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.

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[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]

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Received September 21, 1960

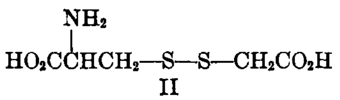
A general method for the synthesis of unsymmetrical aliphatic disulfides has been developed from a procedure previously described in the literature. The route involves the formation of an alkylsulfenyl thiocyanate, prepared from the desired mercaptan and thiocyanogen. Treatment of the sulfenyl thiocyanate 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

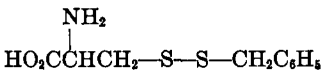
$CH_3CH_2—S—S—CH_2CH_2CH_3$

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

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[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).

TABLE I

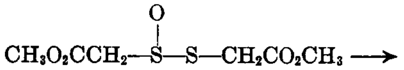
ALIPHATIC DISULFIDES PREPARED *Via* ALKYLSULFENYL THIOCYANATES

VIII					B.P.°/Mm. or	M_R		Calcd.			Found		
R	R'	Yield, %	n_D^{25}	d^{25}	M.P.°	Calcd.	Obs.	C	H	S	C	H	S
$C_6H_5CH_2$[a]	$CH_2CO_2CH_3$	58	1.5774	1.2044	120/0.3	62.66	62.86	52.60	5.30	28.09	52.27	5.36	28.22
$C_6H_5CH_2$[b]	$CH_2CO_2CH_3$	45.4	1.5770	1.2045	120/0.3								
$C_6H_5CHCH_3$	$CH_2CO_2CH_3$	62.5	1.5689	1.1795	120/0.2	67.28	67.31	54.51	5.82	26.46	54.21	5.80	26.36
$p\text{-}NO_2C_6H_4CH_2$	$CH_2CO_2CH_3$	54.7			52.5–53[c]			43.94	4.06	23.46	43.73	4.26	23.32
$p\text{-}CH_3OC_6H_4CH_2$	$CH_2CO_2CH_3$	48.0	1.5762	1.2406	142/0.15	68.92	68.94	51.14	5.46	24.82	50.66	5.66	24.69
$C_6H_5CH_2$	$CHCO_2H$ CH_2CO_2H	51.5			147–148			48.51	4.44	23.55	48.53	4.79	23.33
$C_6H_5CH_2$	$(CH_2)_5CH_3$	59.5	1.5487	1.0143	117/0.3	74.87	75.36	64.93	8.39	26.67	64.67	8.50	27.06
$C_6H_5CH_2$	$C(CH_3)_3$	62.0	1.5636	1.0537	87/0.3	65.63	65.45	62.25	7.59	30.16	62.24	7.74	30.23
$CH_3(CH_2)_5$	$CH_2CO_2CH_3$	73.0	1.4939	1.0566	86/0.2	61.73	61.26	48.61	8.16	28.84	48.82	7.97	28.78
$(CH_3)_3C$[d]	$CH_2CO_2CH_3$	60.8	1.4991	1.0963	56/0.15	52.21	52.00	43.33	7.21	32.97	43.17	7.37	32.95
$(CH_3)_3C$[e]	$CH_2CO_2CH_3$	22.9	1.4995	1.0966	56/0.15								

[a] *Via* $NCSSCH_2CO_2CH_3$. [b] *Via* $C_6H_5CH_2SSCN$. [c] Recrystallized from ether–petroleum ether (b.p. 30–60°). [d] *Via* $NCSSCH_2CO_2CH_3$. [e] *Via* $(CH_3)_3CSSCN$.

benzyl mercaptan. In our hands the method was unsuccessful.

$[CH_3O_2CCH_2—S]_2 \longrightarrow$



$$CH_3O_2CCH_2—\overset{O}{\overset{\|}{S}}—S—CH_2CO_2CH_3 \longrightarrow$$

IV

$CH_3O_2CCH_2—S—S—CH_2C_6H_5$

V

The Bunte salt method[8] was similarly attempted in the synthesis of VI and although several experiments were preformed at various *p*H values none of the desired disulfide was obtained.

$$C_6H_5COCH_2—S—SO_3Na + HSCH_2CO_2CH_3 \longrightarrow$$

$$C_6H_5COCH_2—S—S—CH_2CO_2CH_3$$

VI

The procedure which seemed most versatile for the synthesis of neutral disulfides involved the production of an alkylsulfenyl thiocyanate (VII) followed by displacement of thiocyanic acid from VII with a second mercaptan. Lecher[9] prepared several alkylaryl disulfides by this method but the only aliphatic thiol to be investigated was ethyl mercaptan.

$$RSH + (SCN)_2 \longrightarrow \underset{VII}{R—S—SCN} \xrightarrow{R'SH}$$

$$\underset{VIII}{R—S—S—R'} + HSCN$$

Ethylsulfenyl thiocyanate (VII. R = C_2H_5) was found[9] to be a volatile unstable substance which decomposed within fifteen to thirty minutes at 0°. In contrast, the arylsulfenyl thiocyanates were reasonably stable compounds and could be prepared with little difficulty. Ethylsulfenyl thiocyanate was found to decompose readily when treated with warm water or alcohols but afforded a 71% yield of 1-phenyl-1,2-dithiabutane (VIII. R = CH_2CH_3, R' = C_6H_5) when allowed to react with thiophenol at 0°. The only recent application of this method involved the preparation of II in 32% yield.[7] The experimental conditions employed for this synthesis however were unsuitable for large amounts of neutral molecules and thus reaction conditions similar to those reported by Lecher have been employed. The method has been found to be quite versatile and to produce reasonable yields (50–70%) of pure unsymmetrical aliphatic disulfides (Table I). In general the sulfenyl thiocyanates have not been isolated and the yields reported are based on the amount of initial mercaptan used.

The disulfide V was initially synthesized in 58% yield by treatment of VII (R = $CH_2CO_2CH_3$) with benzyl mercaptan. The substance could be readily isolated by distillation and was characterized as a single pure substance, rather than an

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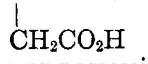
[9] H. Lecher and M. Wittwer, *Ber.*, 55B, 1474 (1922).

equimolar mixture of two symmetrical disulfides, by the elemental analysis and physical properties. The infrared spectrum was of little aid on this point, other than to identify the functional groups present, since in the cases studied, the spectra of the unsymmetrical disulfides were the sum of their symmetrical counterparts. To establish further the identity of V, the mercaptans were allowed to react in reverse order. Thus treatment of VII ($R = C_6H_5CH_2$) with methyl mercaptoacetate afforded a 45.5% yield of V, identical in all respects to the previous preparation. In addition to providing increased confidence in the purity of V, the synthetic value of the sulfenyl thiocyanate method is considerably enhanced by the fact that either mode of combination of the two mercaptans is successful. Some discretion as to the choice of alkylsulfenyl thiocyanate is necessary, however, as the displacement of thiocyanic acid by the second mercaptan appears to be subject to some steric requirements. Thus the 60.8% yield of VIII [$R = CH_2CO_2CH_3$, $R' = C(CH_3)_3$]*via* VII ($R = CH_2CO_2CH_3$) was lowered to 22.9% when *t*-butylsulfenyl thiocyanate [VII $R = (CH_5)_3C$] was employed.

Preliminary experiments[10] involving the effect of solvent on the course of the reaction between benzylsulfenyl thiocyanate and methyl mercaptoacetate indicate dioxane, rather than ether, may also be employed for the displacement of thiocyanic acid from VII. For example VII($R = C_6H_5CH_2$), isolated by removal of the ether but not purified, was redissolved in dry dioxane. Addition of the theoretical amount, based on the amount of benzyl mercaptan employed, of methyl mercaptoacetate in dry dioxane, afforded a 42.9% yield of V. A similar experiment using methanol as the solvent resulted in the formation of benzyl disulfide and unchanged thiol. In all cases in which benzylsulfenyl thiocyanate was isolated the crude yield was 85–95%. An indication of the yield in the second step was obtained when a weighed portion of VII ($R = C_6H_5CH_2$), isolated without purification, was redissolved in ether and treated with an equivalent amount of methyl mercaptoacetate. A 71% yield of V, based on sulfenyl thiocyanate, resulted.

Another modification leading to more versatile reaction conditions was employed in the synthesis of VIII ($R = C_6H_5CH_2$, R ′ =  $\underset{\displaystyle CH_2CO_2H}{\overset{}{CHCO_2H}}$). As thiols capable of zwitterion formation or possessing several polar functional groups are generally quite insoluble in relatively nonpolar solvents, it was of some interest to determine whether an ether insoluble mercaptan could be used in a two phase reaction with VII. Accordingly, solid α-mercaptosuccinic acid was added to an ether solution of VII ($R = C_6H_5CH_2$). The displacement reaction progressed in the usual fashion and afforded VIII ($R = C_6H_5CH_2$, R′ =  $\underset{\displaystyle CH_2CO_2H}{\overset{}{CHCO_2H}}$) in 51.5% yield. The application of this method to the synthesis of unsymmetrical peptides containing cystine will be reported separately.

The effect of temperature on the course of the overall reaction was also studied in several cases. The intermediate, benzylsulfenyl thiocyanate, decomposed rapidly above 0° and thus the preparation of VIII ($R = C_6H_5CH_2$, $R' = (CH_3)_3C$) was conducted at −80°. The yield of disulfide was increased from 62% to 69%. The yield of V was also increased (49% to 58%) by conducting the reaction at −15° rather than 0°; however, several experiments involving the preparation of V at −80° gave indications of incomplete reaction and resulted in somewhat lower yields (35–45%).

The physical properties of the disulfides prepared in this study are listed in Table I. With the exception of the two disulfides containing highly polar functional groups which were solids, the substances were readily distillable liquids. Unless subjected to temperatures above 170–200° the unsymmetrical disulfides showed no tendency to disproportionate and were unchanged after several months storage at room temperature. The single exception encountered thus far seems to be VIII ($R = C_6H_5CH_2$, $R' = CH_2CH_2OH$) which could be readily prepared and distilled but disproportionated after standing several hours at room temperature. As the purity of this material has not been verified by elemental analysis, the physical properties are not included in Table I.

Further extensions of this method of synthesis as well as the results of cleavage experiments of these and other disulfides will be reported in a separate communication.

EXPERIMENTAL[11]

α-Phenethyl mercaptan was prepared in 51.5% overall yield from α-phenethylbromide by the method of Siegel,[12] b.p. 75–77° at 5 mm.; reported,[12] 71–72° at 4 mm.

p-Nitrobenzyl mercaptan was prepared in 52.5% overall yield from *p*-nitrobenzyl chloride[13]; m.p. 51–52°; reported,[14] m.p. 52°.

All other mercaptans were obtained from Eastman Organic Chemicals and were recrystallized or distilled prior to use.

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(10) The reactions of several alkylsulfenyl thiocyanates with various substrates will be reported in a separate communication.

(11) Boiling points and melting points are uncorrected Elemental analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Micro-Tech Laboratories, Skokie, Ill.

(12) S. Siegel and A. F. Graefe, *J. Am. Chem. Soc.*, **75**, 4521 (1953).

(13) G. M. Bennett and W. A. Berry, *J. Chem. Soc.*, 1666 (1927).

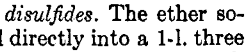
(14) W. S. Hoffman and E. E. Reids, *J. Am. Chem. Soc.*, **45**, 1833 (1923).

Preparation of thiocyanogen in diethyl ether. The thiocyanogen solution was prepared as described by Wood[15] using a somewhat modified technique. To an ice cold solution of 70.0 g. (0.214 mole) of lead nitrate in 160 ml. of water was added a cold solution of 32.4 g. (0.4 mole) of sodium thiocyanate in 160 ml. of water. The fine precipitate of lead thiocyanate was washed with large volumes of ice water and thoroughly dried, in the dark, *in vacuo* over phosphorus pentoxide. The lead thiocyanate was powdered and, if necessary, redried over phosphorus pentoxide. A 45.0-g. (0.139 mole) sample of the lead thiocyanate was suspended in 150 ml. of anhydrous ether in a 1-l. three neck flask, equipped with a mechanical stirrer, drying tube, and stopper. The suspension was cooled to 5–10° and treated with a cold solution of 18.6 g. (0.116 mole) of bromine in 400 ml. of anhydrous ether. The bromine solution was added in small portions with rapid stirring. After each addition the bromine color was allowed to disappear before the next portion was added. After the bromine addition was complete, the suspended solids were allowed to settle and the completely colorless thiocyanogen solution was decanted. The cold thiocyanogen solution was used immediately, following the general procedure of Lecher[9] described below.

Preparation of the unsymmetrical disulfides. The ether solution of thiocyanogen was decanted directly into a 1-l. three neck flask fitted with a mechanical stirrer, dropping funnel, and drying tube. The solution was cooled to 5–10° or in some cases to lower temperatures, and 0.1 mole of mercaptan, in 200 ml. of dry ether, was added dropwise with stirring. The addition required about 2 hr. after which no odor of mercaptan remained. The second mercaptan, 0.1 mole in 100 ml. of anhydrous ether, was added rapidly to the cold solution containing the alkylsulfenyl thiocyanate. The addition required about 0.5 hr. after which the reaction mixture was stirred for another 0.5 hr. at 5–10° and 1 hr. at room temperature.

The ether solution was washed six to eight times or until colorless with water to remove the thiocyanic acid and dried over magnesium sulfate. The ether was removed *in vacuo* and the residual liquid, usually clear, was distilled using a 6-inch Vigreux column at 0.1 to 0.3 mm. Usually two distillations afforded analytically pure disulfide. The yields reported in Table I represent the amount of disulfide obtained having physical constants identical to the sample on which the analytical results were obtained. No attempt was made to redistill the foreruns which contained mainly unsymmetrical disulfide and whatever symmetrical disulfide was present. The yields, therefore, represent minimum values of pure disulfide obtainable by this method.

Preparation of 5-phenyl-3,4-dithiapentane-1,2-dicarboxylic acid (VIII. $R = C_6H_5CH_2$, $R' = \underset{\displaystyle CH_2CO_2H}{\underset{|}{CHCO_2H}}$). The desired disulfide was prepared by the method described above with the following modifications. To a cold etheral solution of benzylsulfenyl thiocyanate was added 15.0 g. (0.1 mole) of solid α-mercaptosuccinic acid. The acid was added in small portions over a period of 1 hr. with vigorous stirring. The clear solution was stirred an additional hour, washed with water and dried. Removal of the ether afforded 20.0 g. of a yellow solid which was recrystallized twice from an ethyl acetate–benzene mixture (1:4) to yield 14.0 g. (51.5%) of white crystals, m.p. 147–148°. A mixture melting point of the disulfide with a sample of α-mercaptosuccinic acid m.p. 147–148°, melted at 125–138°.



Preparation of methyl-5-phenyl-3,4-dithiapentanoate (V). A. *Using dioxane.* Thiocyanogen in ether was prepared in the usual manner from 18.7 g. (0.117 mole) of bromine and 45.0 g. (0.17 mole) of lead thiocyanate. The thiocyanogen solution was cooled to −80° and 9.92 g. (0.08 mole) of benzyl mercaptan in 100 ml. of dry ether was added in 1 hr. The solution was stirred 0.5 hr., washed ten times with 100-ml. portions of ice water and dried at 0°, over magnesium sulfate, for 1.5 hr. The ether was removed *in vacuo*, under nitrogen, at −8°. The crude liquid benzylsulfenyl thiocyanate which weighed 12.37 g. (85.5%, 0.068 mole) was redissolved in 100 ml. of dry dioxane at 0° and treated with 7.23 g. (0.068 mole) of methyl mercaptoacetate in 100 ml. of dry dioxane. The reaction mixture was stirred and allowed to warm to room temperature over a 2.5-hr. period. The dioxane was removed *in vacuo* and the residue dissolved in ether, washed with water and dried. Removal of the ether followed by distillation of the residue yielded 7.85 g. (52.0% based on benzylsulfenyl thiocyanate) of product, b.p. 120° at 0.2 mm., n_D^{25} 1.5783. The infrared spectra of the products obtained with and without isolation of benzylsulfenyl thiocyanate were identical.

B. *Using diethyl ether.* Following the procedure described in A, 9.3 g. (0.075 mole) of benzyl mercaptan afforded 12.8 g. (94.1%) of crude benzylsulfenyl thiocyanate when treated with thiocyanogen in ether at −80°. A 5.0-g. (0.028 mole) sample of the liquid sulfenyl thiocyanate was redissolved in ether and immediately added to 2.92 g. (0.028 mole) of methyl mercaptoacetate in 100 ml. of dry ether at −10°. After stirring 2.5 hr. the ether solution was worked up in the usual manner and distilled. The yield of II was 4.4 g. (70.05%), b.p. 115–116° at 0.15 mm, n_D^{25} 1.5785.

C. *Using methanol.* Using the method described in A, 9.92 g. (0.08 mole) of benzyl mercaptan in ether was converted to 12.8 g. (88.4%, 0.071 mole) of crude benzylsulfenyl thiocyanate. The intermediate was dissolved in dry methanol at 0° and treated with 7.49 g. (0.071 mole) of methyl mercaptoacetate in 100 ml. of cold dry methanol. After stirring 2.5 hr. the methanol was removed *in vacuo* and replaced with ether. The ether solution was washed with water, dried, and concentrated under vacuum. A 1.0-g. aliquot of the remaining residue was treated with 5 ml. of methanol and 0.01 mole of sodium methoxide. The solution was warmed 15 min. and treated with 2.18 g. (0.009 mole) of diphenylcarbamyl chloride. Upon cooling 0.65 g. of the *N,N*-diphenylthiocarbamate derivative of methyl mercaptoacetate was obtained, m.p. 116–117°.[16]

Anal. Calcd. for $C_{16}H_{15}O_3NS$: C, 63.76; H, 5.02. Found: C, 64.14; H, 5.23.

A mixture melting point with a sample of the derivative prepared from authentic methyl mercaptoacetate melted at 117°.

The remaining residue was crystallized from methanol and afforded 5.0 g. (28.5%) of benzyl disulfide m.p. 69–70°; reported[17] 71.5°. Although some of V may have been present the reaction mixture was not characterized further.

CHAPEL HILL, N. C.

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[15] J. L. Wood, *Org. Reactions*, 3, 240 (1946).

[16] We are indebted to Mr. Kenneth Shepard for the elemental analysis of this substance.

[17] D. F. Twiss, *J. Chem. Soc.*, 105, 36 (1914).