zation from an ethanol–ether mixture afforded 4.15 g. (59%) of white powder XVIIIb, m.p. 175–180° dec., reported[36] m.p. 175–180° dec. A mixture melting point with cysteine hydrochloride (m.p. 175–178°) was depressed.

Phenyl β-Naphthyl Disulfide (XVIIIc) from Phenylthiomethyl Methyl Ether.—To 0.05 mole of thiocyanogen in 250 ml. of cold ether was added 7.7 g. (0.05 mole) of XIXa. After 0.5 hour, 8.1 g. (0.05 mole) of β-thionaphthalene was added in portions. Workup in the usual manner and crystallization of the residue from ethanol afforded 8.50 g. (63.5%) of XVIIIc, m.p. 74–74.5°; reported[37,38] m.p. 76°, 67.5°. The mixture melting point with β-thionaphthalene was depressed.

3-Carboxy-6-phenyl-4,5-dithiahexanoic Acid (XVIIIa) from Benzylthiomethyl Methyl Ether.—A solution of 4.20 g. (0.025 mole) of XIXb in 100 ml. of acetone was added to 0.025 mole of thiocyanogen in 150 ml. of ether at 0. The yellow solution was then treated with 3.75 g. (0.025 mole) of mercaptosuccinic acid. Evaporation of the solvent afforded a brown solid which was dried over potassium hydroxide, washed with *n*-hexane and crystallized from water to yield 2.70 g. (40%) of XVIIIa, m.p. 148–149°. A mixture melting point with an authentic sample of disulfide was not depressed.

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(36) H. Bretschneider and W. Klötzer, *Monatsh. Chem.*, **81**, 589 (1950).

(37) H. Lecher and M. Wittwer, *Ber.*, **55B**, 1474 (1922).

(38) H. Emde, German Patent 804,572 (1951); *C. A.*, **46**, 529 (1952).

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, THE UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C.]

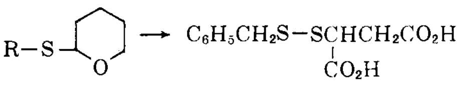
Chemistry of Aliphatic Disulfides. V. Preparation of Some Open-chain Unsymmetrical Cystine Derivatives from Thioethers of Cysteine[1,2]

BY RICHARD G. HISKEY AND WILLIAM P. TUCKER[3]

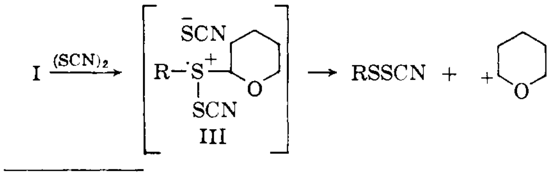
RECEIVED JULY 18, 1962

Several unsymmetrical disulfides, including two unsymmetrical open-chain cystine derivatives, have been prepared in reasonable yield from the corresponding S-triphenylmethyl or S-(2-tetrahydropyranyl)-thioethers using thiocyanogen-zinc chloride. The S-benzhydryl thioethers can likewise be removed with this agent.

In the preceding report[2] it was established that the sulfenyl thiocyanate method[4] can be applied to the synthesis of unsymmetrical open-chain cystine derivatives. Of additional interest was the observation that unsymmetrical disulfides could be obtained directly from S-(2-tetrahydropyranyl) thioethers and related hemithioacetals. For example, a 58% yield of 3-carboxy-6-phenyl-4,5-dithiahexanoic acid (II) resulted from treatment of benzyl 2-tetrahydropyranyl sulfide (Ia, R = $C_6H_5CH_2$) with thiocyanogen and mercaptosuccinic acid. A somewhat lower yield of II (25%) resulted from a similar reaction involving S-(2-tetrahydropyranyl)-succinic acid (Ib, R = $CH(CO_2H)CH_2CO_2H$), thiocyanogen and benzyl mercaptan. The facile cleavage of the hemithioacetals by electrophiles is presumably due to the fact that a stabilized carbonium ion can be ejected from the intermediate sulfonium salt III. To test this view several other thioethers capable of reacting in a similar manner were considered.



Ia, b II



From the viewpoint of peptide synthesis the S-triphenylmethyl group has several desirable features. S-Tritylcysteine derivatives are usually easily handled solids (in contrast to the S-tetrahydropyranyl analogs) and have been successfully employed for the synthesis of peptides.[5,6] In these preparations the trityl group was used to block the nitrogen and sulfur functions of cysteine; the former group could be selectively removed with warm acetic acid. Detritylation of both functions could be accomplished with dry hydrogen chloride in chloroform. The expectation that trityl sulfides would cleave with thiocyanogen was strengthened by the reported[7] iodine-catalyzed conversion of phenyltrityl sulfide to triphenylcarbinol and diphenyl disulfide.

Preparation of the desired S-trityl thioethers was readily accomplished in good yield by treatment of the appropriate mercaptan with triphenylcarbinol and boron fluoride. When benzyl triphenyl methyl sulfide (IVa, R = $C_6H_5CH_2$) was added to a thiocyanogen solution followed by mercaptosuccinic acid, II was obtained in 20–28% yield with a comparable amount of trityl thiocyanate. A similar reaction involving S-tritylmercaptosuccinic acid (IVb, R = $CH(CO_2H)CH_2CO_2H$), thiocyanogen and benzyl mercaptan produced II in 43% crude yield. Dibenzyl sulfide did not react with thiocyanogen.

$$RSH + (C_6H_5)_3COH \longrightarrow \underset{\text{IVa, b}}{RSC(C_6H_5)_3} \longrightarrow II + (C_6H_5)_3CSCN$$

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[1] Supported in part by research grant A-3416 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, United States Public Health Service.

[2] Part IV of this series, R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4789 (1962).

[3] Abstracted in part from a dissertation submitted by W. P. Tucker to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, August, 1962.

[4] R. G. Hiskey, F. I. Carroll, R. M. Babb, J. O. Bledsoe, R. T. Puckett and B. W. Roberts, *J. Org. Chem.*, **26**, 1152 (1961).

[5] G. Amiard, R. Heymes and L. Velluz, *Bull. soc. chim. France*, 698 (1956).

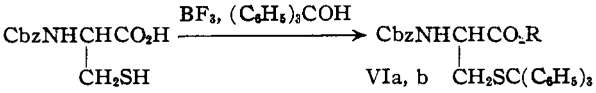
[6] L. Velluz, G. Amiard, J. Bartos, B. Goffinet and R. Heymes, *ibid.*, 1464 (1956).

[7] D. S. Tarbell and D. P. Harnish, *J. Am. Chem. Soc.*, **74**, 1862 (1952).

The lower yields of II obtained from IV compared with I could reflect the decreased electron density around the sulfur atom in the trityl sulfides. Therefore, it was anticipated the yield of disulfide might be increased by addition of a Lewis acid. A catalyst of this type could function either to cleave the trityl thioether prior to reaction with thiocyanogen,[8] or the Lewis acid could enhance the reactivity of the thiocyanogen in a manner similar to the catalytic effect of Lewis acids on electrophiles in aromatic substitution. When aluminum bromide was added to trityl sulfides, cleavage occurred, but extensive decomposition also resulted. On the other hand, addition of IVb to a solution of thiocyanogen and boron fluoride followed by addition of benzyl mercaptan provided only traces of II. Zinc chloride proved to be much more effective.

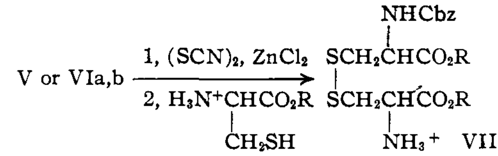
When IVa was allowed to react with a thiocyanogen solution containing 1.2 molar equivalents of anhydrous zinc chloride, a yellow coloration was produced which was discharged on addition of mercaptosuccinic acid. The trityl thiocyanate produced could be extracted with benzene leaving crude II which was purified by recrystallization from an ethyl acetate mixture. The yield of II obtained by this procedure was 78%. In a similar manner a 43% yield of pure II resulted from IVb. Substitution of mercuric chloride for zinc chloride gave similar results; however, neither the purity nor yield of II was increased. Zinc chloride was also applied to Ia,b with substantial improvement in yield of II. In an effort to develop the usefulness of the zinc chloride–thiocyanogen reagent the amount of Lewis acid employed was varied. The results of these experiments are recorded in Table I. With trityl sulfides an increase in the amount of zinc chloride employed from 0–8 moles increased the yields of II from 20% to 80%. The tetrahydropyranyl sulfides were, however, more sensitive to excess zinc chloride. The amount of II obtained from I was drastically reduced and with 6 moles of Lewis acid only a dark oil could be obtained. Maximum yields of II were obtained when equivalent amounts of catalyst were used.

The method was next applied to the S-(2-tetrahydropyranyl)-(V) and S-triphenylmethyl-(VI) derivatives of N-carbobenzoxycysteine. Both V and VIa could be obtained in good yield from the corresponding thiol using boron fluoride and either dihydropyran or triphenylcarbinol. The latter substance was stored as the crystalline diethylamine salt; V was previously reported.[2] Attempts to prepare VIa with triphenylmethyl chloride and triethylamine were unsuccessful. Treatment of VIa with thiocyanogen–zinc chloride followed by addition of cysteine hydrochloride gave monocarbobenzoxycystine (VIIa, R = H) in 81% yield. The material, obtained as a powder, was identical with an authentic sample of VIIa prepared by the method of Greenstein, *et al.*,[9,10] and with the sample previously[2] obtained from N-carbobenzoxycysteine. In the latter case the yield was 57%. The specific rotation of VIIa, obtained from VIa, was $[\alpha]^{23}\mathrm{D}$ −120°, in close agreement with the reported[10] value of −126°. Similar treatment of V likewise produced VIIa in 36% yield. The specific rotation of this preparation was $[\alpha]^{23}\mathrm{D}$ −118°. The properties of VIIa produced from V were identical with the other samples of VIIa obtained. Methyl N-carbobenzoxy-S-tritylcysteinate (VIb), prepared by the action of diazomethane on VIa, was also converted into an unsymmetrical open-chain cystine derivative. Treatment of VIb with thiocyanogen–zinc chloride followed by cysteine methyl ester hydrochloride afforded monocarbobenzoxycystine bis-methyl ester hydrochloride (VIIb), $[\alpha]^{25}\mathrm{D}$ − 90°, in 15.5% yield. The bis-methyl ester hydrochloride was previously prepared[10] by direct esterification of VIIa. The reported rotation was $[\alpha]^{25}\mathrm{D}$ − 82.5°. Repetition of this preparation afforded authentic VIIb, $[\alpha]^{23}\mathrm{D}$ − 86°, identical in all respects to VIIb obtained *via* VIb. These experiments indicate that unsymmetrical open-chain cystine derivatives can be prepared directly from blocked cysteines or the thiol[2] with a minimal amount of racemization under conditions which avoid disulfide interchange.



$$\underset{\displaystyle \mathrm{CH_2SH}}{\mathrm{CbzNHCHCO_2H}} \xrightarrow{\mathrm{BF_3,\ (C_6H_5)_3COH}} \underset{\displaystyle \mathrm{CH_2SC(C_6H_5)_3}}{\mathrm{CbzNHCHCO_2R}}$$

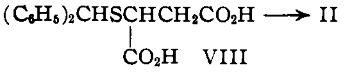
VIa, b



$$\text{V or VIa,b} \xrightarrow[\mathrm{2,\ \underset{\displaystyle CH_2SH}{H_3N^+CHCO_2R}}]{\mathrm{1,\ (SCN)_2,\ ZnCl_2}} \begin{array}{l} \quad\mathrm{NHCbz} \\ \mathrm{SCH_2CHCO_2R} \\ \mathrm{SCH_2CHCO_2R} \\ \quad\mathrm{NH_3^+} \end{array}$$

VIIa,b

In order to evaluate more fully the potential of the sulfenyl thiocyanate method for use in the synthesis of more complex cystine peptides,[2] preliminary experiments on the selective removal of thioethers were initiated. Since benzyl sulfides were inert to the action of thiocyanogen–zinc chloride, whereas trityl sulfides were rapidly cleaved with this reagent, the S-benzhydryl group was investigated. Treatment of S-benzhydrylmercaptosuccinic acid (VIII) with thiocyanogen–zinc chloride followed by benzyl mercaptan afforded II in 44% yield. As might be expected, VIII was cleaved less rapidly than IVb. Thus the S-(2-tetrahydropyranyl), S-triphenylmethyl and S-benzylhydryl sulfides appear to offer a definite reactivity gradient toward thiocyanogen and preferential cleavage may well be possible. Compounds containing several other S-protective groups utilized in peptide synthesis were treated with thiocyanogen–zinc chloride but did not afford unsymmetrical disulfide. These included 3-carbobenzoxy-4-carboxy-2,2-dimethylthiazolidine[11] and S-benzylthiomethylmercaptosuccinic acid.[12]



$$\underset{\displaystyle \mathrm{CO_2H}}{\mathrm{(C_6H_5)_2CHSCHCH_2CO_2H}} \longrightarrow \mathrm{II}$$

VIII

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[8] D. P. Harnish and D. S. Tarbell, *J. Am. Chem. Soc.*, **70**, 4123 (1948), have reported cleavage of benzyl and related sulfides with aluminum bromide.

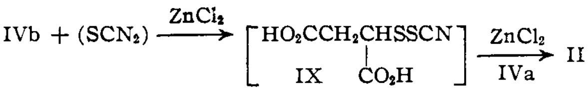
[9] R. Marshall, M. Winitz, S. M. Birnbaum and J. P. Greenstein, *ibid.*, **79**, 4538 (1957).

[10] L. Zervas, L. Benoiton, E. Weiss, M. Winitz and J. P. Greenstein, *ibid.*, **81**, 1729 (1959).

[11] J. Sheehan and D. H. Yang, *ibid.*, **80**, 1158 (1958).

[12] P. J. E. Pimlott and G. T. Young, *Proc. Chem. Soc.*, 257 (1958).

A reaction of some interest is that involving S-trityl sulfides in both steps of the sulfenyl thiocyanate reaction sequence. When IVb was treated first with thiocyanogen–zinc chloride and then IVa added. II was obtained in 80% yield. It would appear that the intermediate sulfenyl thiocyanate IX behaves as a derivative of thiocyanogen and



$$\mathrm{IVb} + (SCN_2) \xrightarrow{ZnCl_2} \left[\begin{array}{c} HO_2CCH_2\underset{\displaystyle CO_2H}{\underset{|}{C}}HSSCN \\ \mathrm{IX} \end{array}\right] \xrightarrow[\mathrm{IVa}]{ZnCl_2} \mathrm{II}$$

reacts with IVa much as IVb reacted with thiocyanogen. That zinc chloride alone may not be responsible for the cleavage of IV was indicated by treatment of IVb with a fivefold excess of zinc chloride in ether. A deep yellow color was observed and the solution gave a positive thiol test with nitroprusside, but addition of water and work-up led to 90% recovery of IVb.

The conversion of two trityl thioethers to the corresponding unsymmetrical disulfide is of value when the preparation of the corresponding mercaptans is tedious or impractical. Further, with the availability of triphenylmethylmercaptan[13] a number of trityl thioethers may be obtained by displacement of a leaving group on carbon or conjugate addition to an unsaturated system. These sulfides in turn provide unsymmetrical disulfides which would probably be otherwise inaccessible or difficultly available.[14] The conversion of two S-trityl thioethers to the unsymmetrical disulfide indicates, however, that symmetrical disulfides may also result from S-trityl derivatives. Thus the merits of the sulfenylthiocyanate method as a general route to unsymmetrical open-chain cystine peptides must await further evaluation. Experiments of this type are currently in progress.

Experimental[15]

Benzyl Triphenylmethyl Sulfide (IVa).—Following the general procedure of Greeg, *et al.*,[16] 5 ml. of boron fluoride–ether complex was added to a suspension of 12.4 g. (0.1 mole) of benzyl mercaptan and 26.0 g. (0.1 mole) of triphenylcarbinol in 70 ml. of dry ether. The solution was allowed to stand 0.5 hour, washed twice with 5% sodium hydroxide, water and dried. Removal of solvent afforded an oil which crystallized when triturated with hot ethanol. The sulfide was recrystallized from ethanol to yield 24.3 g. (67%) of sulfide, m.p. 92–93°.

Anal. Calcd. for $C_{26}H_{22}S$: C, 85.25; H, 6.04; S, 8.76. Found: C, 85.15; H, 5.90; S, 8.82.

S-Triphenylmethylmercaptosuccinic Acid (IVb).—Following the procedure described for IVa gave a 93% yield of IVb, m.p. 189–190°. The substance was previously[17] prepared in 50% yield by alkylation of mercaptosuccinic acid with triphenylmethyl chloride; m.p. 186–187°.

TABLE I

EFFECTS OF ZINC CHLORIDE ON YIELD OF DISULFIDES FROM THIOETHERS

$$R\text{–}S\text{–}R' + (SCN_2) \xrightarrow{ZnCl_2} R\text{–}S\text{–}SCN \xrightarrow{R''SH} R\text{–}S\text{–}S\text{–}R''$$

R	R′	Molar equiv. of $ZnCl_2$	R″	Yield, % (Crude, m.p., °C.)	Yield, % (Pure m.p. 147–148°)
			Ia		
$C_6H_5CH_2$	THP[a]	None	MSA[b]	50 (138–49)	40
$C_6H_5CH_2$	THP	1.25	MSA	100 (142–145)	77
$C_6H_5CH_2$	THP	3.0	MSA	80 (135)	25
$C_6H_5CH_2$	THP	6.0[c]	MSA	0	
			Ib		
MSA	THP	None	$C_6H_5CH_2$	67 (127–37)	41
MSA	THP	1.25	$C_6H_5CH_2$	78 (143–45)	57
MSA	THP	6.0	$C_6H_5CH_2$	82 (139–43)	57
			IVa		
$C_6H_5CH_2$	$(C_6H_5)_3C$	None	MSA		20–28
$C_6H_5CH_2$	$(C_6H_5)_3C$	1.2	MSA		78
			IVb		
MSA	$(C_6H_5)_3C$	None	$C_6H_5CH_2$	43 (140–45)	
MSA	$(C_6H_5)_3C$	8.0	$C_6H_5CH_2$		67
MSA	$(C_6H_5)_3C$	8.0[d]	$C_6H_5CH_2$	55 (138–145)	
MSA	$(C_6H_5)_3C$	8.0[e]	$C_6H_5CH_2$	80 (147–149)	55

[a] Tetrahydropyranyl. [b] Mercaptosuccinic acid. [c] The reaction mixture became very dark after addition of the sulfide and a red-brown oil formed; no disulfide could be isolated. [d] Acetonitrile was used as solvent for both sulfide and mercaptan. [e] This experiment differs from the others involving S-trityl derivatives in that the S-trityl derivative was added to the thiocyanogen in 10 minutes rather than one hour.

S-Benzhydrylmethylmercaptosuccinic acid (VIII) was prepared in 74% yield from mercaptosuccinic acid, benzhydrol and boron fluoride–ether complex; m.p. 163–164°.

Anal. Calcd. for $C_{17}H_{16}O_4S$: C, 64.60; H, 5.11. Found: C, 64.76; H, 5.26.

N-Carbobenzoxy-S-triphenylmethylcysteine Diethylamine Salt (VI).—A solution of N-carbobenzoxycysteine in ether was treated with triphenylcarbinol and boron fluoride–ether complex. After the ether solution was washed and dried a 10% excess of diethylamine was added. The precipitated salt was filtered, washed with water, and dried; m.p. 163–167°. Recrystallization from acetone gave 67% of the sulfide, m.p. 165–167°. An analytical sample recrystallized three times from acetone melted at 168–170°.

Anal. Calcd. for $C_{34}H_{38}N_2O_4S$: C, 71.50; H, 6.71; N, 4.91; S, 5.61. Found: C, 71.68; H, 6.61; N, 4.80; S, 5.74.

Methyl N-Carbobenzoxy-S-triphenylmethylcysteinate (VIb).—To 5.71 g. (0.01 mole) of VI-diethylamine salt in 150 ml. of ether was added 30 ml. of 0.5 *N* hydrochloric acid. The mixture was shaken until the solid dissolved. The ether layer was washed twice with water, dried, and treated with excess diazomethane until the yellow color persisted. Evaporation of the solvent afforded a quantitative yield of VIb as a thick, clear oil.

3-Carboxy-6-phenyl-4,5-dithiahexanoic Acid (II) from S-Triphenylmethylmercaptosuccinic Acid (IVb).—To a cold stirred solution of 0.0125 mole of thiocyanogen in 150 ml. of ether was added 13.6 g. (0.1 mole) of anhydrous zinc chloride followed by rapid addition of 4.91 g. (0.0125 mole) of IVb in 100 ml. of ether. The addition required 10 minutes. The resulting mixture was treated immediately and rapidly with a solution of 1.55 g. (0.0125 mole) of benzyl mercaptan in 50 ml. of ether. The bright yellow color obtained when the sulfide was introduced faded completely giving a clear, colorless solution. The solution

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(13) N. Kharasch and H. R. Williams, *J. Am. Chem. Soc.*, **72**, 1843 (1950).

(14) For example, Mr. J. A. Kepler of this Laboratory has prepared

$C_6H_5COCH_2SS\underset{\displaystyle CH_2COC_6H_5}{\underset{|}{C}}HCOC_6H_5$ *via* the two trityl thioethers.

$C_6H_5CO\underset{\displaystyle SC(C_6H_5)_3}{\underset{|}{C}}HCH_2COC_6H_5$ was obtained from dibenzoylethylene and trityl mercaptan while $C_6H_5COCH_2SC(C_6H_5)_3$ resulted from trityl mercaptide and phenacyl bromide.

(15) The amino acids used in this work are of the L-configuration and were obtained from the Mann Research Laboratories. Optical rotations were performed with a Rudolf polarimeter model 80 equipped with a model 200 photoelectric attachment. Elemental analysis by Micro-Tech Laboratories, Skokie, Ill. Melting points were taken in capillary tubes and are uncorrected.

(16) D. C. Gregg, H. A. Iddles and P. W. Stearns, *J. Org. Chem.*, **16**, 246 (1951).

(17) E. Billman and N. V. Due, *Bull. soc. chim. France*, [4] **35**, 390 (1924).

was stirred cold for 0.5 hour and at room temperature for 1 hour. During this period an oil was deposited in the flask. The mixture was washed 3 times with water, dried and evaporated. Trituration with benzene afforded 2.70 g. (80%) of II, m.p. 147–148°. One recrystallization from a benzene–ether mixture gave 1.86 g. (55%) of disulfide; reported[4] m.p. 147–148°.

3-Carboxy-6-phenyl-4,5-dithiahexanoic Acid (II) from S-(2-Tetrahydropyranyl) Thioethers (I).—The following general procedure was used to evaluate the usefulness of zinc chloride. To a cold solution of 0.0125 mole of thiocyanogen was added the desired amount of anhydrous zinc chloride. This was followed by addition of 0.0125 mole of the tetrahydropyranyl sulfide in 100 ml. of ether over a 0.5-hour period. The reaction mixture was stirred for an additional 0.5 hour and then treated with 0.0125 mole of mercaptan during 0.33 hour. After stirring at 0–5° for 0.5 hour and at room temperature for 1 hour the reaction mixture was washed 3 times with water, dried and evaporated. The residue was washed with *n*-hexane to remove the red-brown tarry substance formed, filtered and dried. Crystallization of the crude material from ethyl acetate–benzene (1:4) gave II. In the cases involving Ib it was necessary to employ an ether–dioxane mixture (3:1) to dissolve the sulfide. The reaction mixture became heterogeneous when this solution was added. When mercaptosuccinic acid was the mercaptan used in the second step it was added as a solid in small portions. Benzyl mercaptan was added as a solution in 50 ml. of ether.

Monocarbobenzoxycystine (VIIa) from N-Carbobenzoxy-S-(2-tetrahydropyranyl)-cysteine (V).—To a cold solution of 0.01 mole of thiocyanogen in 100 ml. of ether was added 2.06 g. (0.015 mole) of anhydrous zinc chloride followed by the addition of 0.01 mole of V in 100 ml. of ether over a period of 0.5 hour. (The free acid was prepared by suspending 4.47 g. (0.01 mole) of the benzylamine salt[2] in 100 ml. of ether and shaking with 30 ml. of 0.05 *N* hydrochloric acid until complete solution. The ether layer was separated and dried.) The colorless solution was stirred at 0° for 0.5 hour then treated with a solution of 1.76 g. (0.01 mole) of cysteine hydrochloride monohydrate in 80 ml. of N,N-dimethylformamide during 0.5 hour. An additional 20 ml. of N,N-dimethylformamide was added and the solution stirred cold for 1 hour and at room temperature for 1 hour. The solvents were removed *in vacuo* at room temperature to leave an orange oil which was washed 3 times with ether, treated with 150 ml. of aqueous diethylamine (5 g. per 100 ml.) and filtered. The residue was washed with aqueous diethylamine, the filtrate and washings combined and acidified with excess acetic acid. The product precipitated on cooling and appeared as 1.34 g. (36%) of VIIa, $[\alpha]^{23}\text{D}$ − 118° (*c* 1 in 5 *N* hydrochloric acid). This preparation was identical with the material obtained from the thiol,[2] VI or cystine.[10]

Monocarbobenzoxycystine (VIIa) from N-Carbobenzoxy-S-triphenylmethylcysteine (VI).—In a similar manner 0.0125 mole of VI, generated from the diethylamine salt, afforded 3.80 g. (81%) of VIIa, $[\alpha]^{23}\text{D}$ − 121° (*c* 1 in 5 *N* hydrochloric acid).

Anal. Calcd. for $C_{14}H_{18}N_2O_6S_2$: C, 44.9; H, 4.8; N, 7.5; S, 17.1. Found: C, 45.07; H, 4.94; N, 7.52; S, 16.89.

Monocarbobenzoxycystine (VIIa) was prepared from cystine by the method of Greenstein, *et al.*[9] From 100 g. of cystine 10.0 g. of VIIa was obtained, $[\alpha]^{23}\text{D}$ − 120° (*c* 1 in 1 *N* sodium hydroxide); reported[9,10] −120° and −117.5° under the same conditions.

Monocarbobenzoxycystine Bis-methyl Ester Hydrochloride (VIIb) from Methyl N-Carbobenzoxy-S-triphenylmethylcysteinates (VIb).—A 0.01-mole sample of ester, generated from the diethylamine salt, was treated with thiocyanogen and zinc chloride using the previous conditions. After addition of VIb the solvents were removed and the semi-solid residue taken up in hot acetone. The precipitated solid gave a negative test for disulfide whereas the filtrate gave a strongly positive test. The filtrate was concentrated; the oily solid suspended in water and the *p*H adjusted to 6. The suspension was extracted with ethyl acetate, the extracts washed twice with water and dried. Evaporation left a gummy residue which was washed with ether and dried *in vacuo*. The resulting white powder was dissolved in a 2 *N* hydrogen chloride–methanol solution, evaporated twice and the residue crystallized from a methanol–ether mixture to give 0.68 g. (15.5%) of VIIb, m.p. 155–156°.

A mixture melting point with authentic VIIb prepared by the method of Zervas, *et al.*,[10] was not depressed. The specific rotation of the substance was $[\alpha]^{23}\text{D}$ −90° (*c* 1 in methanol), reported $[\alpha]^{25}\text{D}$ − 82.5° (*c* 1 in methanol).

Monocarbobenzoxycystine Bis-methyl Ester Hydrochloride (VIIb).—The diester hydrochloride was prepared by the method of Zervas, *et al.*,[9,10] 5 g. of monocarbobenzoxycystine affording 3.54 g. of VIIb, m.p. 155–157°, $[\alpha]^{23}\text{D}$ − 86° (*c* 1 in methanol); reported[9] m.p. 159–160°, $[\alpha]^{23}\text{D}$ − 82.5° (*c* 1 in methanol).

3-Carboxy-6-phenyl-4,5-dithiahexanoic Acid (II) from S-Triphenylmethylmercaptosuccinic Acid (IVb) and Benzyl Triphenylmethyl Sulfide (IVa).—A solution of 0.01 mole of thiocyanogen containing 13.6 g. (0.1 mole) of zinc chloride in 150 ml. of ether was treated with a solution of 3.93 g. of IVb in 80 ml. of ether over a 0.5-hour period. The bright yellow solution was stirred at 0° for 0.5 hour and treated with 3.67 (0.01 mole) of IVa in 50 ml. of ether during 0.5 hour. The solution was stirred 0.5 hour at 0 and 1 hour at room temperature. The usual workup afforded 2.17 g. (80%) of crude disulfide, m.p. 141–144°.