2-Substituted Thiobenzothiazole and Related Compounds. I. Novel Methods for the Preparation of 2,2'-Thiobis(benzothiazoles), 2-(N,N-Disubstituted amino)benzothiazoles, and Related Compounds[1]

JOHN J. D'AMICO, SIDNEY T. WEBSTER, ROBERT H. CAMPBELL, AND CHARLES E. TWINE

Monsanto Company, Organic Chemicals Division, Rubber Chemicals Research Laboratories, Nitro, West Virginia

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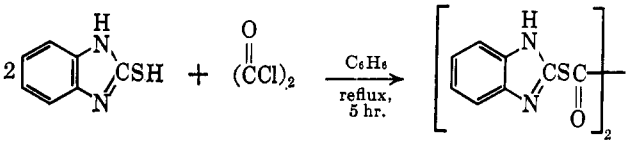
The reactions of 2-mercaptobenzothiazole with oxalyl chloride and 2-chlorobenzothiazole with disubstituted formamides afforded novel methods for the synthesis of 2,2'-thiobis(benzothiazole) (III) and 2-(N,N-disubstituted amino)benzothiazoles, respectively. In the latter reaction, replacing N,N-disubstituted formamide with formamide furnished 2-hydroxybenzothiazole. Depending on reaction conditions, the reaction of 2-mercaptobenzothiazole with 2-chlorobenzothiazole in dimethylformamide gave exclusively III or 2-(N,N-dimethylamino)benzothiazole (IX). The reaction of 2-mercaptobenzothiazole or its sodium salt with 2-chlorobenzothiazole or 2,5-dichlorobenzothiazole in various solvents were investigated and are discussed in terms of steric, orbital overlap, and electronic effects. Possible mechanisms and supporting infrared and ultraviolet data are discussed.

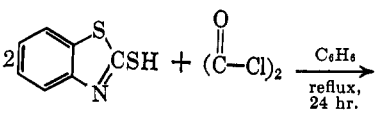
It has been reported[2,3] that the reaction of mercaptans with oxalyl chloride gives dialkyl dithiooxalates. We now report the reactions of this reagent with 2-mercaptobenzimidazole, 2-mercaptobenzothiazole, and 2-mercaptobenzoxazole.

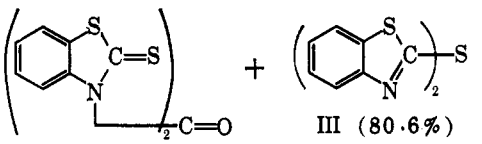
The reaction of 2-mercaptobenzimidazole with oxalyl chloride furnished S,S'-bis(2-benzimidazolyl) 1,2-dithiooxalate (I) in 99% yield. Analysis and infrared spectra were in agreement for the proposed structure of I. The reaction of I with ethyl alcohol furnished 2-mercaptobenzimidazole and ethyl oxalate in yields of 97 and 75.2%, respectively.



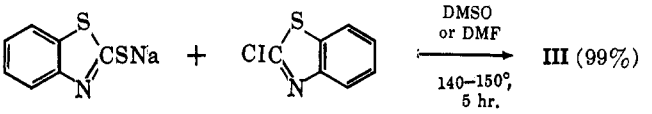
I

The reaction of 2-mercaptobenzothiazole with oxalyl chloride gave carbonyl bis(benzothiazoline-2-thione) (II) and 2,2'-thiobis(benzothiazole) (III) in yields of 19.4 and 80.6%, respectively. Proof of structure for II and III was based on elemental analysis, molecular weight, and infrared and ultraviolet spectra. The ultraviolet spectrum of II contained an absorption maximum at 304 mμ (ε 29,600). The spectra of 2-mercaptobenzothiazole and its N-substituted derivatives possess maxima at 328 mμ (ε 29,000), attributed to the $\begin{matrix}-S\\-N\end{matrix}>C=S$ group,[4] while S-substituted derivatives absorb in the region of 275 mμ (ε 21,000). Product III was also obtained in 99% yield by the reaction of anhydrous sodium 2-mercaptobenzothiazole with 2-chlorobenzothiazole in dimethylformamide or dimethyl sulfoxide. This reaction in dimethylformamide was studied at different temperatures and found to be second order. The details of this kinetic study are reported in paper II.[5]





II (19.4%) III (80.6%)



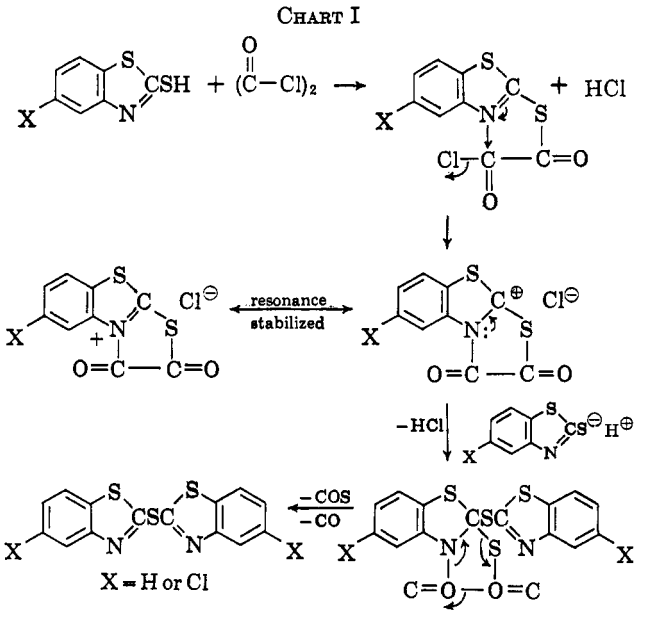
The reaction of 5-chloro-2-mercaptobenzothiazole with oxalyl chloride furnished only one product, 2,2'-thiobis(5-chlorobenzothiazole) (IV). This same product IV was obtained in 99% yield by the reaction of anhydrous potassium 5-chloro-2-mercaptobenzothiazole with 2,5-dichlorobenzothiazole.

The mechanism as illustrated in Chart I is offered for the reaction of oxalyl chloride with 2-mercaptobenzothiazole or its 5-chloro homolog.

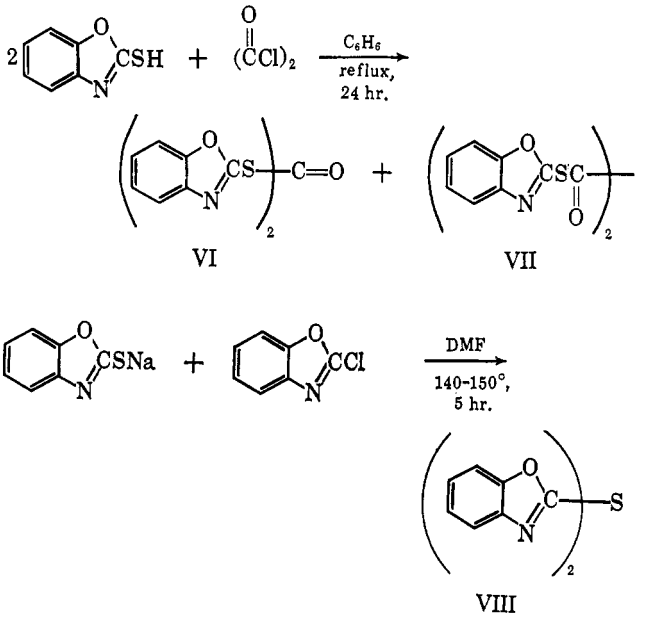
The reaction of 2-mercaptobenzoxazole with oxalyl chloride did not yield 2,2'-thiobis(benzoxazole) (VIII), but instead gave 2,2'-bis(benzoxazolyl) dithiocarbonate (VI) and S,S'-bis(2-benzoxazolyl) 1,2-dithiooxalate (VII) in yields of 41.2 and 57.5%, respectively. It is of interest that the α-diketo groups of VII apparently exhibited interaction. Normally, where both *cis* and *trans* configurations occur, little interaction between the carbonyls is observed in the infrared spectra. However, by using a model of this compound, it was found that if the benzoxazole rings were arranged in planar overlap, only the *cis* configuration of the α-diketo groups existed. This would permit dipolar interactions of the keto group and lead to elevated carbonyl frequencies. The anticipated product VIII was prepared by the reaction of the anhydrous sodium salt of 2-mercaptobenzoxazole with 2-chlorobenzoxazole. Teppema[6] obtained III by treating 2-mercaptobenzo-

(1) Presented at 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.
(2) T. Jones, *J. Chem. Soc.*, **95**, 1904 (1909).
(3) M. E. Arndt, *Ber.*, **56**, 1982 (1923).
(4) H. P. Koch, *J. Chem. Soc.*, 401 (1949).
(5) J. J. D'Amico, R. H. Campbell, S. T. Webster, and C. E. Twine, *J. Org. Chem.*, **30**, 3625 (1965).
(6) J. Teppema, U. S. Patent 2,028,082 (1936).

CHART I



thiazole with 2-chlorobenzothiazole in ethyl alcohol at 25–30° for a period of 3 days. It was decided to study this reaction employing different solvents at 82–83° and the results are cited in Table I. From this



study it was discovered that this was an equilibrium reaction. In isopropyl alcohol, the equilibrium was reached in 30 min. and the yield of III was 72.3%. If the reaction time was extended to 3 and 5 hr., the yield of III was 65.5 and 56.0%, respectively. How-

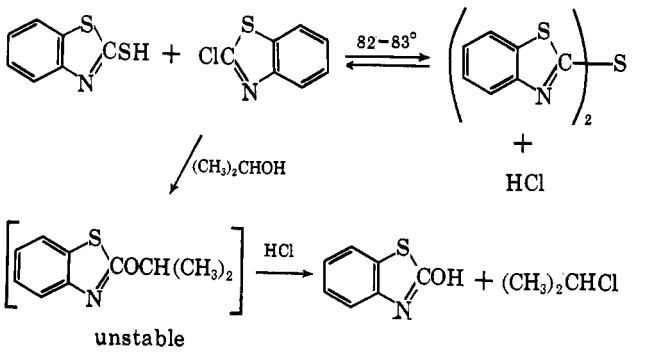


TABLE I

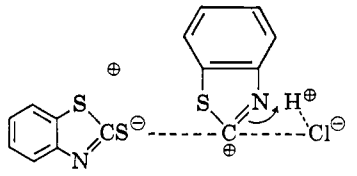
2,2′-THIOBIS(BENZOTHIAZOLE) (III) AND 2-HYDROXYBENZOTHIAZOLE[a]

Solvent	Time, hr.	V.p.c. of crude III: Wt. % III	Wt. % 2-ClBT	% yield of III	M.p., °C., of III	Anal. of III: % N Calcd.	% N Found	% S Calcd.	% S Found	Wt. % (by ultraviolet) MBT	Wt. % (by ultraviolet) 2-BTOH	% recovery of MBT	% yield of 2-BTOH	M.p., °C.: MBT	M.p., °C.: 2-BTOH
Isopropyl alcohol	0.5	93.1	6.9	72.3	101–102[b,c]	9.33	9.16	32.02	32.45	100.0	...	27.7	...	180–181[b,c]	...
Isopropyl alcohol	3.0	95.5	4.5	65.5	101–102[b,c]	9.33	9.11	32.02	32.12	72.9	27.1	34.5	14.4	180–181[b,c]	138–139[c,d]
Isopropyl alcohol	5.0	96.8	3.2	56.0	101–102[b,c]	9.33	9.13	32.02	32.04	58.8	41.2	41.2	33.6	180–181[b,c]	138–139[c,d]
1,2-Bis(2-methoxyethoxy)ethane	5.0	97.7	2.3	33.7	101–102[b,c]	9.33	9.14	32.02	32.04	100.0	...	53.5	...	180–181[b,c]	...
Decalin	5.0	98.5	1.5	70.5	101–102[b,c]	9.33	9.19	32.02	32.29	100.0	...	29.5	...	180–181[b,c]	...
Isopropyl alcohol + 0.3 mole of triethylamine	5.0	...	...	0[e]	...	...	...	...	...	...	...	...	...	...	...

[a] MBT = 2-mercaptobenzothiazole, 2-ClBT = 2-chlorobenzothiazole, and 2-BTOH = 2-hydroxybenzothiazole. [b] Recrystallization from ethyl alcohol. [c] Mixture melting point with authentic sample gave no depression and infrared spectra of the two were superimposable. [d] Obtained by adding water to the filtrate of MBT recrystallization and then recrystallizing from ethyl alcohol. [e] Since no reaction occurred, no attempt was made to recover MBT.

ever, under these conditions a side reaction occurred between 2-chlorobenzothiazole and isopropyl alcohol to give the 2-isopropyloxybenzothiazole which is unstable in an acidic medium to yield 2-hydroxybenzothiazole and isopropyl chloride. Thus, the removal of 2-chlorobenzothiazole by this side reaction would explain the lowering of the yield of product III from 72.3 to 56% and at the same time increasing the formation of 2-hydroxybenzothiazole from 0 to 33.6% as the reaction time was extended from 30 min. to 5 hr. When decalin, a nonpolar solvent, and 1,2-bis(2-methoxyethoxy)ethane, a polar solvent, were employed as the solvent, yields of 70.5 and 33.7% were obtained, respectively. However, it was anticipated that the use of 1 molar equiv. of triethylamine in an isopropyl alcohol medium would drive the equilibrium from left to right and thus increase the yield. However, this was not the case, for none of product III was obtained under these conditions.

By the utilization of these data, an explanation of the reaction of 2-mercaptobenzothiazole with 2-chlorobenzothiazole in different solvents is presented.

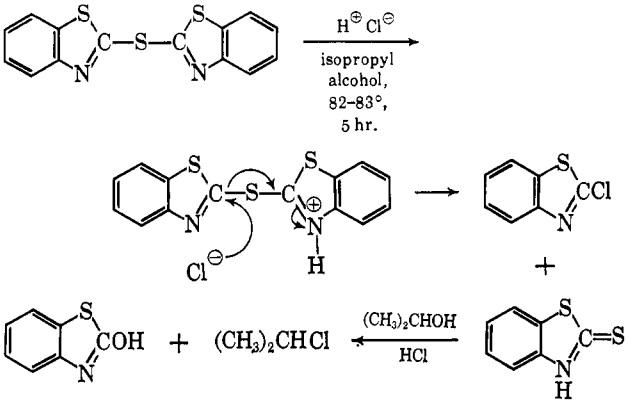


transition state

Steric Effect and Orbital Overlap.—Thus, in the transition state, the benzothiazolyl group would be perpendicular to the line described by the incoming nucleophile, the sp^2 carbon, and the leaving nucleophile. If this is the case, there should be less interference with the incoming nucleophile and the leaving nucleophile than if this carbon were an sp^3. Concerning the orbital overlap, the s orbital of hydrogen could overlap with the p orbital of chlorine. This interaction constitutes partial bond formation between hydrogen and chlorine, helping to stabilize the transition state, and thus speeding up substitution.

Electronic Effect.—Owing to the resulting increase in mutual coulombic attraction, reactions of thiobenzothiazole anions with neutral substrates are facilitated by effects leading to withdrawal of electrons from the substitution site. In our case, this resulted from protonation of the nitrogen. As a consequence, one would expect a marked difference in reactivity between nonpolar decalin with low proton affinity, and easily protonated polar 1,2-bis(2-methoxyethoxy)ethane. As noted above, such was actually the case, for when the solvent was changed from decalin to 1,2-bis(2-methoxyethoxy)ethane the yield of III dropped from 70.5 to only 33.7%. These results indicate the relative ease of protonation of the nitrogen varies inversely with the solvent competition for the proton. As a corollary of this concept, the reaction should be inhibited by strongly basic solvents which would form a salt with 2-mercaptobenzothiazole and thus prevent protonation. Again this was confirmed, for no III was obtained with triethylamine–isopropyl alcohol as the solvent.

A study of the reversible reaction, that is, the reaction of III with hydrogen chloride dissolved in isopropyl alcohol in a mole ratio of 1:1, gave the following yields based on 45.2% of unrecovered III: 2-chlorobenzothiazole, 7.5%; 2-mercaptobenzothiazole, 69.2%; and 2-hydroxybenzothiazole, 40.3%. The following mechanism is offered to explain this reaction.

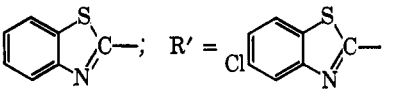


It was anticipated that the following three reactions would have yielded only one product, 2-(5-chlorobenzothiazolyl)thiobenzothiazole (V). However, this was not the case, for III, IV, and V were obtained in the yields shown. An attempt to separate III, IV, and V

$$\text{RSNa} + \text{R'Cl} \xrightarrow[150\text{–}160°,\ 5\text{ hr.}]{\text{DMF}} \underset{34.4\%}{\text{III}} + \underset{22.6\%}{\text{IV}} + \underset{36.4\%}{\text{V}} \quad (1)$$

$$\text{R'SH} + \text{RCl} \xrightarrow[82\text{–}83°,\ 30\text{ min.}]{\text{isopropyl alcohol}} \underset{14.7\%}{\text{III}} + \underset{13.1\%}{\text{IV}} + \underset{2.2\%}{\text{V}} \quad (2)$$

$$\text{RSR} + \text{R'SH} \xrightarrow[110\text{–}120°,\ 5\text{ hr.}]{\text{DMF}} \underset{50.0\%}{\text{III}} + \underset{30.4\%}{\text{IV}} + \underset{19.6\%}{\text{V}} \quad (3)$$



by recrystallization was not successful. Compound V was identified from a mixture of III, IV, and V. The mixture was separated by vapor phase chromatography. Each component was trapped at the outlet tube of the chromatograph. Infrared spectra of each indicated that the first and third chromatographic peaks were III and IV, respectively, while the infrared spectrum of the second peak could be accounted for as a composite of the infrared spectra of III and IV. Furthermore, the order of elution time from g.l.p.c. is consistent with the proposed structures. In order to elucidate the mechanism for the above three reactions, reactions 4 and 5 were attempted and, as noted, no reaction occurred under these conditions.

$$\text{RSR} + \text{R'SR'} \xrightarrow[150\text{–}160°,\ 5\text{ hr.}]{\text{DMF}} \text{no reaction} \quad (4)$$

$$\text{RSR} + \text{R'Cl} \xrightarrow[150\text{–}160°,\ 5\text{ hr.}]{\text{neat}} \text{no reaction} \quad (5)$$

The mechanism illustrated in Chart II is offered for reactions 1, 2, and 3.

The reaction of 2-mercaptobenzothiazole with 2-chlorobenzothiazole in dimethylformamide was studied and, depending on reaction conditions, either III or 2-(N,N-dimethylamino)benzothiazole (IX) was obtained (Table II).

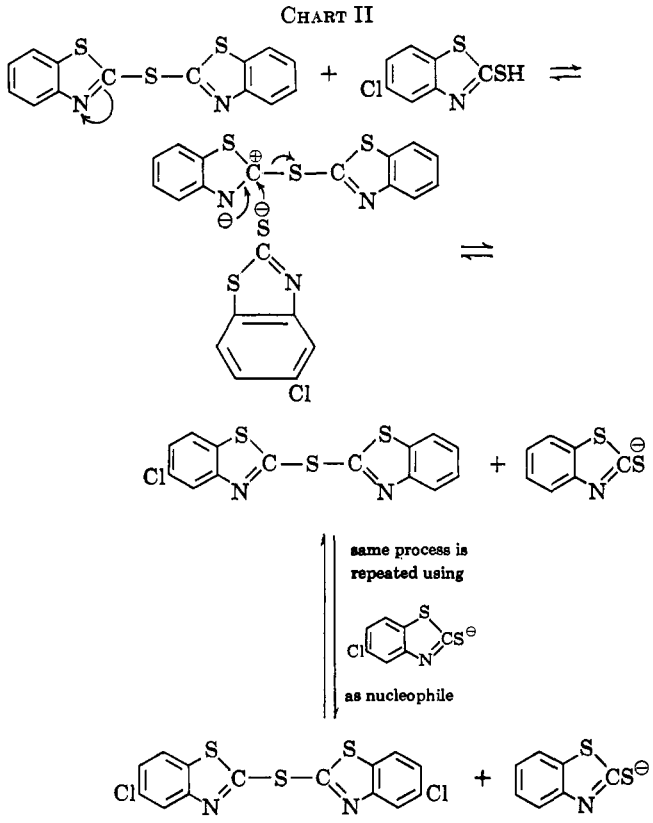
TABLE II

2,2'-THIOBIS(BENZOTHIAZOLE) (III) AND 2-(N,N-DIMETHYLAMINO)BENZOTHIAZOLE (IX)

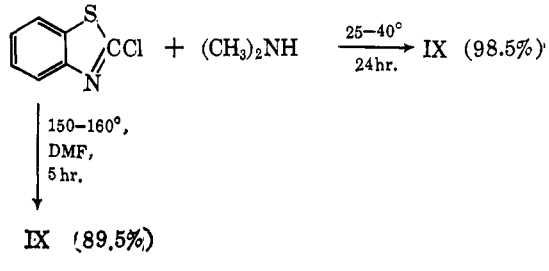
Compd.	Mole ratio MBT: 2-ClBT	Temp., °C.	Time, hr.	% yield of crude	V.p.c. (wt. %) of crude III	V.p.c. (wt. %) of crude IX	V.p.c. (wt. %) of crude 2-ClBT	M.p., °C.	Formula	% N Calcd.	% N Found	% S Calcd.	% S Found
III	1:1	80–90	5	54.3[a]	100.0	...	...	101–102[b]	$C_{14}H_8N_2S_3$	9.33	9.13	32.03	31.78
III	1:1	80–90	24	77.1[a]	97.4	...	2.6	101–102[b]	$C_{14}H_8N_2S_3$	9.33	9.15	32.03	31.94
III	1:2	80–90	5	68.5[a]	81.4	...	18.6	101–102[b]	$C_{14}H_8N_2S_3$	9.33	9.16	32.03	32.02
III and IX	1:1	150–160	5	12.9[a] 75.8[c]	22.3	77.7	...	92–93[d]	$C_9H_{10}N_2S$	15.72	15.50	17.99	17.80
IX	1:2	150–160	5	95.5	...	100.0	...	92–93[b]	$C_9H_{10}N_2S$	15.72	15.30	17.99	17.88

[a] Based on weight of III (total wt. × wt. % of III). [b] Recrystallization from ethyl alcohol. [c] Based on weight of IX (total wt. × wt. % of IX). [d] Four recrystallizations from ethyl alcohol were necessary to obtain IX.

CHART II

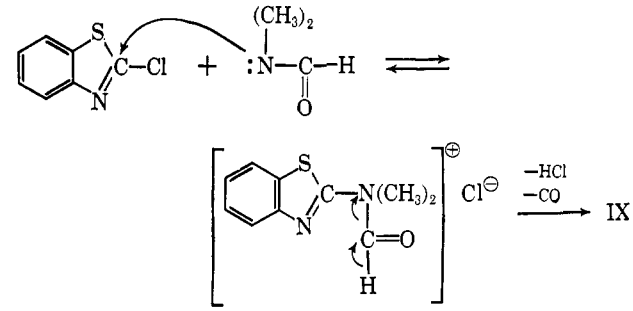


Proof of structure for IX was established by the reaction of 2-chlorobenzothiazole with either dimethylamine or excess dimethylformamide as illustrated by the following reactions. In order to ascertain that IX



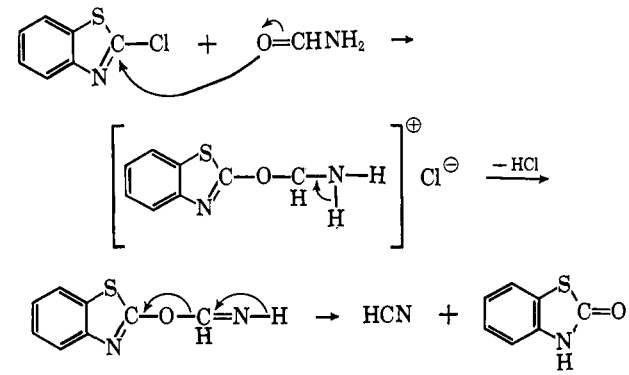
was not formed by the reaction of 2-mercaptobenzothiazole with dimethylformamide, an experiment was conducted employing these reactants and, as expected, 2-mercaptobenzothiazole was recovered in quantitative yield.

The following mechanism is offered for the reaction of 2-chlorobenzothiazole with dimethylformamide.



It appeared desirable to study the reaction of other disubstituted formamides with 2-chlorobenzothiazoles and thus determine whether this route would be a general method for the synthesis of 2-(N,N-disubstituted amino)benzothiazoles. As noted in Table III, yields of 97.5 to 99.5% were obtained by the reaction of 2-chlorobenzothiazole with formylmorpholine or formylhexamethylenimine, respectively. The low yield obtained with dibutylformamide was probably due to losses occurring during distillation. However, it should be mentioned that Coppinger[7] was the first to report that the reaction of benzyl chloride with dimethylformamide at 150° afforded a mixture of dimethylbenzylamine and methyldibenzylamine in low yields.

It was anticipated that the reaction of 2-chlorobenzothiazole with formamide would yield 2-aminobenzothiazole. However, this was not the case, for the product isolated in 90% yield was 2-hydroxybenzothiazole. Bredereck and co-workers[8] reported that alkyl halides reacted with formamide to give formylamino compounds or formates. They also stated that the course of the reaction depends upon the structure of the alkyl halide and is predictable and related to the



(7) G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954).
(8) H. Bredereck, *et al.*, *Angew. Chem.*, **71**, 753 (1959).

TABLE III

2-(N,N-DISUBSTITUTED AMINO)BENZOTHIAZOLE

Compd.	Method	Substituted formamide	Amine	X	R	M.p., °C.	% yield of crude	Formula	% Cl Calcd.	% Cl Found	% N Calcd.	% N Found	% S Calcd.	% S Found
XI	I	Formylmorpholine		H	Morpholino	126–127[a]	97.5	$C_{11}H_{12}N_2OS$			12.72	12.60	14.56	14.31
	II		Morpholine	H	Morpholino	126–127[a]	99.0	$C_{11}H_{12}N_2OS$			12.72	12.62	14.56	14.23
XII	II		Morpholine	Cl	Morpholino	115[a]	98.0	$C_{11}H_{11}ClN_2OS$	13.92	13.76	11.00	10.99	12.59	12.34
XIII	I	Formylhexamethyleneimine		H	Hexamethyleneimino	62–63[a]	99.0	$C_{13}H_{16}N_2S$			12.06	11.64	13.80	13.57
	II		Hexamethyleneimine	H	Hexamethyleneimino	62–63[a]	99.5	$C_{13}H_{16}N_2S$			12.06	11.71	13.80	13.56
XIV	II		Hexamethyleneimine	Cl	Hexamethyleneimino	74–75[b]	97.0	$C_{13}H_{15}ClN_2S$	13.29	13.19	10.50	10.50	12.02	11.74
XV	I	Dibutylformamide		H	Dibutylamino	B.p. 161–163 (1 mm.)	38.2	$C_{15}H_{22}N_2S$			10.68	10.59	12.22	12.23
	II		Dibutylamine	H	Dibutylamino	B.p. 161–163 (1 mm.)	66.0	$C_{15}H_{22}N_2S$			10.68	10.57	12.22	12.30

[a] Recrystallized from ethyl alcohol. [b] Recrystallized from heptane.

stability of the carbonium ion intermediate. In our opinion, the reaction proceeds through an SN2 and not by an SN1 mechanism, and the following mechanism for the reaction of 2-chlorobenzothiazole with formamide is offered.

Experimental Section[9]

Analytical Methods.—Vapor phase chromatographic analyses of III, IV, V, and IX were done with an F & M, Model 720, dual-column programmed-temperature gas chromatograph. A 0.25 in. × 2 ft. stainless steel column packed with 15% SE-30 silicone rubber on Gas Chrom CL, 45–60 mesh (flow rate of helium, 100 cc./min.), was operated isothermally at 260 and 300° and programmed from 140 to 300° at 20°/min. All samples containing 2-mercaptobenzothiazole and 5-chloro-2-mercaptobenzothiazole were dissolved in chloroform and extracted three times with dilute sodium hydroxide solution before chromatographic analysis. Chloroform and dimethylformamide were suitable for preparation of chromatographic samples of III, V, and IX and IV, respectively. The data were rendered quantitative by the use of *p*-terphenyl as an internal standard.

The infrared spectra of all compounds were obtained in chloroform (5000 to 830 cm.$^{-1}$) and dimethylformamide solutions (830 to 600 cm.$^{-1}$), except the infrared spectra of V which was obtained from a film. A Perkin-Elmer Model 21 spectrophotometer with a sodium chloride prism was used in all cases. The ultraviolet spectra of VI, VII, and VIII were determined in chloroform using a Cary Model 11 spectrophotometer.

S,S'-Bis(2-benzimidazolyl) 1,2-Dithiooxalate (I).—To a stirred slurry containing 90.2 g. (0.6 mole) of 2-mercaptobenzimidazole and 600 ml. of anhydrous benzene, 42 g. (0.33 mole) of oxalyl chloride was added dropwise at 50–60° over a 15-min. period. The stirred reaction mixture was heated at reflux for 5 hr. After cooling to 5°, the solid was collected by filtration and air dried at 25–30°: m.p. 195–197° dec., 99% yield. An attempt to recrystallize I from ethyl alcohol gave 2-mercaptobenzimidazole and diethyl oxalate. The infrared spectrum of I contained bands at 3350, 1768, 1302, and 750 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{10}N_4O_2S_2$: N, 16.27; S, 18.62. Found: N, 15.86; S, 18.41.

Proof of Structure.—A stirred slurry containing 68.9 g. (0.2 mole) and I and 100 ml. of ethyl alcohol was heated at reflux for 4 hr. After cooling to 0°, the solid was collected by filtration and air dried at 25–30°. 2-Mercaptobenzimidazole, m.p. 302–303°, was obtained in 97% yield. After recrystallization from ethyl alcohol the melting point remained unchanged. A mixture melting point with an authentic sample was not depressed and the infrared spectra of the two were superimposable. The filtrate was distilled to remove excess alcohol. Distillation of the residue *in vacuo* furnished diethyl oxalate, b.p. 96–97° (20 mm.), in 75.2% yield. The infrared spectrum of diethyl oxalate derived from this method and that of an authentic sample were superimposable.

Anal. Calcd. for $C_7H_6N_2S$: N, 18.65; S, 21.35. Found: N, 18.67; S, 21.33.

Carbonyl Bis(benzothiazoline-2-thione) (II) and 2,2'-Thiobis(benzothiazole) (III). Method I.—The reaction was carried out in a 1-l. three-necked flask equipped with an aqueous sodium hydroxide trap to remove hydrogen chloride and gas sample bottles to collect carbon monoxide and carbonyl sulfide. To a stirred slurry containing 66.9 g. (0.4 mole) of recrystallized 2-mercaptobenzothiazole in 600 ml. of anhydrous benzene, 27.9 g. (0.22 mole) of oxalyl chloride was added dropwise at 50–60° over a period of 15 min. During the addition the color of the reaction mixture changed from yellow to brown and finally to purple. The stirred reaction mixture was heated at reflux for 24 hr. Gas samples were taken at 1-hr. and 5-hr. intervals. The infrared spectra of these samples were superimposable with authentic samples of carbon monoxide and carbonyl sulfide. The stirred reaction mixture was cooled to 30°. The solids (14 g.) were removed by filtration and air dried at 25–30°. II, m.p. 179–180° dec., was obtained in 19.4% yield. The melting point remained unchanged after recrystallization from dimethylformamide. The infrared spectrum of II contained bands at 1735, 1332, 1300, 761, and 728 cm.$^{-1}$.

(9) All melting points were taken upon a Fisher-Johns block and are uncorrected.

Anal. Calcd. for $C_{15}H_{18}N_2OS_4$: N, 7.77; S, 35.58; mol. wt., 360.5. Found: N, 7.70; S, 35.49; mol. wt., 357.0.

The filtrate was evaporated at a maximum temperature of 30–40° at 1–2 mm. The resulting solids were added to 600 ml. of water containing 64 g. (0.4 mole) of 25% aqueous sodium hydroxide and stirred at 25–30° for 1 hr. The solids were collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°, giving III, m.p. 95–97°, in 80.6% yield. After recrystallization from ethyl alcohol, it melted at 101–102°. The vapor phase chromatogram of both the crude and recrystallized sample gave only one peak. The infrared spectrum of III contained bands at 1310, 767, and 732 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_8N_2S_3$: N, 9.33; S, 32.03. Found: N, 9.23; S, 32.03.

III. Method II (Preferred Method).—A stirred mixture containing 56.7 g. (0.3 mole) of anhydrous sodium 2-mercaptobenzothiazole, 49.9 g. (0.29 mole) of 2-chlorobenzothiazole, and 300 ml. of dimethylformamide or dimethyl sulfoxide was heated at 140–150° for 5 hr. After cooling to 25°, the reaction mixture was added to 1000 g. of ice–water containing 48 g. (0.3 mole) of 25% aqueous sodium hydroxide and stirred at 0–10° for 1 hr. The solids were collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 45°. The crude product, m.p. 99–100°, was obtained in 99% yield from reaction in either solvent. After recrystallization from ethyl alcohol the product melted at 101–102°. A mixture melting point of product from either reaction with the product obtained from method I gave no depression and infrared spectra of the three samples were superimposable. The vapor phase chromatogram of both the crude and recrystallized samples gave only one peak.

Anal. Calcd. for $C_{14}H_8N_2S_3$: N, 9.33; S, 32.03. Found (DMF reaction): N, 9.27; S, 32.39. Found (DMSO reaction): N, 9.35; S, 32.22.

III. Method III.—To a stirred solution at 80° of 54 g. (0.3 mole) of 2-mercaptobenzothiazole in 300 ml. of the appropriate solvent, 50.9 g. (0.3 mole) of 2-chlorobenzothiazole was added in one portion. The stirred reaction mixture was heated at 82–83° for the time period specified in Table I and immediately added to 1000 g. of ice–water containing 48 g. (0.3 mole) of 25% aqueous sodium hydroxide. After stirring at 0–10° for 0.5 hr., crude III was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 45°. The weight percentages of III and 2-chlorobenzothiazole in crude III were determined by vapor phase chromatography. To the combined filtrates, concentrated hydrochloric acid was added dropwise until pH 2–3 was obtained. The resulting precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 45°. The weight percentages of 2-mercaptobenzothiazole and 2-hydroxybenzothiazole were determined from the ultraviolet spectrum. The data are summarized in Table I.

2,2′-Thiobis(5-chlorobenzothiazole) (IV). Method I.—To a stirred slurry containing 40.3 g. (0.2 mole) of 5-chloro-2-mercaptobenzothiazole in 500 ml. of anhydrous benzene, 14 g. (0.11 mole) of oxalyl chloride was added dropwise at 50–60° over a 15-min. period. The stirred reaction mixture was heated at reflux for 18 hr. After cooling to 5°, the solids were collected by filtration. The wet solids were added to 600 ml. of water containing 32 g. (0.2 mole) of 25% aqueous sodium hydroxide and stirred for 1 hr. The solids were collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°: m.p. 171–172°, 90% yield. After recrystallization from dimethylformamide, it had m.p. 172–173°. The vapor phase chromatogram of both the crude and recrystallized samples gave only one peak; the infrared spectrum of IV contained bands at 1300, 862, and 800 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_6Cl_2N_2S_3$: Cl, 19.20; N, 7.59; S, 26.05. Found: Cl, 19.38; N, 7.40; S, 26.13.

Method II.—The procedure was identical with method II described for the preparation of III except that 72 g. (0.3 mole) of anhydrous potassium 5-chloro-2-mercaptobenzothiazole, 59.9 g. (0.29 mole) of 2,5-dichlorobenzothiazole, and 300 ml. of dimethylformamide were employed. The crude product, m.p. 165–167°, was obtained in 95% yield. After recrystallization from dimethylformamide it melted at 172–173°. A mixture melting point with the product obtained from method I gave no depression and infrared spectra of the two were superimposable. The vapor phase chromatograms of both the crude and recrystallized sample gave only one peak.

Anal. Calcd. for $C_{14}H_6Cl_2N_2S_3$: Cl, 19.20; N, 7.59; S, 26.05. Found: Cl, 19.12; N, 7.50; S, 26.00.

Mixture of III, IV, and 2-(5-Chlorobenzothiazolyl)thiobenzothiazole (V). Method I.—A stirred mixture of 56.8 g. (0.3 mole) of anhydrous sodium 2-mercaptobenzothiazole, 50.1 g. (0.25 mole) of 2,5-dichlorobenzothiazole, and 300 ml. of dimethylformamide was heated at 150–160° for 5 hr. After cooling to 25°, the reaction mixture was added to 1000 g. of ice–water containing 48 g. (0.3 mole) of aqueous 25% sodium hydroxide. After stirring at 0–10° for 1 hr., the solid was collected by filtration and washed with water until the washings were neutral to litmus. The wet product was reslurried in 600 ml. of water containing 48 g. (0.25 mole) of 25% sodium hydroxide, filtered, washed with water until neutral, and air dried at 45°, giving 77 g. of crude product, m.p. 81–84°, which contained III, IV, and V. An attempt to resolve these compounds by recrystallization was not realized. However, this mixture was resolved by vapor phase chromatography to give 33.6, 27.0, and 39.4 wt. % and 34.4, 22.6, and 36.4% yield of III, IV, and V, respectively. The infrared spectra of III and IV obtained from the vapor phase chromatogram and authentic samples of III and IV were superimposable. The infrared spectrum of V appeared as a composite of III and IV as would be anticipated and contained bands at 1310, 1300, 862, 800, 755, and 733 cm.$^{-1}$.

Method II.—To a stirred solution of 60.5 g. (0.3 mole) of 5-chloro-2-mercaptobenzothiazole in 400 ml. of isopropyl alcohol at 80°, 50.9 g. (0.3 mole) of 2-chlorobenzothiazole was added in one portion. The stirred reaction mixture was heated at 82–83° for 30 min. and immediately added to 1000 g. of ice–water containing 48 g. (0.3 mole) of 25% aqueous sodium hydroxide. After stirring at 0–10° for 30 min., the solid was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 45°. The crude product (30 g.), m.p. 113–116°, contained III, IV, and V. Based on vapor phase chromatography the data in Table IV were obtained.

TABLE IV

Compd.	Wt. %	% yield
III	44.3	14.7
IV	48.3	13.1
V	7.4	2.2

Method III.—A stirred solution of 30 g. (0.1 mole) of III and 20.2 g. (0.1 mole) of 5-chloro-2-mercaptobenzothiazole in 50 ml. of dimethylformamide was heated at 110–120° for 5 hr. The cooled solution was added to 1000 g. of ice–water containing 32 g. (0.2 mole) of 25% aqueous sodium hydroxide and stirred at 5–15° for 1 hr. The solid was collected by filtration, washed with water until the wash water was neutral to litmus, and air dried at 45°. The crude product (33 g.), m.p. 80–85°, contained III, IV, and V. The vapor phase chromatogram of this mixture furnished the data in Table V.

TABLE V

Compd.	Wt. %	% yield
III	45.8	50.0 (recovered)
IV	34.2	30.4
V	20.0	19.6

Attempted Preparation of V. Method IV.—A stirred solution containing 0.1 mole each of III and IV in 300 ml. of dimethylformamide was heated at 150–160° for 5 hr. After cooling to 25°, the solution was added to 2000 g. of ice–water and stirred at 0–10° for 1 hr. The solid was collected by filtration and air dried at 45°. Based on v.p.c. data and the infrared spectrum, no reaction occurred under these conditions.

V. Method V.—A stirred mixture of 20.4 g. (0.1 mole) of 2,5-dichlorobenzothiazole and 30 g. (0.1 mole) of III was heated at 150–160° for 5 hr. and then allowed to cool to 25–30°. V.p.c. analysis and the infrared spectrum revealed the presence of the starting reactants indicating that no reaction occurred under these conditions.

2,2′-(Benzoxazolyl) Dithiocarbonate (VI) and S,S′-Bis(2-benzoxazolyl) 1,2-Dithiooxalate (VII).—To a stirred slurry of 60.4 g. (0.4 mole) of 2-mercaptobenzoxazole and 600 ml. of anhydrous benzene, 28 g. (0.22 mole) of oxalyl chloride was added dropwise at 50–60° over a 15-min. period. The stirred reaction

mixture was heated at reflux for 24 hr. After cooling the stirred reaction mixture to 30°, the precipitate (VI) was collected by filtration and air dried at 25–30°: m.p. 175–176° dec., 41.2% yield. After recrystallization from ethyl acetate–acetone, it had m.p. 176–178° dec. The infrared spectrum VI contained bands at 1738, 1278, 1252, and 756 cm.$^{-1}$; the ultraviolet absorption spectra of VI displayed $\lambda_{max}^{CHCl_3}$ at 333 mμ (ε 9470) and 293 mμ (ε 28,000).

Anal. Calcd. for $C_{15}H_8N_2O_3S_2$: N, 8.53; S, 19.53; mol. wt., 328.4. Found: N, 8.54; S, 19.53; mol. wt., 329.

The filtrate was evaporated at a maximum temperature of 30° at 1–2 mm. The resulting solid (VII) was air dried at 25–30°: m.p. 131–133° dec., 57.7% yield. After recrystallization from ethyl acetate, it had m.p. 154–155° dec. The infrared spectrum of VII contained bands at 1717, 1696, 1278, 1262, and 756 cm.$^{-1}$; the ultraviolet absorption spectra of VII displayed $\lambda_{max}^{CHCl_3}$ at 318 mμ (ε 12,600) and 283 mμ (ε 20,400).

Anal. Calcd. for $C_{16}H_8N_2O_4S_2$: N, 7.86; S, 18.00; mol. wt., 356.4. Found: N, 7.92; S, 18.01; mol. wt., 349.

2,2′-Thiobis(benzoxazole) (VIII).—To a stirred solution of 37.4 g. (0.21 mole) of anhydrous sodium 2-mercaptobenzoxazole in 200 ml. of dimethylformamide, 30.7 g. (0.2 mole) of 2-chlorobenzoxazole was added in one portion. The stirred reaction mixture was heated at 140–150° for 5 hr. After cooling to 25°, the reaction mixture was added to 1000 g. of ice–water containing 31.8 g. (0.21 mole) of 25% aqueous sodium hydroxide. After stirring at 0–10° for 1 hr., the precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 45°. The product, m.p. 140–145°, was obtained in 52% yield. After recrystallization from toluene it melted at 160°. The infrared spectrum of VIII contained bands at 1278, 1236, and 760 cm.$^{-1}$. The ultraviolet absorption spectra of VIII displayed $\lambda_{max}^{CHCl_3}$ at 312 mμ (ε 18,600) and 285 mμ (ε 25,100).

Anal. Calcd. for $C_{14}H_8N_2O_2S$: N, 10.44; S, 11.95; mol. wt., 268.3. Found: N, 10.35; S, 11.60; mol. wt., 276.

Reaction of III with Alcoholic Hydrogen Chloride.—To a stirred solution of 100 ml. of isopropyl alcohol containing 3.7 g. (0.1 mole) of hydrogen chloride, 30 g. (0.1 mole) of III was added in one portion. The stirred solution was heated at 82–83° for 5 hr. After cooling to 25°, 500 ml. of water containing 32 g. (0.2 mole) of 25% aqueous sodium hydroxide was added. After stirring at 25–30° for 30 min., unreacted III was collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°. III (54.8%), m.p. 100–101°, which contained 3.4 wt. % of 2-chlorobenzothiazole by vapor phase chromatography, was recovered. After recrystallization from ethyl alcohol, III (*Anal.* Calcd. for $C_{14}H_8N_2S_2$: N, 9.33; S, 32.03. Found: N, 9.48; S, 32.15.) melted at 101–102°. The combined filtrate was made acidic with concentrated hydrochloric acid, and the resulting precipitate was collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°. The product (8 g.) melted at 137–170°. Based on the ultraviolet spectrum this mixture contained 65.5% 2-mercaptobenzothiazole and 34.5% 2-hydroxybenzothiazole. After two recrystallizations from ethyl alcohol, 2-mercaptobenzothiazole, m.p. 180–181°, was isolated. Based on 45.2% of unrecovered III, the following yields were obtained: 2-chlorobenzothiazole, 7.5%; 2-mercaptobenzothiazole (*Anal.* Calcd. for $C_7H_5NS_2$: N, 8.38; S, 38.34. Found: N, 8.19; S, 38.03.), 69.2%; and 2-hydroxybenzothiazole, 40.3%.

Reaction of 2-Mercaptobenzothiazole with 2-Chlorobenzothiazole in Dimethylformamide. III and 2-(N,N-Dimethylamino)benzothiazole (IX).—A stirred solution containing 0.3 mole of 2-mercaptobenzothiazole and 0.3 or 0.6 mole of 2-chlorobenzothiazole in 300 ml. of dimethylformamide was heated as described in Table II. After cooling to 25°, 700 ml. of water containing 48 g. (0.3 mole) of 25% aqueous sodium hydroxide was added. The stirred reaction mixture was maintained at 0–10° for 2 hr. The resulting solid was collected by filtration, washed with water until neutral, and air dried at 45–50°. All recrystallized samples of III gave only one peak on the vapor phase chromatogram. A mixture melting point of III derived by this method with an authentic sample was not depressed and infrared spectra of all samples were superimposable. The infrared spectrum of IX contained bands at 1450, 1290, 757, and 728 cm.$^{-1}$. The data are summarized in Table II.

Proof of Structure of IX. Method I.—A stirred solution of 50.9 g. (0.3 mole) of 2-chlorobenzothiazole in 300 ml. of dimethylformamide was heated at 150–160° for 5 hr. After cooling to 25°, 700 ml. of water containing 48 g. (0.3 mole) of 25% aqueous sodium hydroxide was added and stirred at 0–10° for 2 hr. The resulting solid was collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°. The product, m.p. 92–93°, was obtained in 89.5% yield. After recrystallization from heptane, the melting point remained unchanged. The vapor phase chromatograms of both the crude and recrystallized product gave only one peak. A mixture melting point with IX prepared above gave no depression and the infrared spectra of the two were superimposable.

Anal. Calcd. for $C_9H_{10}N_2S$: N, 15.72; S, 17.99. Found: N, 15.71; S, 18.01.

Method II.—To a stirred solution of 900 g. (5.0 moles) of 25% aqueous dimethylamine, 84.8 g. (0.5 mole) of 2-chlorobenzothiazole was added in one portion. An exothermic reaction set in causing a temperature rise from 24 to 38° over a 2-hr. period. The reaction mixture was stirred at 25–30° for 24 hr. The resulting solid was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°. The product, m.p. 91–92°, was obtained in 98.5% yield. After recrystallization from heptane it melted at 92–93°. A mixture melting point with products obtained from the above two methods gave no depression and the infrared spectra of the three samples were superimposable.

Anal. Calcd. for $C_9H_{10}N_2S$: N, 15.72; S, 17.99. Found: N, 16.00; S, 17.98.

2-(N,N-Dimethylamino)-5-chlorobenzothiazole (X).—This reaction was carried out in the same manner as described in method II above except 102 g. (0.5 mole) of 2,5-dichlorobenzothiazole was employed. The crude product, m.p. 106–108°, was obtained in 90.5% yield. After recrystallization from heptane it melted at 113–114°. The infrared spectrum of X contained bands at 1448, 1285, 862, and 803 cm.$^{-1}$.

Anal. Calcd. for $C_9H_9ClN_2S$: Cl, 16.67; N, 13.17; S, 15.08. Found: Cl, 17.12; N, 13.11; S, 14.90.

Attempted Reaction of 2-Mercaptobenzothiazole with Dimethylformamide.—A stirred solution of 85 g. (0.5 mole) of 2-mercaptobenzothiazole in 200 ml. of dimethylformamide was heated at 150–160° for 5 hr. After cooling to 25°, 700 ml. of water containing 80 g. (0.5 mole) of 25% aqueous sodium hydroxide was added and stirred at 25–30° for 30 min. To this stirred solution concentrated hydrochloric acid was added dropwise until pH 3 was reached. The resulting precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 50°. 2-Mercaptobenzothiazole, m.p. 180–181°, was recovered in quantitative yield. A mixture melting point with an authentic sample gave no depression.

2-(N,N-Disubstituted amino)benzothiazole (XI–XV). Method I. XI, XIII, and XV.—A stirred solution of 34 g. (0.2 mole) of 2-chlorobenzothiazole in 0.8 mole of the appropriate substituted formamide (Table III) was heated at 180–190° for 5 hr. and then cooled to 30°. For XI and XIII, 700 ml. of water containing 32 g. (0.2 mole) of aqueous sodium hydroxide was added. The stirred reaction mixture was stirred at 0–10° for 1 hr. The precipitate was collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°. For XV, 400 ml. of water containing 32 g. (0.2 mole) of 25% aqueous sodium hydroxide and 500 ml. of ethyl ether were added and stirring was continued for 15 min. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed *in vacuo* at a maximum temperature of 30°. The residue was distilled *in vacuo*. The data are summarized in Table III.

Method II. XI–XV.—To a stirred solution containing 1.5 moles of the appropriate amine in 100 ml. of water, 0.5 mole of 2-chlorobenzothiazole or 2,5-dichlorobenzothiazole was added over a 5-min. period. An exothermic reaction occurred, causing a temperature rise from 25 to 45°. The stirred reaction mixture was heated at 90–100° for 5 hr. and then cooled to 30°. For all compounds except XV, 400 g. of ice–water was added and the mixture was stirred at 0–10° for 30 min. The resulting precipitate was collected by filtration, washed with water until neutral to litmus, and air dried at 25–30°. For XV, 400 ml. of water and 500 ml. of ethyl ether were added. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed *in vacuo*, and the residue was distilled *in vacuo*. A mixture melting point of XI and XIII obtained from methods I and II, respectively,

was not depressed and the infrared spectra were superimposable. The data are summarized in Table III.

2-Hydroxybenzothiazole.—A stirred solution of 42.4 g. (0.25 mole) of 2-chlorobenzothiazole in 90.1 g. (2.0 moles) of formamide was heated at 180–190° for 5 hr. During this heating period hydrocyanic acid was liberated. After cooling to 10°, 200 g. of ice–water was added and stirring was continued at 0–10° for 1 hr. The resulting precipitate was collected by filtration, washed with 100 ml. of cold water, and air dried at 45°. The product, m.p. 118–121°, was obtained in 90% yield. After recrystallization from dilute ethyl alcohol it melted at 138–139°. A mixture melting point with an authentic sample was not depressed and the infrared spectra of the two were superimposable.

Anal. Calcd. for C_7H_5NOS: N, 9.27; S, 21.21. Found: N, 9.44; S, 21.27.

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2-Substituted Thiobenzothiazole and Related Compounds. II.[1,2] A Kinetic Study of the Reaction of 2-Chlorobenzothiazole with the Sodium Salt of 2-Mercaptobenzothiazole

JOHN J. D'AMICO, ROBERT H. CAMPBELL, SIDNEY T. WEBSTER, AND CHARLES E. TWINE

Monsanto Company, Organic Chemicals Division, Rubber Chemicals Research Laboratories, Nitro, West Virginia

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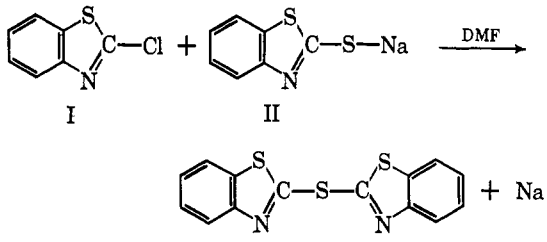
The kinetics of the reaction of 2-chlorobenzothiazole (I) with the sodium salt of 2-mercaptobenzothiazole (II) in dimethylformamide to yield 2,2′-thiobis(benzothiazole) (III) were studied. Rate constants for the reaction were determined at various temperatures. The reaction was found to be second order with an activation energy of 20.9 ± 1.6 kcal. and an activation entropy of −18.0 e.u. An analytical scheme for the determination of I, II, and III was developed and applied to the measurement of the rate constants. The rate constants obtained from the concentrations of I, II, and III were in good agreement and eliminated the presence of possible competitive and consecutive reactions under the cited conditions.

In order to propose a plausible mechanism for the reaction of 2-chlorobenzothiazole (I) with the sodium salt of 2-mercaptobenzothiazole (II) to yield 2,2′-thiobis(benzothiazole) (III) and sodium chloride in part I[2] of this series of publications, a knowledge of the reaction order of reaction 1 was essential.



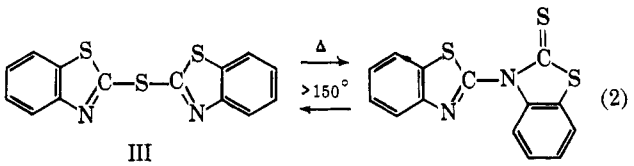
(1)

Brower and co-workers[3] reported the reaction of I with piperidine to be a second-order reaction and Lemons and co-workers[4] indicated that the reaction of I with ammonia is also a second-order reaction.

Gilman and co-workers[5] prepared 2-ethoxybenzothiazole by the reaction of I with sodium ethoxide, but no kinetic data for the reaction were reported.

The knowledge of several possible competitive and consecutive reactions made it highly desirable to follow initially all concentrations of I, II, and III at higher temperatures, and to determine the extent of such interfering reactions. Evidence was given in part I[2] of this series for the existence of the competitive reaction where I reacts with DMF at 150–160° to give 2-(N,N-dimethylamino)benzothiazole in 89.5% yield.

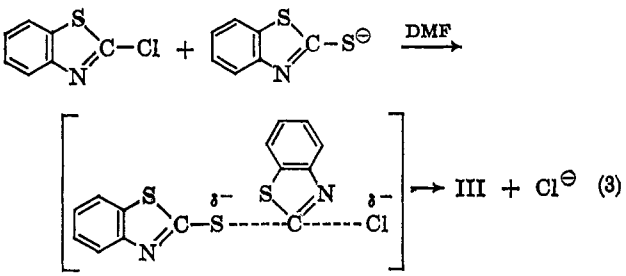
A consecutive reaction discussed in part III[6] of this series involving the rearrangement of III to 3-(2-benzothiazolyl)-2-benzothiazolinethione (reaction 2) could exist and cause erroneous conclusions.



(2)

In view of these possible sources of error, it was deemed essential that any study made must be sufficiently comprehensive to detect and correct for any of these interfering reactions, if present, under the conditions selected. Therefore, specific analytical methods based on ultraviolet spectroscopy and vapor phase chromatography (v.p.c.) were developed and applied to the determination of I, II, and III in DMF as described in the Experimental Section.

The reaction of I with II was thought to involve a nucleophilic displacement of chloride ion of I (S_N2) by II anion (reaction 3). On the other hand, there was the



(3)

(1) Presented at the 16th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Pa., March 2, 1965.

(2) Paper I: J. J. D'Amico, S. T. Webster, R. H. Campbell, and C. E. Twine, *J. Org. Chem.*, **30**, 2618 (1965).

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