tallized from a benzene-hexane mixture, giving 29 g. (57%) of white product melting at 97–98°.

Anal. Calcd. for C_9H_6ClNOS: C, 51.06; H, 2.85; N, 6.61. Found: C, 51.18; H, 3.27; N, 6.23.

α-Acetyl-4-chlorophenylmercaptoacetonitrile (IX). From the reaction of 7.5 g. (0.041 mole) of 4-chlorophenylmercaptoacetonitrile with 9 g. (0.1 mole) of ethyl acetate in 100 ml. of absolute ethanol containing 4.5 g. (0.083 mole) of sodium methylate there was obtained by the above procedure 3.9 g. of crude product, which crystallized on acidification of the aqueous extract of the reaction mixture. After two recrystallizations from benzene-hexane, with the aid of decolorizing charcoal (Darco G 60), rosettes of white needles were obtained, melting at 113°.

Anal. Calcd. for $C_{10}H_8ClNOS$: C, 53.21; H, 3.57. Found: C, 53.43; H, 3.40.

2,4-Diamino-5-arylmercaptopyrimidines. The preparation of these compounds followed the method of Russell and Hitchings[7] for 2,4-diamino-5-arylpyrimidines. The α-acylarylmercaptoacetonitriles (crude in most cases) were treated with an excess of diazomethane in ether and the resulting β-methoxyacrylonitriles were condensed with guanidine. This procedure is exemplified below. The pyrimidines prepared by this procedure are listed in Table IV.

2,4-Diamino-5-(4′-chlorophenylmercapto)pyrimidine (X). To 12 g. (0.057 mole) of α-formyl-4-chlorophenylmercaptoacetonitrile in 150 ml. of ether was added an ethereal solution of diazomethane prepared from 12.4 g. (0.12 mole) of nitrosomethylurea. The mixture was allowed to stand in an open wide-mouthed Erlenmeyer flask for 2 days, after which time a sirupy residue remained. This was dissolved in 75 ml. of absolute ethanol and added to a solution of guanidine in ethanol, prepared by dissolving 1.31 g. (0.057 g. atom) sodium in 75 ml. of absolute ethanol, followed by the addition of 5.42 g. (0.057 mole) of guanidine hydrochloride. This mixture was heated to reflux temperature for 5 hr., cooled, and filtered. The precipitate was washed well with water and dried; weight, 8.3 g. (58% crude yield); m.p. 228–231°. Recrystallization from an 85:15 ethanol-toluene mixture with the aid of decolorizing charcoal (Darco G 60) yielded 5.9 g. of off-white product melting at 231–233°.

2,4-Diamino-5-(4′-chlorophenylmercapto)-6-methylpyrimidine (XI). α-Acetyl-4-chlorophenylmercaptoacetonitrile (17 g., 0.075 mole) was treated with diazomethane [from nitrosomethylurea (15 g., 0.15 mole)] as in the previous experiment. The product, after removal of the ether and excess diazomethane, was treated with guanidine [from the hydrochloride (8.0 g., 0.084 mole)] and sodium (1.8 g., 0.078 g.-atom) in 200 ml. of ethanol. After 5 hr. on the steam bath, the product was isolated as in the previous example. It was purified by reprecipitation with sodium hydroxide from solution in acetic acid, followed by recrystallization from 85% ethanol. Colorless needles were obtained (5.0 g., 25%); m.p. 223–224°.

2,4-Diamino-6(4′-chlorophenylmercapto)pyrimidine. A mixture of 5 g. (0.035 mole) of 2,4-diamino-6-chloropyrimidine,[15] 5 g. (0.035 mole) of 4-chlorothiophenol, 4.8 g. (0.035 mole) of anhydrous potassium carbonate, and 50 ml. of ethylene glycol was heated to refluxing for 10 min., and then placed on the steam bath overnight. The mixture was then poured into several volumes of water, made strongly basic with sodium hydroxide, chilled, and filtered. The white precipitate, 6.0 g., was recrystallized three times from ethanol, yielding long white needles (4.1 g.) melting at 219°.

Anal. Calcd. for $C_{10}H_9ClN_4S$: C, 47.52; H, 3.59; N, 22.17. Found: C, 47.75; H, 3.25; N, 22.57.

Ultraviolet absorption peaks were as follows: (a) in 0.1*N* hydrochloric acid: λ_{max}, 292 mμ (Em × 10^{-3} 12.6); λ_{min} 264 mμ (Em × 10^{-3} 7.7). (b) in *p*H 11.0 buffer: λ_{max} 288 mμ (Em × 10^{-3} 9.5); λ_{min} 262 mμ (Em × 10^{-3} 6.1).

Absorption spectra. Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer, with 1 cm. quartz cuvettes. The absorptions were measured at a concentration of 10 mg. per liter in 0.1*N* hydrochloric acid and Sørensen glycine-sodium hydroxide buffer at *p*H 11.0, or in 95% ethanol or other solvents as noted.

Acknowledgments. The authors are indebted to Kurt Ledig for technical assistance in the preparation of some of the compounds reported here, to Samuel W. Blackman, Veronica Purdey, and Charles Marr for the microanalyses, and to Mrs. Linda Wright Sheehan for the determination of the ultraviolet absorption spectra.

TUCKAHOE, N. Y.

---

(15) B. Roth, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, 72, 1914 (1950).

[CONTRIBUTION FROM THE INDUSTRIAL AND BIOCHEMICALS DEPARTMENT
E. I. DU PONT DE NEMOURS AND CO., INC. EXPERIMENTAL STATION]

The Reaction of Disodium Ethylenebisdithiocarbamate with Trichloromethanesulfenyl Chloride[1]

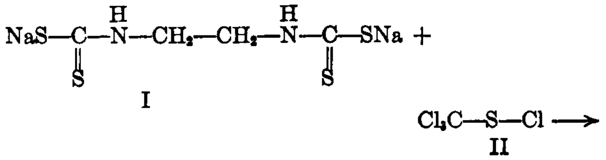
H. L. KLOPPING

Received August 12, 1960

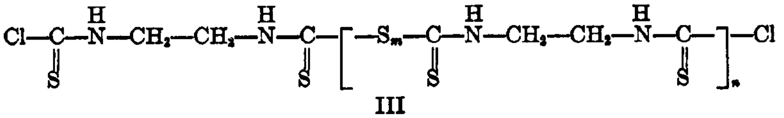
The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride (II) in aqueous medium gives a complex mixture of solids. The main components of this mixture are a polymer (III), bis(trichloromethyl)-ethylenebistrithiopercarbamate (IV), bis(trichloromethyl)-*N*-(trichloromethylthio)ethylenebistrithiopercarbamate (V), and bis(trichloromethyl)-*N*,*N*′-bis(trichloromethylthio)ethylenebistrithiopercarbamate (VI). The mechanism of formation of these compounds is discussed. A method for the specific synthesis of the most chemically stable component (IV) is described. This method, which involves inactivation of the —NH— groups of I toward II, consists in reaction of an emulsion containing free ethylenebisdithiocarbamic acid (IX), water, and an inert immiscible solvent with II in the presence of a large excess of hydrogen ions.

The reaction between disodium ethylenebisdithiocarbamate (I) and trichloromethanesulfenyl chloride[2] (II) was considered to be of interest because I contains four sites capable of reacting with II (two —NH—groups and two mercaptide groups), and II contains four chlorine atoms all of which are capable, under the proper conditions, of reacting with mercaptides.[3] A variety of reaction products could therefore be expected to form.

Products formed in aqueous medium. Slow addition of II to a well agitated, cooled, dilute aqueous solution of I gave a solid material which, as expected, consisted of a complex mixture of reaction products (*cf.* Experiment 1). By means of extraction with hot benzene, this mixture could be separated into a benzene insoluble, polymeric material (III) and a benzene soluble mixture of low molecular weight materials. The latter mixture was found to contain, in addition to some unidentified debris, bis(trichloromethyl)ethylenebistrithiopercarbamate (IV), bis(trichloromethyl) - *N* - (trichloromethylthio)ethylenebistrithiopercarbamate (V), and bis(trichloromethyl) - *N,N′* - bis(trichloromethylthio)ethylenebistrithiopercarbamate (VI):



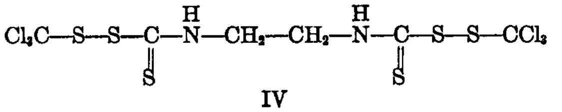
$$\underset{\text{I}}{NaS-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-SNa} + \underset{\text{II}}{Cl_3C-S-Cl} \longrightarrow$$



$$Cl-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-\left[-S_m-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-\right]_n-Cl$$

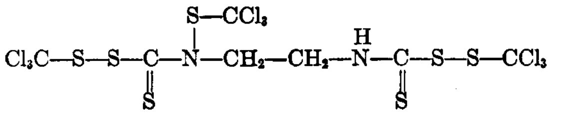
III

m = 1 or 2 n averages close to 5



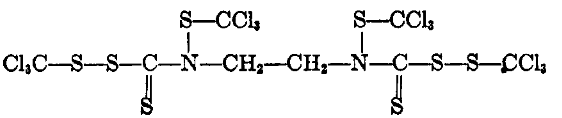
$$Cl_3C-S-S-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-S-CCl_3$$

IV



$$Cl_3C-S-S-\underset{\underset{S}{\|}}{C}-\overset{\overset{S-CCl_3}{|}}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-S-CCl_3$$

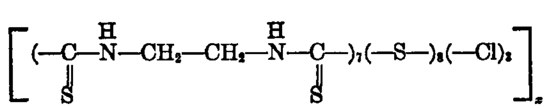
V



$$Cl_3C-S-S-\underset{\underset{S}{\|}}{C}-\overset{\overset{S-CCl_3}{|}}{N}-CH_2-CH_2-\overset{\overset{S-CCl_3}{|}}{N}-\underset{\underset{S}{\|}}{C}-S-S-CCl_3$$

VI

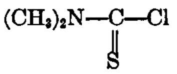
The structure III assigned to the polymeric material shows that it is built up of an average of five ethylenebisthiocarbamyl units joined together by mono- and disulfide linkages, and capped by thiocarbamyl chloride end groups. This structure is in accordance with the mechanism of its formation discussed below and with the experimental evidence of Experiment 1. The compound is very similar in appearance and physical properties to polyethylenethiuram monosulfide[4] (VII) and disulfide[5] (VIII) which are obtained by treatment of aqueous I with, respectively, phosgene or common oxidizing-agents. The elemental formula $C_{28}H_{42}N_{14}S_{22}Cl_3$ can be written as



$$\left[(-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-)_7(-S-)_8(-Cl)_3\right]_x$$

The proportion of —S— atoms to ethylenebisthiocarbamyl units indicates that there is one disulfide linkage for every two monosulfide linkages. The proportion of these units to chlorine atoms (assuming the latter to be present exclusively in thiocarbamyl chloride end groups) indicates an average chain length of close to five units.

The conclusion that the chlorine atoms must be present in the form of thiocarbamyl chloride end groups is based on the following considerations. First, the formation of these groups is to be expected on the basis of the mechanism of polymer formation discussed below. Second, aqueous suspensions of the polymer gradually turn acidic on standing at room temperature and show an increasingly positive reaction for chloride ions. Third, the infrared spectrum of III contains no evidence for the presence of $-CCl_3$ groups or any common C—Cl linkage (no bands in the 12.7–15 μ region). Neither is there any indication that the chlorine is present in the form of amine hydrochloride groups (the band at 3.15 μ is very sharp). However, the spectrum is not in disagreement with the presence of thiocarbamyl chloride groups, as the spectrum of the model compound dimethylthiocarbamyl chloride:



$$(CH_3)_2N-\underset{\underset{S}{\|}}{C}-Cl$$

contains no peaks in the 12.7–15 μ region either.[6]

The structure of IV is based on the mode of formation of the compound, its elemental analysis and its infrared spectrum. The latter contains bands at 12.65, 13.10, and 13.47 μ, which may be

---

(1) Presented in part at the Symposium of the Delaware Section of the American Chemical Society, Newark, Del., February 14, 1959, and at the 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 15, 1959.

(2) The chemistry of this compound has been reviewed by G. Sosnovsky, *Chem. Reviews*, 58, 509 (1958).

(3) H. J. Backer and E. Westerhuis, *Rec. Trav. Chim.*, 71, 1065 (1952); *Rec. Trav. Chim.*, 71, 1071 (1952); *Rec. Trav. Chim.*, 71, 1082 (1952).

(4) R. A. Ludwig and G. D. Thorn, *Plant Disease Reptr.*, 37, 127 (1953); British Patent 819,779.

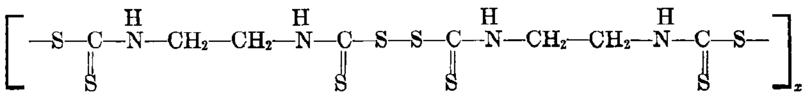
(5) H. L. Klopping and G. J. M. van der Kerk, *Rec. Trav. Chim.*, 70, 958 (1951); L. Wheschky and O. Flieg, German Patent 919,350.

(6) The major absorption bands in the infrared spectrum of this compound are at 7.24, 8.09, 8.61, 9.48, 10.40, and 11.65 μ.

assigned to the —CCl_3 groups, and a sharp band at 3.12 μ (NH stretching) which indicates that the —S—CCl_3 groups are attached to sulfur rather than to nitrogen. Moreover, the spectrum contains no SH bands.

The structures of V and VI are based on the elemental analyses and on the fact that these compounds can be synthesized by reacting IV with II (*cf*. Experiment 3).

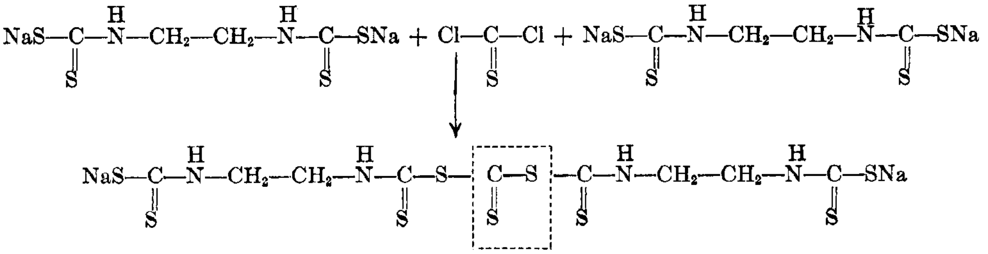
Mechanism of the reaction in aqueous medium. On the basis of a combination of published information and the experimental results presented in this paper, the formation of the products III through VI is proposed to take place as follows. Trichloromethanesulfenyl chloride (II) is known to be capable of oxidizing reducing agents such as sulfur dioxide in aqueous solution, whereby II itself is reduced to thiophosgene.[7] In the present reaction, the reducing agent is an aqueous solution of I; oxidation of this compound is known to yield polyethylenethiuram disulfide,[5] VIII, a cyclic or linear polymer in which ethylenebisthiocarbamyl units are joined together by means of disulfide linkages:



$$\left[-S-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-S-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-\right]_x$$

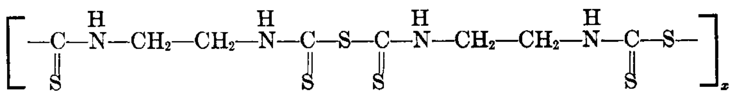
VIII

The thiophosgene produced in this process is also capable of reacting with dithiocarbamates.[8] The initially formed trithiocarbonyl linkages are unstable:



$$NaS-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-SNa + Cl-\underset{\underset{S}{\|}}{C}-Cl + NaS-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-SNa$$
$$\downarrow$$
$$NaS-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-\boxed{\underset{\underset{S}{\|}}{C}-S}-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-SNa$$

and eliminate carbon disulfide with formation of monosulfide linkages, so that the final product is polyethylenethiuram monosulfide (VII):

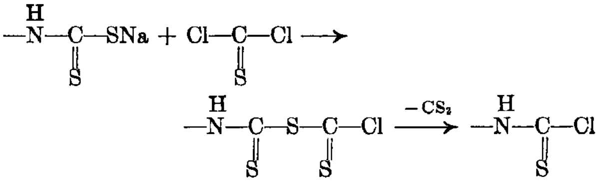


$$\left[-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-\underset{\underset{S}{\|}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-\right]_x$$

VII

As these reactions can take place simultaneously, the polymers actually formed are expected to be of a mixed nature, containing both disulfide and monosulfide linkages.

Instead of reacting with two sodium dithiocarbamate end groups, thiophosgene may react with one such group—which may be part of a molecule of I or of an already formed polymer chain—with formation of a thiocarbamyl chloride end group:



$$-\overset{H}{N}-\underset{\underset{S}{\|}}{C}-SNa + Cl-\underset{\underset{S}{\|}}{C}-Cl \longrightarrow -\overset{H}{N}-\underset{\underset{S}{\|}}{C}-S-\underset{\underset{S}{\|}}{C}-Cl \xrightarrow{-CS_2} -\overset{H}{N}-\underset{\underset{S}{\|}}{C}-Cl$$

In view of the low temperature of the reaction mixture, a considerable proportion of these end groups escapes hydrolysis.

The experimental evidence indicates that the chlorine in the polymer is largely, if not exclusively, present in the form of these end groups. The absence of infrared absorption bands for —CCl_3 groups indicates that these latter groups do not enter the polymer in detectable amounts, so that II does not appear to enter into metathetical reactions with —NH— or dithiocarbamate groups as long as reduction of II by I is possible. Thus, formation of IV, V, and VI should be negligible during this stage of the reaction.[9]

As the reaction proceeds, however, the concentration of I diminishes and as a result more and more molecules of II escape reduction and react, as such, with the polymer present in the reaction mixture. What happens in this reaction between II and the polymeric product is illustrated by a model experiment (No. 4) in which II was treated with pure polyethylenethiuram disulfide, VIII, prepared by oxidation of I. In this experiment, the initially chlorine free polymer broke down with formation of 1) a polymer containing 13% Cl

---

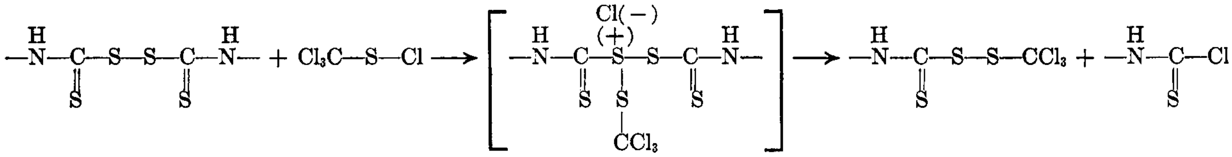
(7) French Patent 1,152,827. G. Malcolm Dyson, *Org. Syntheses*, Coll. Vol. I, 509 (1932).

(8) G. M. Zbirovsky and V. Ettel, *Coll. Czechosl. Chem. Comm.* 10, 1896 (1958).

(9) This conclusion is borne out by the observation that samples of the reaction product withdrawn during the early stages of the reaction consist largely of polymeric material. These polymer samples are very low in chlorine content.

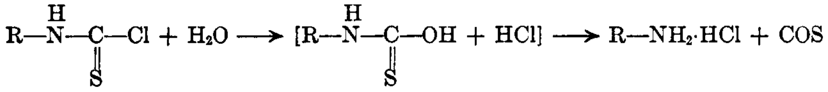
(39% of the weight of the starting material), 2) compound IV (30%), and 3) the usual residue containing V and VI. The latter compounds may either form directly from polymer fragments or *via* IV. The latter route is illustrated by Experiment 3, in which IV was treated with II to give V and VI.

As regards the mechanism of this breakdown reaction between polymer and II, the nature of the products formed is a strong indication that the exchange reaction between sulfenyl chlorides and disulfides discovered by Moore and Porter[10] plays an important part. Application of this exchange reaction to the present case, II attacking the disulfide bonds in the polymer, shows how the end groups discussed above may enter the picture:



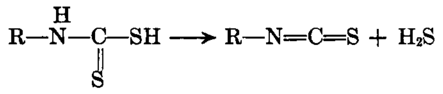
$$-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-S-S-\underset{\overset{\|}{S}}{C}-\overset{H}{N}- + Cl_3C-S-Cl \longrightarrow \left[-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-\overset{\overset{Cl(-)}{(+)}}{\underset{\underset{CCl_3}{\overset{|}{\underset{|}{S}}}}{S}}-S-\underset{\overset{\|}{S}}{C}-\overset{H}{N}-\right] \longrightarrow -\overset{H}{N}-\underset{\overset{\|}{S}}{C}-S-S-CCl_3 + -\overset{H}{N}-\underset{\overset{\|}{S}}{C}-Cl$$

Other reactions likely to occur in aqueous medium are 1) hydrolysis of thiocarbamyl chloride groups:



$$R-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-Cl + H_2O \longrightarrow [R-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-OH + HCl] \longrightarrow R-NH_2\cdot HCl + COS$$

and 2) hydrolysis of dithiocarbamate groups with loss of hydrogen sulfide[5,11]:

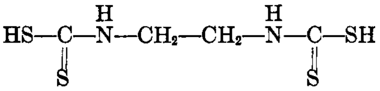


$$R-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-SH \longrightarrow R-N=C=S + H_2S$$

followed by polymerization of the isothiocyanates. These reactions most likely contribute to the formation of the debris normally found in the crude reaction product.

Specific synthesis of IV. As the *S,S'*-disubstitution product (IV) turned out to be the most chemically stable among the reaction products described, the development of a specific method of synthesis for this compound became an important goal of this investigation. The approach to this goal was to modify the original reaction of Experiment 1 in such a fashion that all reactions other than *S*-substitution would be suppressed. These reactions were 1) polymer formation, and 2) *N*-substitution (formation of products V and VI). In attempting to suppress polymer formation, a helpful clue was, of course, the mechanism of polymer formation discussed above: Polymer formation should not occur if oxidation-reduction reactions between I and II were avoided.

The latter reactions can only occur where I can act as a reducing agent—*i.e.*, in aqueous solution. Thus, avoiding polymer formation required avoiding the combination of I with water in the reaction mixture. This left a choice between two alternatives: 1) carry out the reaction under anhydrous conditions, or 2) use an aqueous system but render I insoluble in water by modifying its structure in some way. The first alternative is studied using dry I in hexane as described in Experiment 5. The result of this experiment was encouraging in that it was in accordance with the mechanism of polymer formation described above, the percentage of polymer in the crude product being very low. However, excessive *N*-substitution had occurred under these conditions. The second alternative was studied using, instead of I, free ethylenebisdithiocarbamic acid IX, which is insoluble in water and easily prepared in aqueous suspension by acidifying an aqueous solution of I.



$$HS-\underset{\overset{\|}{S}}{C}-\overset{H}{N}-CH_2-CH_2-\overset{H}{N}-\underset{\overset{\|}{S}}{C}-SH$$

IX

Addition of II to this aqueous suspension (Experiment 6) gave a product which again was very low in polymer content. However, it also contained a high percentage of *N*-substituted compounds V and VI. In this three phase reaction, the two hydrophobic phases (ethylenebisdithiocarbamic acid and II) lumped together, and in the next experiment (No. 10), hexane was added to eliminate this difficulty. It was found that under these conditions an emulsion formed which remained intact during the addition of II. In spite of these improved mixing conditions, a high percentage of *N*-substituted materials was again present in the reaction product.

In the course of further studies with the emulsion system, conditions were found under which both polymer formation and *N*-substitution were strongly suppressed. In experiments discussed up to this point, the emulsion had been prepared by adding to the stirred mixture of aqueous I and hexane (or some other inert immiscible solvent such as carbon tetrachloride or chloroform) an amount of hydrochloric acid just sufficient to convert I to free ethylenebisdithiocarbamic acid. However, when a large excess of hydrochloric acid was added

---

(10) C. G. Moore and M. Porter, *J. Chem. Soc.*, 2890 (1958).

(11) R. A. Ludwig, G. D. Thorn, and C. H. Unwin, *Can. J. Botany*, **33**, 42 (1955).

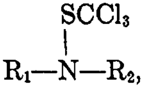
TABLE I

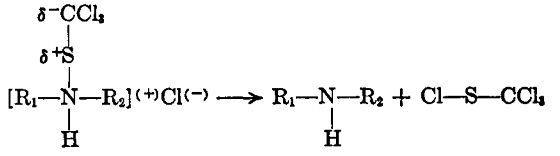
SUMMARY OF EXPERIMENTAL RESULTS

Exp. No.	Starting Materials: I or derivative	H$_2$O, ml.	II	Acid	Org. solvent	Product: Weight, g.	Composition, %: III	IV	V + VI
1	I, 25.6 g. (0.1 mole)	300	12.5 ml. (0.115 mole)	—	—	24.3	58	32	10
2	I, 36 g.	200	44 ml. (0.4 mole)	—	Hexane, 500 ml.	15.0	Predominantly	V +	VI
3	IV, 10.2 g. (0.02 mole)	—	22 ml. (0.2 mole)	—	—	14.4	"		"
4	VIII, 11 g. (0.052 mole)	300	7.5 ml. (0.068 mole)	—	—	17.6	39	30	30
5	I, 25.6 g. (0.1 mole)	—	22 ml. (0.2 mole)	—	Hexane, 250 ml.	46.0	6	37	57
6	IX, 42.4 g. (0.2 mole)	1050	44 ml. (0.4 mole)	—	—	76.7	5	45	50
7	I, 25.6 g. (0.1 mole)	100	22 ml. (0.2 mole)	Concd. HCl, 100 ml.	Hexane, 100 ml.	47.5[a]	2	91	7
8	I, 25.6 g. (0.1 mole)	150	22 ml. (0.2 mole)	Concd. HCl, 50 ml.	Hexane, 100 ml.	32.1[a]	"	"	"
9	I, 25.6 g. (0.1 mole)	175	22 ml. (0.2 mole)	Concd. HCl, 25 ml.	Hexane, 100 ml.	19.0[a]	"	"	"
10	I, 25.6 g. (0.1 mole)	183	22 ml. (0.2 mole)	Concd. HCl, 16.6 ml.	Hexane, 100 ml.	17.0[a]	"	"	"

[a] Solid obtained by filtering the reaction mixture. Products dissolved in hexane filtrate (mostly V + VI) not included.

(Experiment 7), the emulsion upon reaction with II yielded a product which consisted of over 90% of IV.

Subsequent experiments (No. 8 and 9, see also 10) showed that reducing this excess of hydrochloric acid in the reaction mixture proportionally reduced the yield of IV. It was also found that other suitable mineral acids (*e.g.*, sulfuric acid) had the same effect as hydrochloric acid. Thus, it appeared that a high concentration of hydrogen ions in the reaction mixture was capable of inactivating the —NH— groups of ethylenebisdithiocarbamic acid toward II. This effect is reminiscent of the observation made by Argyle and Dyson[12] that compounds of the general formula  $R_1{-}\overset{\overset{\displaystyle SCCl_3}{|}}{N}{-}R_2$, when treated with dry hydrogen chloride in ligroin, quantitatively regenerate the hydrochloride of the original amine and trichloromethanesulfenyl chloride. In view of the basic character of these thiolamine derivatives, the regenerative reaction probably involves the approach of a proton toward the lone pair of electrons on the nitrogen, with formation of an unstable quaternary intermediate:



$$[R_1{-}\overset{\overset{\overset{\delta^-CCl_3}{|}}{\delta^+S}}{\underset{\underset{H}{|}}{\overset{|}{N}}}{-}R_2]^{(+)}Cl^{(-)} \longrightarrow R_1{-}\underset{\underset{H}{|}}{N}{-}R_2 + Cl{-}S{-}CCl_3$$

In the case of the present reaction, the degree of S—N bond formation was found to be inversely proportional to the hydrogen ion concentration in the medium. It would appear, therefore, that the trichloromethanesulfenyl cation (or the strongly polarized trichloromethanesulfenyl chloride molecule) approaching the lone pair of electrons on the —NH— groups of the ethylenebisdithiocarbamic acid has to compete with hydrogen ions, the mass activity of the latter ions determining the degree of S—N bond formation.

EXPERIMENTAL

A summary of the experimental results is given in Table I. A detailed description of the experiments is given below.

Experiment 1. Reaction of I with II in aqueous medium. Isolation of III and IV. A solution of 25.6 g. (0.1 mole) of I in 300 ml. of water was cooled in an ice bath. While stirring vigorously, II was added dropwise at a rate of 4 ml. per hr. Gradually, a light yellow solid precipitated. Addition was continued until a filtered sample of the reaction mixture no longer gave a precipitate when mixed with ferrous sulfate solution. At that moment, 12.5 ml. (0.115 mole) of II had been added.

The reaction mixture was stirred for two additional hours. The precipitate was then filtered, washed with water, and dried. The dried product, a light cream colored powder, weighed 24.3 g. It melted at 122–130° with decomposition and then resolidified to give a product melting at 175–185°.

This crude product was separated into its components as follows: a) *Isolation of the polymeric product* (III). Five grams of the above reaction product was extracted twice with 200 ml. of boiling benzene. The residue was washed with hot benzene and dried. It weighed 2.9 g. (58% of original crude product) and melted at 131–135°, with decomposition and resolidification. (The resolidified material melted at 165–170°.)

Anal. Calcd. for $(C_{28}H_{42}N_{14}S_{22}Cl_3)_x$: C, 24.2; H, 3.0; N, 14.1; S, 50.9; Cl, 7.7. Found: C, 24.0; H, 3.0; N, 14.1; S, 50.3; Cl, 7.7.

The major absorption bands in the infrared (potassium bromide disc) spectrum of product III are at 3.15 (sharp),

---

(12) C. S. Argyle and G. M. Dyson, *J. Chem. Soc.*, 1629 (1937).

6.63, 7.24, 7.42, 7.58, 8.00, 8.92, 9.30, 10.53, 10.80, and 11.65 μ.

An aqueous slurry of product III on agitation at room temperature gradually turned acidic and showed an increasingly positive reaction for chloride ions.

Attempts to determine the average molecular weight of product III were unsuccessful, because of either insufficient solubility or insufficient stability under the conditions of the method of determination. The product slowly decomposed on standing at room temperature.

b) *Isolation of* IV. The hot benzene extracts from above were combined and vacuum concentrated until crystallization occurred.

The mixture was cooled to 8° and scratched until no further separation of crystalline material occurred.

Filtration, washing with a little benzene, and drying gave 1.6 g. (32% of the original crude product) of white crystals, melting at 141–142° with decomposition. The orange melt resolidifies.

Anal. Calcd. for $C_6H_6N_2S_6Cl_6$ (IV): C, 14.1; H, 1.2; N, 5.5; S, 37.6; Cl, 41.6. Found: C, 14.3; H, 1.4; N, 5.8; S, 37.6; Cl, 41.6.

The major absorption bands in the infrared spectrum of IV are at 3.12, 6.85, 7.29, 7.73, 8.05, 9.43, 10.86, 12.65, 13.10, and 13.47 μ.

The benzene filtrate from IV was treated with an excess of hexane and cooled in ice. The solid obtained by filtration weighed 0.4 g. (8% of the original crude product) and melted at 75–80°. It consisted of a mixture of compounds V and VI. A larger quantity of this solid was prepared and separated into its components by methods described in Experiment 2.

Experiment 2. Reaction of I *with an excess of* II *in water-hexane mixture. Isolation of* V *and* VI. A solution of 36 g. (0.14 mole) of I in 200 ml. of water was added dropwise, over a period of 15 min., to a stirred solution of 44 ml. (0.4 mole) of II in 500 ml. of hexane. At first, the temperature of the reaction mixture dropped from 25° to 15° and then slowly increased to room temperature while a light yellow solid separated. Gradually, the reaction mixture turned into a thick suspension. Stirring was continued. The temperature rose gradually to about 35° and then, rather suddenly, to 40°, while the solid dissolved almost completely.

Stirring was continued for 3 hr. After standing overnight, the hexane layer was separated and dried over anhydrous sodium sulfate. The hexane was removed by evaporation *in vacuo* until the volume was reduced to about half. At this point a cloudiness occurred in the liquid.

After standing overnight in the refrigerator, the mixture was filtered. The solid product, after drying, weighed 15 g. and melted at 75–80°. It consisted mainly of a mixture of V and VI.

This mixture was dissolved in boiling hexane and the solution was allowed to cool slowly. The first fraction to crystallize consisted predominantly of V. After several recrystallizations from hexane this product was obtained in the form of white needles melting at 98–99° (4.1 g.).

Anal. Calcd. for $C_7H_5N_2S_7Cl_9$ (V): C, 12.7; H, 0.8; N, 4.2; S, 34.0; Cl, 48.3. Found: C, 12.9; H, 0.8; N, 4.6; S, 34.8; Cl, 48.4.

On cooling the filtrate from V in ice, a second fraction was obtained which consisted mainly of VI. After several recrystallizations from hexane, this compound was recovered as a white microcrystalline powder, m.p. 80–84° (4.6 g.).

This compound is very unstable and decomposes rapidly in boiling hexane.

Anal. Calcd. for $C_8H_4N_2S_8Cl_{12}$ (VI): C, 11.8; H, 0.5; N, 3.5; S, 31.7; Cl, 52.5. Found: C, 12.2; H, 0.7; N, 3.9; S, 32.8; Cl, 51.3.

Both compounds V and VI decompose rather rapidly on standing at room temperature.

Experiment 3. Synthesis of V *and* VI *starting from* IV *and* II. To 10.2 g. (0.02 mole) of IV was added sufficient II to make a stirrable suspension (22 ml.). The mixture was stirred until the evolution of heat and hydrogen chloride had ceased. The mixture was then spread out on a watch glass and allowed to dry in a stream of air.

The solid, which weighed 14.4 g. and melted at 75–80°, was separated into its main components V and VI as described above (Experiment 2).

Experiment 4. Reaction of VIII *with* II. A solution of 14 g. of I in 200 ml. of water was stirred and kept at 0–3°. Dilute aqueous hydrochloric was added until the *p*H was 5. This solution was oxidized by slowly introducing chlorine gas until it no longer contained free I. The suspension was filtered and the white solid, consisting of VIII, was washed with water. The wet cake, corresponding to a dry weight of 11 g., was resuspended in 300 ml. of water. The suspension was kept at 3 to 5° and stirred, while 7.5 ml. of II was added over a period of 2 hr. The suspension was filtered, washed with water, and dried. The solid, which weighed 17.6 g., was subjected to the hot benzene extraction procedure of Experiment 1 and yielded 6.8 g. (39%) of polymer containing 13.0% chlorine, 5.2 g. (30%) of IV, m.p. 139–141° dec., and 5.2 g. (30%) of a residue consisting mostly of a mixture of V and VI, m.p. 75–80°, which was separated as described in Experiment 2.

Experiment 5. Reaction of I *with* II *in hexane.* One hundred grams of I hexahydrate (theor. 29.5% H_2O) was refluxed with benzene using a Dean-Starke trap. After 7 hr., no additional water collected in the trap; the volume of the water was 29.5 ml., and the solid weighed 71 g.

A 25.6-g. sample (0.1 mole) of anhydrous I was slurried in 250 ml. of hexane. While stirring at room temperature, 22 ml. (0.2 mole) of II was added over a period of 3 hr. There was no heat evolution. Stirring was continued until an aqueous extract of a sample of the reaction mixture gave a negative test (no precipitate with ferrous sulfate solution) for I. The mixture was filtered, washed with hexane, and dried. The solid weighed 40 g. The filtrate on evaporation left a mixture of V and VI, 16 g. The solid contained 10 g. of sodium chloride, 3 g. of polymer, 17 g. of IV and 10 g. of the mixture of V and VI, so that the composition of the organic portion of the reaction product was polymer III, 6%; IV, 37%; and V + VI, 57%.

Experiment 6. Reaction of IX *with II in aqueous suspension.* A solution of 73 g. (0.2 mole) of I hexahydrate in 1000 ml. of water was stirred and cooled in ice. Hydrochloric acid, 6*N*, was added dropwise until precipitation was complete.

Then, 44 ml. (0.4 mole) of II was added over a period of 30 min. The cooling bath was then removed and stirring was continued at room temperature until the lumps of product formed initially had broken up (16 hr.). The solid was collected on a filter, washed with water, and dried. It weighed 76.7 g. (theor. yield if product consisted entirely of IV, 102 g.). The composition of this product, as determined by the hot benzene extraction method described in Experiment 1, was: polymer III, 5%; IV, 45%; residue containing mixture of V and VI, 50%.

Experiments 7 through 10. Reaction of IX *with* II *in water-hexane emulsion in the presence of decreasing excesses of hydrochloric acid. Experiment 7.* To a solution of 25.6 g. (0.1 mole) of I in 100 ml. of water was added 100 ml. of hexane. The mixture was kept at 10°, and 100 ml. of 37% hydrochloric acid was added over a period of 20 min. with vigorous stirring. The emulsion of IX thus prepared[13] was allowed to warm up to 18°. Then, with vigorous stirring, 22 ml. (0.2 mole) of II was added over a period of 4 min., without external cooling. The temperature rose rapidly to 40°, then gradually dropped back to room temperature. After stirring for 2 more hr., the product was collected on a filter, washed with hexane and water, and dried. It weighed 47.5 g. (theor. yield if product consisted entirely of IV, 51.1 g.). The com-

---

[13] Since 0.1 mole of I requires 16.6 ml. of 37% hydrochloric acid for its neutralization, the concentration of hydrochloric acid in the aqueous phase of the reaction mixture was 15.4%.

position of this product, as determined by the hot benzene extraction method of Experiment 1, was: polymer, 2%; IV, 91%; residue containing V + VI, 7%.

Experiment 8. Experiment 7 was repeated using a mixture of 50 ml. of water and 50 ml. of concd. hydrochloric acid instead of 100 ml. of concd. hydrochloric acid.[14] The yield of solid product was 32.1 g. (62%), and its composition was the same as in the preceding experiment. The hexane layer of the reaction mixture contained most of the mixture of V + VI formed in this reaction.

Experiment 9. Experiment 7 was repeated using a mixture of 25 ml. of concd. hydrochloric acid and 75 ml. of water instead of 100 ml. of concd. hydrochloric acid.[15] The yield of solid product was 19.0 g. (37%), and its composition was the same as that of the product of Experiment 7. Most of the mixture of V and VI formed in this reaction was dissolved in the hexane layer of the filtrate..

Experiment 10. Experiment 7 was repeated using a mixture of the amount of concd. hydrochloric acid theoretically required to neutralize 0.1 mole of I (16.6 ml.) and 83.4 ml. of water, instead of 100 ml. of concd. hydrochloric acid. The yield of solid product was 17.0 g. (33%), and its composition was the same as in the case of Experiment 7. The hexane layer of the filtrate contained most of the mixture of V and VI formed in this reaction.

WILMINGTON, DEL.

---

[14] Concentration of hydrochloric acid in the aqueous phase: 7.7%.

[15] Concentration of hydrochloric acid in the aqueous phase: 1.5%.

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA]

A Synthesis of Unsymmetrical Aliphatic Disulfides[1]

RICHARD G. HISKEY, F. I. CARROLL,[2] ROBERT M. BABB,[3a] JAMES O. BLEDSOE,[3a]
REGINALD T. PUCKETT,[3b] AND BRYAN W. ROBERTS[3c]

Received September 21, 1960

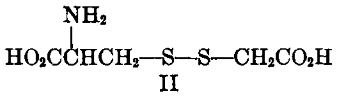
A general method for the synthesis of unsymmetrical aliphatic disulfides has been developed from a procedure previously described in the literature. The route involves the formation of an alkylsulfenyl thiocyanate, prepared from the desired mercaptan and thiocyanogen. Treatment of the sulfenyl thiocyanate with a second mercaptan results in displacement of thiocyanic acid and the formation of an unsymmetrical disulfide. Several examples of aliphatic disulfides containing the methoxyl, nitro, carbomethoxy and carboxy groups have been prepared in 50–70% yield.

The increased interest in the chemical behavior of the disulfide bond in natural macromolecules has prompted an investigation of the synthesis and general reactivity of unsymmetrically substituted aliphatic disulfides. The unsymmetrical disulfides are desirable for study, as a disulfide bond crosslinking two peptide chains, composed of different arrangements of amino acids, may be considered an unsymmetrical aliphatic disulfide containing reactive functional groups as side chains. The present report concerns our preliminary studies on the synthesis of such molecules.

Although several methods of preparation of *mixed* disulfides have been reported, the scope of these syntheses remain unexplored. The published examples of molecules of this type, with the exception of a few cyclic aliphatic disulfides, are limited to: (a) purely aliphatic molecules with no functional groups [4,5] represented by 3,4-dithiaheptane (I)[5]; (b) disulfides composed of cysteine and another mercaptocarboxylic acid such as penicillamine,[6b] β-mercaptopropionic acid,[6a] or thioglycolic acid (II)[6a,7]; and (c) disulfides containing cysteine or another mercaptocarboxylic acid and cysteamine,[6a] β-mercaptoethanol,[6a] or, in one case,[8] benzyl mercaptan (III). Thus virtually all known unsymmetrical aliphatic disulfides contain only the carboxyl and/or amino residues as functional groups. Evaluation of the available synthetic routes in terms of neutral molecules containing functional groups led to the conclusion that, in general, the published methods would not be applicable since either oxidation[4–6] or the formation of the disulfide in aqueous solution[8] was involved. Initially however several attempts were made to utilize the published procedures[4,6] for the synthesis of methyl 5-phenyl-2,3-dithiapentanoate (V) by treatment of IV with

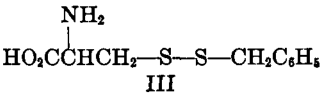
$CH_3CH_2—S—S—CH_2CH_2CH_3$

I



$$HO_2C\overset{NH_2}{\overset{|}{C}}HCH_2—S—S—CH_2CO_2H$$

II



$$HO_2C\overset{NH_2}{\overset{|}{C}}HCH_2—S—S—CH_2C_6H_5$$

III

---

[1] Supported in part by a Frederick Gardner Cottrell Grant from the Research Corporation.

[2] Tennessee Eastman Corporation Fellow, 1959–1960.

[3] (a) Undergraduate research student. (b) Supported by the National Science Foundation Undergraduate Research Program, Summer 1960. (c) 1959–1960.

[4] L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **69**, 1710 (1947).

[5] D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

[6] (a) A. Schoberl and H. Grafje, *Ann.* **617**, 71 (1958). (b) A. Schoberl, H. Tausent, and H. Grafje, *Angew. Chem.*, **68**, 213 (1956).

[7] H. Lamfrom and S. O. Nielsen, *Compt. rend. Lab. Carlsberg, Ser. Chim.*, **30**, 360 (1958).

[8] J. M. Swan, *Nature*, **180**, 643 (1957).