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CHEMISTRY OF ALIPHATIC DISULFIDES—XIII

FORMATION OF UNSYMMETRICAL DISULFIDES FROM S-BENZHYDRYL THIOETHERS[1-3]

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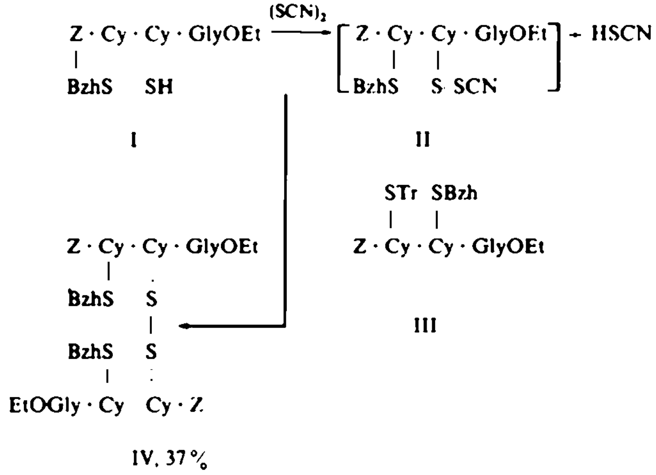
Abstract Conditions have been devised for the oxidation of S-benzhydryl thioethers with thiocyanogen. The procedure involves the use of a trifluoroacetic acid–acetic acid solvent. These conditions do not effect a disulfide bond present in the substrate.

IN A previous report,[1] the relative reactivity of the S-trityl and S-benzhydryl derivatives of bound cysteine toward a sulfenylthiocyanate was compared. Treatment of ethyl N-carbobenzoxy-S-trityl-L-cysteinyl-S-benzhydryl-L-cysteinylglycinate (III) with the sulfenylthiocyanate, II, derived from ethyl N-carbobenzoxy-S-benzhydryl-L-cysteinyl-L-cysteinylglycinate (I) provided the unsymmetrical cystine derivative, IV. The preparation of IV by this route represents the first stage of a general synthetic scheme designed to provide cyclic *bis*-cystine derivatives similar to VI. The second aspect of the proposed scheme requires an oxidative method for the conversion of the



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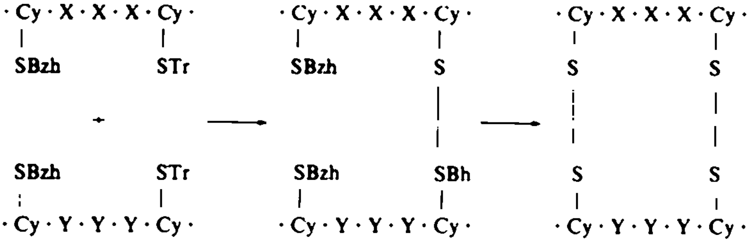
[1] Part XII of this series, R. G. Hiskey, T. Mizoguchi and E. L. Smithwick, Jr., *J. Org. Chem.* **32**, 97 (1967).

[2] Supported by Research Grants RG-7966 from the National Institute of General Medical Sciences and A-3416 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U.S. Public Health Service.

[3] The following abbreviations have been incorporated into the text: Tr = CPh$_3$, Bzh = CHPh$_2$, DCC = N,N'-dicyclohexylcarbodiimide, TLC = thin layer chromatography, TFA = trifluoroacetic acid.

[4] National Science Foundation Cooperative Fellow, 1964–1966.

two S-benzhydryl-L-cysteine residues of V to the *bis*-cystine derivative, VI. The present report describes our initial studies on this aspect of the synthetic problem.



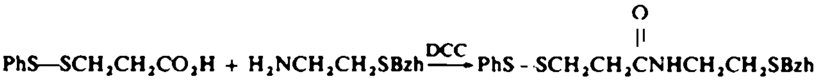
V VI

In order to firmly establish the relative reactivity of the S-trityl and S-benzhydryl groups, the reaction of these derivatives with a stable, isolable sulfenylthiocyanate was studied. When 2-naphthylsulfenylthiocyanate (VII) was allowed to react with trityl benzyl sulfide, a 96% yield of 2-naphthyl benzyl disulfide (VIII) was obtained. Treatment of benzhydryl benzyl sulfide with VII under the same conditions provided approximately 10% of VIII and 20% of 2-naphthyl disulfide, resulting from decomposition of VII. In view of these results it was apparent that more vigorous conditions would be required to affect the removal of the S-benzhydryl group with thiocyanogen. A complicating feature was the restrictions imposed by the presence of the disulfide bond in V. Since acid catalyzed fission of the S—S bond is well-known, the desired conditions should be sufficiently acidic to cleave the S-benzhydryl group and yet mild enough to avoid disulfide interchange.

$$\underset{\text{VII}}{C_{10}H_7S\ \ SCN} + TrSCH_2C_6H_5 \rightarrow \underset{\text{VIII, 96\%}}{C_{10}H_7S-SCH_2C_6H_5}$$

$$\text{VII} + BzhSCH_2C_6H_5 \rightarrow \underset{10\%}{\text{VIII}} + \underset{20\%}{[C_{10}H_7S]_2}$$

The synthetic route to a suitable model system was available from previous studies[5] on the linear *bis*-disulfides. In the present experiments, the substrate to be utilized, N-(2-benzhydrylthioethyl)5-phenyl-4,5-dithiapentanamide (XI), was prepared in 91% yield from 2-benzhydrylthioethylamine (X) and 5-phenyl-4,5-dithiapentanoic acid (IX).



$$\underset{\text{IX}}{PhS—SCH_2CH_2CO_2H} + \underset{\text{X}}{H_2NCH_2CH_2SBzh} \xrightarrow{DCC} \underset{\text{XI, 91\%}}{PhS-SCH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_2CH_2SBzh}$$

IX X XI, 91%

Since the scheme to be tested involved the oxidation of two S atoms, protected by the S-benzhydryl group, to a disulfide bond, the formation of the *tris*-disulfide[5], N-(3-thiapropyl)5-phenyl-4,5-dithiapentanamide disulfide, (XII) was studied. The

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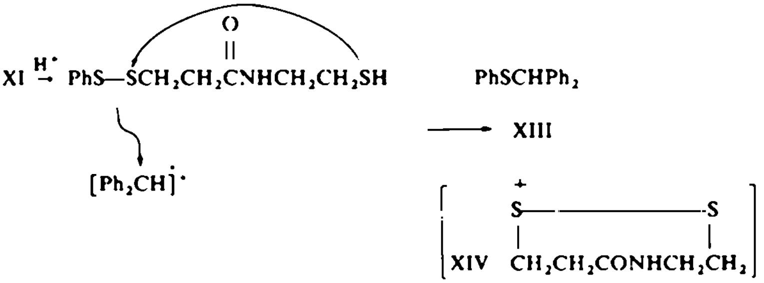
[5] R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.* 87, 3965 (1965).

results of the experiments designed to determine the optimum conditions for the conversion of XI to XII are listed in Table 1. When XI was dissolved in trifluoroacetic acid at temperatures from − 10° to 25°, immediate reaction occurred and benzhydryl phenyl sulfide (XIII) precipitated from the reaction mixture in 81 % yield. Although

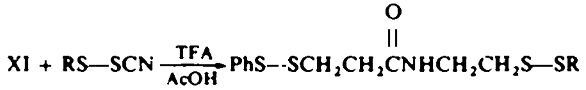
$$\mathrm{XI} \xrightarrow[\text{Acid}]{(\mathrm{SCN})_2} [C_6H_5S\text{—}SCH_2CH_2CONHCH_2CH_2S]_2$$

XII

the mechanism of this reaction has not been established, a plausible route involves acid-catalyzed cleavage of the S-benzhydryl group, followed by cleavage of the disulfide bond.[6] When XI was dissolved in trifluoroacetic acid which had been diluted with acetic acid (4:1), a 75 % yield of XIII was obtained; further dilution (1:4) provided no evidence of XIII but did afford trace amounts of the desired *tris*-disulfide, XII.



The optimum conditions for removal of the S-benzhydryl group with thiocyanogen were eventually established as a 1:1 (v/v) mixture of trifluoroacetic acid–acetic acid. Under these conditions a 48 % yield of XII was obtained. Although these data indicate that symmetrical disulfides can be prepared from two S-benzhydryl thioethers, the synthesis of an unsymmetrical disulfide under these conditions remained to be established. In order to determine whether acid-catalyzed disulfide interchange would preclude the preparation of unsymmetrical disulfides, XI was allowed to react with VII under the conditions previously utilized. This reaction provided N-[4-(2-naphthyl)-3,4-dithiabutyl] 5-phenyl-4,5-dithiapentanamide (XVIa) in 51 % yield. When the sulfenylthiocyanates from thiophenol and benzyl mercaptan were generated *in situ*



$$\mathrm{XI} + RS\text{—}SCN \xrightarrow[\text{AcOH}]{\text{TFA}} PhS\text{—}SCH_2CH_2\overset{O}{\overset{\|}{C}}NHCH_2CH_2S\text{—}SR$$

XVI a, R = $C_{10}H_7$, 51 %
b, R = Ph, 14 %
c, R = CH_2Ph, 31 %

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[6] No evidence is presently available concerning the existence of the cyclic disulfide, XIV, since the intractable, polymeric substance which remained after the removal of XIII and evaporation of the reaction mixture could not be purified. Similar treatment of the corresponding S-trityl thioether N-(2-tritylthioethyl)5-phenyl-4,5-dithiapentanamide[5] (XV) provided a mixture of two components which could not be resolved; modifications in the procedure also failed to produce isolable fragments, but none of the components exhibited a mobility (TLC) similar to authentic trityl phenyl sulfide. Additional experiments which are designed to substantiate the presence of XIV are currently in progress.

and allowed to react with XI, the corresponding unsymmetrical *bis*-disulfides XVIb, c were obtained in 14 and 31% yield, respectively. Since acid-catalyzed disulfide interchange of these compounds would be expected to produce phenyl disulfide, samples of XII and XVIa were subjected to the reaction conditions; no phenyl disulfide could be detected by TLC and starting material recoveries were 52 and 66%, respectively. When a sample of XII was dissolved in TFA at room temperature and stirred for an equal period of time, extensive decomposition was indicated by TLC with one component exhibiting a mobility similar to phenyl disulfide. As a check, phenyl disulfide was subjected to the work-up conditions and 76% was recovered. These experiments indicate that the proposed synthetic scheme for the preparation of VI can probably be realized. The synthesis of molecules related to VI will be described in a subsequent report.

TABLE 1. OXIDATION OF N-(2-BENZHYDRYLTHIOETHYL)-5-PHENYL-4,5-DITHIAPENTANAMIDE (XI) WITH THIOCYANOGEN

Solvent	Catalyst[a]	Temp °C	Reaction Time, hr	Result
CH_2Cl_2	$Hg(OAc)_2$	25	1	[b]
CH_2Cl_2	$SnCl_2$	25	1	[b]
$MeCO_2Et$		0	1	[b]
$MeCO_2Et$	$ZnCl_2$	0	1·5	[b]
$MeCO_2Et$	$AlCl_3$	0	2	[b]
$MeCO_2Et$	$BF_3 \cdot Et_2O$	0	1	[b]
$MeCO_2H$	$BF_3 \cdot Et_2O$	0	1	[b]
$MeCO_2H$	$BF_3 \cdot Et_2O$	25	7	[b]
CF_3CO_2H		25	0·25	81% XIII
CF_3CO_2H, $MeCO_2H$ (4:1)		0	0·75	75% XIII
CF_3CO_2H, CH_2Cl_2 (1:5)		25	5	[b]
CF_3CO_2H, $MeCO_2Et$ (1:1)		25	17	[c]
CF_3CO_2H, $MeCO_2H$ (1:4)		0	2·5	[c]
CF_3CO_2H, $MeCO_2H$ (3:1)		−10	2	20% XII
CF_3CO_2H, $MeCO_2H$ (1:1)		−10	6·5	48% XII

[a] One equivalent of catalyst added.

[b] TLC of the reaction mixture indicated extensive decomposition of the starting material; no spot corresponding to authentic XII was present.

[c] TLC indicated a trace amount of XII was present

EXPERIMENTAL[7]

2-*Naphthylsulfenylthiocyanate* (VII) was prepared by modifying the procedure of Lecher and Wittwer[8]. Thiocyanogen was generated from 47·4 g (0·145 mole) lead thiocyanate and 21·0 g (0·13 mole) Br_2 in 400 ml

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[7] M.ps are uncorrected and were obtained in capillary tubes. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois; Crobaugh Laboratories, Charleston, West Virginia; and Triangle Laboratory, Carrboro, North Carolina. TLC was conducted on microscope slides and both 5 × 20 and 20 × 20 cm. Pyrex plates using uniform coatings of silica gel GF_{254}. The chromatograms were developed with I_2 vapor and/or viewed under UV light. Solvent systems for TLC were: benzene: dioxan:acetic acid (90:25:4—System A); n-butanol:acetic acid:water (4:1:5—System B); chloroform: ethyl acetate (1:1—System C); and chloroform:benzene (1:1—System D).

Commercial reagents were of the highest quality available. Trifluoroacetic acid and AcOH were dried over $CaSO_4$ prior to use. NMR spectra were recorded on a Varian Associates A-60 spectrometer using TMS as the internal standard.

[8] H. Lecher and M. Wittwer, *Ber. Dtsch. Chem. Ges.* 55B, 1474 (1922).

ether at 5°. When the characteristic color of Br_2 had disappeared, 10·0 g (0·062 mole) 2-naphthyl mercaptan was added in one portion and the reaction mixture was stirred in the dark[9] at 0–5° for 4 hr. The yellow reaction mixture was filtered and the filtrate was washed with cold 0·4% $NaHCO_3$aq until the wash solns were negative to $FeCl_3$aq. The ether soln was dried, filtered, and the solvent removed *in vacuo*. The light yellow solid residue was dissolved in hot n-hexane, treated with activated charcoal, filtered, and the filtrate cooled overnight. The product appeared as 13·4 g (99% of theory based on mercaptan) of flocculent, pale yellow solid, m.p. 61·5–63·0°. Lit.[7] m.p. 64·5–65°; ν_{max}^{KBr} 2140 cm^{-1}. (Found: C, 60·97; H, 3·26; N, 6·09; S, 29·46. Calc. for $C_{11}H_7NS_2$: C, 60·80; H, 3·25; N, 6·45; S, 29·51%.)

Trityl benzyl sulfide was prepared by refluxing 24·8 g (0·095 mole) trityl carbinol, 12·4 g (0·10 mole) benzyl mercaptan, 0·1 g *p*-toluenesulfonic acid, and 110 ml benzene under a Dean-Stark apparatus for 2 hr. The benzene soln was washed with 200 ml distilled water, dried, and the solvent removed *in vacuo* to yield a viscous oil. The oil was dissolved in a minimum amount of 30–60° pet. ether, filtered and cooled. The product appeared as 32·4 g (84%) of white solid, m.p. 90·5–91·5°. Lit.[10] m.p. 92–93°. A mixture m.p. with an authentic sample was not depressed.

Benzhydryl benzyl sulfide was prepared by the procedure used for trityl benzyl sulfide. After recrystallization from 30–60° pet. ether the yield was 95·5%, m.p. 70–71°. Lit.[11] m.p. 70·5°.

2-*Naphthyl benzyl disulfide* (VIII) was prepared by dissolving 1·09 g (0·005 mole) of VII in 50 ml CH_2Cl_2 at 0–5° in the absence of light. To this stirred yellow soln was added a soln of 1·83 g (0·005 mole) trityl benzyl sulfide in 50 ml CH_2Cl_2. The addition required 20 min and the reaction mixture was stirred for 30 additional min, then allowed to warm slowly to room temp while stirring for 1 hr.[12] The yellow soln was concentrated to 10 ml *in vacuo* and applied to a 2·5 × 80 cm column of Florisil (150 g, 100–200 mesh). The product was eluted from the column with 90–100° pet. ether and the appropriate fractions were evaporated *in vacuo* to yield a white solid residue. Recrystallization from 30–60° pet ether gave 1·35 g (96%) product, m.p. 57–58°. This material was homogeneous on TLC (Systems A, C, and D) and nitroprusside negative until alcoholic NaCN soln was applied; ν_{max}^{KBr} 3050, 1575, 1485, 810, 740, 694 cm^{-1}; τ 2·42 (7·1 H, m), 2·85 (5·2 H, s), 6·16 (2·0 H, s). (Found: C, 72·60; H, 5·12; S, 22·90. $C_{17}H_{14}S_2$ requires: C, 72·30; H, 5·00; S, 22·71%.)

An analogous reaction in which the order of addition was reversed yielded 1·24 g (88%) of identical product.

Attempted preparation of VIII *from* VII *and benzhydryl benzyl sulfide*. The previous procedure was followed except that 1·45 g (0·005 mole) benzhydryl benzyl sulfide was used. Column chromatography afforded a mixture of 2-naphthyl disulfide and VIII. Fractional crystallization from 30–60° pet ether gave 20% and 10% yields of 2-naphthyl disulfide, m.p. 139–140°, and VIII, respectively (averages of several attempts).

2-*Benzhydrylthioethylammonium chloride* was prepared by modifying the procedure of Hiskey and Adams.[13] A soln of 11·5 g (0·1 mole) 2-mercaptoethylammonium chloride was allowed to react with 19·3 g (0·105 mole) benzhydrol and 14 ml BF_3-Et_2O (0·11 mole of BF_3) in 100 ml glacial AcOH. The yellow-brown soln was heated at 80–90° for 15 min with occasional stirring and then allowed to cool to room temp. The crude product was precipitated by the addition of 1·2 l. of ether. The white solid was recovered and the excess AcOH was removed *in vacuo* over NaOH pellets. The dry solid was dissolved in hot EtOH, filtered, and the filtrate evaporated *in vacuo* to yield 22·5 g (80%) of white solid, m.p. 166–167°. This material was homogeneous on TLC (System B), gave a positive ninhydrin test, but a negative nitroprusside test. Recrystallization from AcOEt raised the m.p. to 167–168°; ν_{max}^{KBr} 2800–3200 (broad), 1590, 1480, 1440, 745, 690 cm^{-1}. (Found: C, 64·36; H, 6·21; N, 4·87; S, 11·97. $C_{15}H_{18}NSCl$ requires: C, 64·38; H, 6·48; N, 5·01; S, 11·46%.)

2-*Benzhydrylthioethylamine* (X) was prepared by dissolving the hydrochloride salt in warm water, adjusting the pH to 10, and extracting continuously with ether for 12 hr. The ether was removed *in vacuo*

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[9] Although the sulfenylthiocyanate is stable for several months at 10° in the dark, it rapidly decomposes at room temp, especially when solns are allowed to stand in bright light. The major product of this decomposition has been shown to be 2-naphthyl disulfide.

[10] R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.* **84**, 4794 (1962).

[11] A. Schönberg, O. Schütz, and J. Peter, *Ber. Dtsch. Chem. Ges.* **62B**, 1663 (1929).

[12] In order to establish that cleavage occurred prior to the work-up, the reaction was monitored by TLC (System C); after 1 hr no VII was present and only VIII was observed.

[13] R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.* **30**, 1340 (1965).

and the residue was extracted with n-hexane overnight in a Soxhlet apparatus. The solvent was removed and the solid residue was recrystallized from hot AcOEt. Filtration yielded a white crystalline product, m.p. 74–75° (yields averaged 60% based on pure hydrochloride); homogeneous on TLC (System B); positive ninhydrin test, but negative nitroprusside test; ν_{max}^{KBr} 3320, 1585, 1480, 1000–1120 (broad), 740, 690 cm^{-1}; τ 2·80 (10·0 H, m), 4·90 (1·0 H, s), 7·57 (3·9 H, m), 9·06 (2·0 H, s). (Found: C, 74·12; H, 7·15; N, 5·83; S, 13·15. $C_{15}H_{17}NS$ requires: C, 74·03; H, 7·04; N, 5·76; S, 13·17%.)

5-Phenyl-4,5-dithiapentanoic acid (IX) was prepared according to the procedure of Hiskey and Harpp[5] in yields averaging 80%, m.p. 57–58°, Lit.[5] m.p. 57–58°.

N-(*2-Benzhydrylthioethyl*) *5-phenyl-4,5-dithiapentanamide* (XI) was prepared at −10° by adding a soln of 23·1 g (0·112 mole) N,N′-dicyclohexylcarbodiimide in 65 ml CH_2Cl_2 to a stirred soln of 23·6 g (0·11 mole) of IX and 32·3 g (0·133 mole) of X in 175 ml CH_2Cl_2. The reaction mixture was stirred for 3 hr and allowed to warm to room temp. The mixture was filtered and the filtrate was washed with 100 ml portions of 1N HCl, 5% $NaHCO_3$aq, distilled water, and sat NaClaq. The dried soln was filtered and the CH_2Cl_2 was removed *in vacuo* to give a yellow-white solid residue. The solid was recrystallized from AcOEt-n-hexane to yield 44·0 g (91%) of crystalline, white product, m.p. 84–85°; homogeneous on TLC (System A); ν_{max}^{KBr} 3270, 1635, 1525, 737, 698 cm^{-1}; τ 2·75 (15 H, m), 4·90 (1·0 H, s), 6·90 (5·0 H, m), 7·50 (4·0 H, m). (Found: C, 65·29; H, 5·76; N, 3·25; S, 21·86. $C_{24}H_{25}NOS_3$ requires: C, 65·56; H, 5·73; N, 3·19; S, 21·88%.)

Benzhydryl phenyl sulfide (XIII) was prepared by the procedure used for trityl benzyl sulfide. After recrystallization from AcOEt–n-hexane the yield was 91%, m.p. 77–78°, Lit.[11] m.p. 78°.

Rearrangement of XI *in trifluoroacetic acid*. A soln of 2·0 g (0·0045 mole) of XI in 10 ml trifluoroacetic acid was stirred at room temp for 2–3 min before a flocculent white ppt formed. Stirring was continued for 15 min and the reaction was quenched at that time by the addition of 200 ml distilled water. The ppt was recovered by filtration and washed thoroughly with distilled water. The dried white powder, 1·01 g (81%), was homogeneous on TLC (System A) and melted at 74–75·5°. A mixture m.p. with an authentic sample of XIII was not depressed. Recrystallization from AcOEt-n-hexane failed to raise the m.p.

Identical samples of XIII could also be obtained when trifluoroacetic-glacial acetic acid mixtures (1:1) were used at 0° and at −10°, however, the yields were somewhat lower.

N-(*3-Thiapropyl*) *5-phenyl-4,5-dithiapentanamide disulfide* (XII) was prepared by dissolving 0·88 g (0·002 mole) of XI in 10 ml trifluoroacetic acid and 10 ml glacial AcOH at −10°. The soln was added in small portions to a soln of thiocyanogen which had been generated from 0·5 g (0·0015 mole) lead thiocyanate and 0·17 g (0·00106 mole) Br_2 in AcOEt at −10°. The addition required 10 min and the reaction mixture was maintained at −10° (±2°) while stirring for 6 hr. The cold soln was partially neutralized by the addition of solid $NaHCO_3$ (pH ~ 5), filtered, and the filtrate was diluted with 100 ml AcOEt. The soln was neutralized with 5% $NaHCO_3$aq, washed with water and sat NaClaq, and dried. The solvent was removed *in vacuo* to yield an oily residue which was dissolved in a minimum amount of benzene and applied to a 1·5 × 50 cm column of silicic acid (40 g, 100 mesh). The effluent was monitored by TLC and the desired material was eluted from the column with benzene–AcOEt (1:1). Recrystallization from AcOEt-n-hexane gave 0·26 g (48%) of solid, m.p. 96–98°; homogeneous on TLC (Systems A and C). One additional recrystallization raised the m.p. to 109–110°, Lit.[5] m.p. 110·5–111·5°. A mixture m.p. with an authentic sample was not depressed.

N-[4-(*2-Naphthyl*) *3,4-dithiabutyl*] *5-phenyl-4,5-dithiapentanamide* (XVIa, R = *2-Naphthyl*)

General procedure for the preparation of unsymmetrical bis-disulfides from S-benzhydrylthioethers. A soln of 0·44 g (0·001 mole) of XI in 25 ml trifluoroacetic acid and 25 ml glacial AcOH at −10° was stirred for 1 hr and then diluted by the addition of 200 ml AcOEt. After allowing the reaction mixture to cool to −10°, 0·22 g (0·001 mole) of VII was added in small portions over a period of 2 hr. The temp was maintained at −10° for 2 hr, then allowed to warm slowly to 5° while stirring for 3 hr. The yellow soln was neutralized with 5% $NaHCO_3$aq, washed with distilled water, sat NaClaq, and dried. The filtered soln was evaporated *in vacuo* to yield a small amount of oil which was dissolved in a minimum amount of benzene and applied to a 1·5 × 50 cm column of Florisil (40 g, 100–200 mesh). The *bis*-disulfide was eluted from the column using AcOEt–benzene (1:3) and appeared as a viscous oil. The oil was dissolved in AcOEt, decolorized with activated charcoal, and crystallized by the addition of n-hexane to the cloud point. The product appeared as 0·22 g (51%) of white solid, m.p. 94–95°; homogeneous on TLC (Systems A and C); ν_{max}^{KBr} 3280, 3040, 1635, 1535, 815, 735, 680 cm^{-1}. (Found: C, 58·21; H, 5·09; N, 3·03; S, 30·08. $C_2H_{21}NOS_4$ requires: C, 58·43; H, 4·90; N, 3·24; S, 29·71%.)

N-(*4-phenyl-3,4-dithiabutyl*) *5-phenyl-4,5-dithiapentanamide* (XVIb, R = *phenyl*) was prepared by the general procedure previously described. Phenylsulfenylthiocyanate was generated by the addition of a soln of 0·15 g (0·0013 mole) thiophenol in 40 ml AcOEt to 0·001 mole thiocyanogen in 30 ml AcOEt. The addition required 40 min and the reaction temp was maintained at 0–5°. After stirring for 1 hr, the phenylsulfenylthiocyanate soln was added to a soln of XI as previously described. Chromatographic separation and purification under the same conditions yielded 0·06 g (14%) white solid, m.p. 63–64°; homogeneous on TLC (System C); ν_{max}^{KBr} 3345, 3040, 1635, 1530, 1435, 730, 680 cm^{-1}. (Found: C, 53·76; H, 5·38; N, 3·97; S, 33·14. $C_{17}H_{19}NOS_4$ requires: C, 53·51; H, 5·02; N, 3·67; S, 33·61%.)

N-(5-phenyl-3,4-dithiapentyl) 5-phenyl-4,5-dithiapentanamide (XVIc, R = *benzyl*) was prepared in the same manner as XVIb. Separation and purification required the same conditions and yielded 0·12 g (31%) white crystals, m.p. 57–58°; homogeneous on TLC (System C); ν_{max}^{KBr} 3330, 3050, 2910, 1635, 1535, 735, 695 cm^{-1}. (Found: C, 54·80; H, 5·29; N, 3·78; S, 32·63. $C_{18}H_{21}NOS_4$ requires: C, 54·65; H, 5·35; N, 3·54; S, 32·41%.)

Treatment of XV *with trifluoroacetic acid.* Addition of 1·17 g (0·0023 mole) of XV[5] to 5 ml stirred trifluoroacetic acid at room temp produced a yellow soln which became deep red in about 5 min. The reaction was quenched after 15 min by addition to 100 ml distilled water. The resulting oil was triturated with additional water and with n-hexane, and ultimately dissolved in boiling n-hexane. After standing overnight at 0°, the oil which separated was examined by TLC (Systems A and D). The soln contained two components, one of which exhibited a R_f value similar to that of XII; neither component had a R_f value comparable to that of trityl phenyl sulfide.

A similar experiment involving 5·16 g (0·01 mole) of XV dissolved in 20 ml trifluoroacetic acid was quenched after 15 min by addition to $NaHCO_3$aq. The products were extracted into AcOEt and this soln was treated as in the general procedure for XVIa. The solvent was removed *in vacuo* and the resulting oil was dissolved in $CHCl_3$ and applied to a 2·5 × 80 cm column of silica gel (150 g, 0·05–0·2 mm). TLC of the effleunt indicated at least 10 components, but none with a mobility similar to trityl phenyl sulfide.

A repeat of this latter procedure using a 1 min reaction time resulted in a complex mixture from which only starting material could be obtained. Chromatography under the same conditions afforded 2·2 g (43%) of XV, m.p. 97–99°. A mixture m.p. with an authentic sample was not depressed.

In another experiment, 20 ml trifluoroacetic acid was cooled to −10° and 0·52 g (1 mmole) of XV was added. The yellow-orange soln which resulted was stirred at −10° to −15° for 15 min, then quenched and worked up as above. TLC (System A) indicated at least 4 components, but only starting material could be identified and isolated. Column chromatography gave 0·16 g (31%) of XV, m.p. 99–101°. A mixture m.p. was not depressed.

Trityl phenyl sulfide was prepared by the procedure used for trityl benzyl sulfide. After recrystallization from n-hexane, the yield was 86·5%, m.p. 105–106°. Lit[14] m.p. 106°.

Stability of bis-disulfides in trifluoroacetic acid–acetic acid at −10°

a. To a stirred mixture of 2 ml trifluoroacetic acid and 2 ml AcOH at −10° was added 54·5 mg (0·1 mmole) of XII. The soln was stirred at this temp (±3°) for 6 hr, then added to a stirred mixture of 200 ml distilled water and 100 ml AcOEt and neutralized by adding solid $NaHCO_3$ (pH ~6). The mixture was transferred to a separatory funnel and the organic layer was washed with 5% $NaHCO_3$aq, water, and sat NaClaq. The AcOEt soln was dried and evaporated *in vacuo* to recover 28·2 mg (52%) starting material, m.p. 107–109° and homogeneous on TLC (System C). A mixture m.p. was not depressed.

b. When 43·2 mg (0·1 mmole) of XVIa was treated in the same manner, 28·5 mg (66%) starting material was recovered, m.p. 93–95° and homogeneous on TLC. A mixture m.p. was not depressed.

Treatment of XII *with trifluoroacetic acid.* A soln of 54·5 mg (0·1 mmole) of XII in 2 ml trifluoroacetic acid was stirred at room temp for 6 hr. Neutralization and washing as above gave an AcOEt soln which contained 5 components as evidenced by TLC (System C). One component had a mobility corresponding to phenyl disulfide and a second appeared to be similar to starting material.

Recovery of phenyl disulfide under analogous conditions. A mixture of 0·5 g (2·3 mmole) phenyl disulfide and 50 ml water was stirred at room temp for 1 hr and solid $NaHCO_3$ was added until a sat soln was tained. Little, if any, solid had dissolved. A clear soln was obtained by adding 10 ml AcOEt. The mixture was transferred to a separatory funnel where the organic layer was washed as in the previous experiments. The dry AcOEt soln was evaporated *in vacuo* to yield a white solid residue which was recrystallized from n-hexane to give 0·38 g (76%), m.p. 59–60°. A mixture m.p. was not depressed.

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