the isolation of very small quantities of white solids having melting points of 40–45° and 183–5° (after softening at 160°). These substances have properties similar to those exhibited by phenylcyanamide (m. p. 47°),[16] and triphenylisomelamine (m. p., 185°).[17]

Disubstituted thioureas.—As shown in Table I, 2-mercaptobenzothiazole is not formed when 2-chlorobenzothiazole is refluxed with disubstituted thioureas in alcohol for one hour. Neither is it formed when such solutions are refluxed for periods up to 40 hours, nor when disubstituted thioureas are refluxed for several hours in an excess of 2-chlorobenzothiazole (b. p., 247°). With exception of the latter case, when the disubstituted thioureas undergo partial decomposition during the refluxing at high temperatures, the greater part of the starting materials may be recovered unchanged.

In one instance, a stable addition compound was formed between 2-chlorobenzothiazole and a disubstituted thiourea. Seventeen grams of 2-chlorobenzothiazole and 15 g. of *N,N′-o*-phenylenethiourea (thiobenzimidazolone) were refluxed for one hour in 100 cc. of alcohol. The insoluble gray solid was filtered off and washed with alcohol and benzene. It weighed 27.5 g. (86% yield) softened at 220-2° and melted with decomposition at 233–4°. This substance is insoluble in ordinary organic solvents and has been shown by analysis to consist of a simple addition compound.

Anal. Calc'd for $C_{14}H_{10}ClN_3S_2$: N, 13.1; S, 20.0; Cl, 11.1.
Found: " 13.0; " 19.9; " 11.9.

Trisubstituted thioureas.—No reactions occurred when the trisubstituted thioureas listed in Table I were refluxed with 2-chlorobenzothiazole in alcohol, and the starting materials were recovered.

Reactions of 2-chloro-6-nitrobenzothiazole.—Ten and six-tenths grams of 2-chloro-6-nitrobenzothiazole and 3.8 g. of thiourea were refluxed for one hour in 75 cc. of

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[16] HOFFMAN, *Ber.*, **18**, 3221 (1885).

[17] HOFFMAN, *ibid.*, **18**, 3223 (1885).

alcohol. After refluxing for a few minutes, the solution assumed an orange-yellow color and crystals of 2-mercapto-6-nitrobenzothiazole having a like color separated. The reaction mixture was cooled; the crystals were separated by filtration, washed with cold alcohol, and dried. The filtrate and washings were poured into 500 cc. of ice water, and the yellow crystals which separated were isolated as described above. Thus, 9.9 g. was obtained by direct crystallization from the reaction mixture, and 0.6 g. by dilution with water, or a total of 10.5 g. which represents a quantitative yield; m. p., 225–7°.

Anal. Calc'd for $C_7H_4N_2O_2S_2$: N, 13.2; S, 30.3.
Found: " 13.2; " 30.1.

Data contained in Table II represent results obtained when 1/20 mole each of 2-chloro-6-nitrobenzothiazole and the indicated thiourea were refluxed in 75 cc. of alcohol for the given periods of time. As in Table I, the melting points given are those of the crude products.

Monosubstituted thioureas.—The procedure used in isolating 2-mercapto-6-nitrobenzothiazole from reactions involving monosubstituted thioureas differed from that described above only in that the product obtained by dilution with water was extracted with an excess of 10% sodium hydroxide and filtered, and the mercaptan was precipitated by addition of dilute hydrochloric acid. The rate of formation of 2-mercapto-6-nitrobenzothiazole from 2-chloro-6-nitrobenzothiazole and monosubstituted thioureas is noticeably slower than when thiourea is used, as judged by the elapsed time between the beginning of refluxing and the appearance of the mercaptan in the form of insoluble orange-yellow crystals. This difference in rate of reaction becomes quite apparent when a reaction with a monosubstituted thiourea and one employing thiourea are carried out simultaneously.

TABLE II

REACTIONS WITH 2-CHLORO-6-NITROBENZOTHIAZOLE

THIOUREA	TIME, (HRS.)	YIELD, %	M.P., °C.
Thiourea	1	100	255–7
Allyl-	1	94	248–50
Phenyl-	1	92	249–52
o-Tolyl-	1	93	254–6
s-Diphenyl-	12.5	49	225–30
s-Dicyclohexyl-	1	94	251–3
N,*N*-Dimethyl-*N*′-phenyl-	50	0	

Disubstituted thioureas.—Upon completion of refluxing, the solid products isolated as previously described were combined, and the mercaptan extracted in 10% sodium hydroxide solution. As shown in Table II, the reaction with *s*-diphenylthiourea was very slow, while that with *s*-dicyclohexylthiourea appeared to proceed at a rate only slightly lower than similar reactions with monosubstituted thioureas. The alkali-insoluble material from the reaction involving *s*-dicyclohexylthiourea was boiled with toluene to remove soluble impurities. There remained 4.0 g. of a grayish-white solid which after recrystallization from alcohol consisted of white crystals of *s*-dicyclohexylurea; m.p., 229–30°.

Anal. Calc'd for $C_{13}H_{24}N_2O$: N, 12.5. Found: N, 12.1.

The formation of this substance may be readily explained. When a disubstituted thiourea reacts with an organic halide in the manner described in the foregoing pages, there is formed not cyanamide, but rather the disubstituted diimide, RN:C:NR. This, in turn, may react with any water present in the hot alcoholic reaction medium to form the corresponding urea.

It is significant that the crude products from reactions involving disubstituted thioureas had a marked odor of mustard oils. The appearance of such products is indicative of decomposition of the thioureas during refluxing.

Trisubstituted thioureas.—In the only case studied, namely that of *N*,*N*-dimethyl-*N'*-phenylthiourea, we have been unable to identify 2-mercapto-6-nitrobenzothiazole as a product of the reaction. However, by extraction with aqueous sodium hydroxide and acidification of the clear alkaline extract, there was isolated 8.4 g. of a pale tan solid, m.p., 80–110°. Repeated recrystallization of this material from glacial acetic acid (in an effort to isolate the mercaptan) resulted in a progressive lowering of the melting point to a value of 67–9° after the fourth crystallization. This behavior is indicative of a progressive acetylation. The final product was small in amount and was found by analysis to contain 8.5% nitrogen and 17.6% sulfur. This product has not been identified.

The alkali-insoluble fraction (10.0 g.) was recrystallized from toluene. It consisted mainly of bright yellow crystals of 2-dimethylamino-6-nitrobenzothiazole; m.p., 197.5–199°.

Anal. Calc'd for $C_9H_9N_3O_2S$: N, 18.8; S, 14.3.
Found: " 18.4; " 14.5.

During the prolonged refluxing to which the reactants concerned were subjected (50 hours) the trisubstituted thiourea was apparently decomposed, and dimethylamine was thereby liberated. The free amine must then have reacted with the 2-chloro-6-nitrobenzothiazole with elimination of hydrogen chloride to form the 2-dimethylamino derivative.

DISCUSSION

The foregoing data indicate that there is a definite gradation in the reactivity of thiourea and its substituted derivatives toward 2-chlorobenzothiazoles, the corresponding mercaptans being produced most readily by thiourea, more slowly and less completely by monosubstituted thioureas, and slowly if at all by disubstituted compounds. In no case was a reaction of this type observed with a trisubstituted thiourea.

Since it is logical to assume that the primary reaction consists in the formation of an addition compound, the efficiency of a given thiourea may be thought of in terms of the ease with which it forms such addition compounds. Goldschmidt and co-workers[8, 9] have studied the rates of formation of addition compounds between methyl and ethyl iodides and thiourea, its mono- and disubstituted derivatives. Largely from conductivity data they have established the following order of decreasing reactivity,

$$\text{thiourea} > \text{mono-} > \text{di-} > \text{trisubstituted,}$$

this order being identical with that found in the present study.

The difference in yields of mercaptans obtained with the various types of thioureas cannot be attributed to differences in the techniques employed in the isolation of the products. In each instance the method used insured the complete removal of any mercaptan formed in the reaction. The method employing alkali extraction might conceivably result in high yields in terms of mercaptan in the case of reactions with 2-chloro-6-nitrobenzothiazole, since any unchanged chloro compound would probably be at least partially converted to 2-hydroxy-6-nitrobenzothiazole by the action of sodium hydroxide. The hydroxy compound would, in this event, appear along with the mercaptan upon acidification of the aqueous solution of the combined sodium salts. However, no such complication was encountered in the present studies, since, when there appeared to be any reaction whatever, sufficient time was allowed for the complete utilization of the chloro compound.

The markedly greater reactivity of 2-chloro-6-nitrobenzothiazole as compared with 2-chlorobenzothiazole, as evidenced by results obtained in reactions with disubstituted thioureas, and by relative yields of mercaptans with monosubstituted thioureas, provides further evidence as to the effect of a nitro group in the 6-position upon the lability of the halogen atom in the 2-position in the thiazole ring.[18] Another factor concerned in the apparent reactivities of the two halides lies in the relative solubilities of the corresponding mercaptans in alcohol. The nitro-substituted mercaptan is almost insoluble in hot alcohol whereas 2-mercaptobenzothiazole is very soluble under the same conditions and appreciably soluble at room temperature. Hence, should the reactions in question involve an equilibrium situation, those producing mercaptans of low solubility would be expected to occur the more readily.

Mercaptobenzothiazoles produced by the interaction of 2-chlorobenzothiazoles and thiourea are of a degree of purity limited only by the purity of the starting materials. 2-Mercaptobenzothiazole prepared by the usual method[15] possesses a yellow color which is extremely difficult if not impossible to remove by the ordinary methods of purification. However, when this material is prepared as described in this paper, it is perfectly white and of a high degree of purity.

A study of reactions of halides of the type used in this investigation with thiourea in aqueous media has led to results which seem worthy of further study. Accordingly, these reactions will be described in a later communication.

SUMMARY

1. It has been shown that the interaction of 2-chlorobenzothiazoles and thiourea leads to the formation of high yields of the corresponding mercaptans, and a mechanism for the reaction has been suggested.

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[18] *Cf.* Teppema and Sebrell, *J. Am. Chem. Soc.*, **49**, 1780–1 (1927).

2. A brief study of the relative reactivities of a number of substituted thioureas has indicated the following order of decreasing reactivity,

thiourea > mono- > di- > trisubstituted.

3. Methods for the preparation of 2-chlorobenzothiazoles and of s-dicyclohexylthiourea have been described.

4. The reaction between 1,1′-methylenebispiperidine and sulfur has been shown to result in the formation of piperidine pentamethylenedithiocarbamate.