TABLE III
KINETIC DATA FOR THE SIMULTANEOUS EXCHANGE OF TRITIUM AND DEUTERIUM IN $II_T$ AND $II_D$ IN SODIUM METHOXIDE–METHANOL SOLUTION AT 70.0 ± 0.05°

| Time, sec. | Radioactivity, c./min.-mg.[a] | Mole % $II_D$ | $10^6k_T$ | $10^6k_D$ |
|---|---|---|---|---|
| 0 | 4614 | 88.6 | .. | .. |
| 64,500 | 3894 | 70.1 | 2.85 | 4.02 |
| 86,640 | 3722 | 65.1 | 2.70 | 3.96 |
| 108,960 | 3401 | 59.9 | 3.06 | 4.02 |
| 129,960 | 3258 | 55.6 | 2.93 | 4.03 |
| 151,140 | 3135 | 52.7 | 2.80 | 3.88 |
| 172,800 | 2942 | 49.2 | 2.86 | 3.86 |
| 194,580 | 2732 | 46.1 | 2.97 | 3.82 |
| 216,060 | 2658 | 42.9 | 2.82 | 3.85 |
| 1,670,400 | 331 | 9.4 | .. | .. |
| | | | 2.87 ± 0.08 | 3.98 ± 0.11 |

[a] Efficiency = 12.31%; actual counting level was 20–40 times higher.

2.7660 g. (0.0166 mole) of 9-tritiofluorene (prepared as described above) was diluted to 200 ml. in a volumetric flask. The solution was divided among ten sealed Pyrex vessels, and maintained at 69.3 ± 0.05° as described in method C, withdrawing samples every hour. Each sample was worked up by adding the red mixture to 30 ml. of water and 30 ml. of ether and washing the ether layer with 30-ml. portions of water until washings were no longer basic. The ether solution was then dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in a stream of dry nitrogen. After recrystallization from 3–5 ml. of ethanol, each sample was dried at 50° under vacuum, and finally analyzed by scintillation counting.[46]

**Trapping Experiments: 1,1,1,2,2,3,3-heptafluoro-4-hexanol from 1-Hydroheptafluoropropane.**—To 38 g. (0.22 mole) of 1-hydroheptafluoropropane (prepared from perfluorobutyric acid[13]) in 120 ml. of dry ether cooled to −40° in an atmosphere of dry nitrogen was added simultaneously with rapid stirring over a period of 40 min., 120 ml. of a 0.2 *M* solution of methyllithium in ether (Foote Mineral Co., Exton, Pa.) and 23 g. (0.4 mole) of freshly distilled propionaldehyde in 120 ml. of ether; *ca.* 2 l. of methane evolved through a condenser cooled to −80°. After allowing the mixture to warm to 20° over *ca.* 2 hr., the solution was neutralized with 3 *N* sulfuric acid. The ether layer was separated, washed once with 30 ml. of water, and dried over sodium sulfate. Distillation after removal of the ether gave fraction 1, b.p. 35–80°; fraction 2, 9 g., b.p. 80–103°; and fraction 3, 5 g., b.p. 103–112°; leaving a residue of 7 g. Although fractions 2 and 3 were largely 2-butanol (7.7-min. v.p.c. peak), vapor phase chromatography[46] indicated they were *ca.* 10 and 15%, respectively, of the fluorinated hexanol. The product hexanol was isolated by preparative vapor phase chromatography.[46] The infrared spectrum, v.p.c. retention time (25.6 min.) and b.p. of this product was identical with that of an authentic sample of 1,1,1,2,2,3,3-heptafluoro-4-hexanol prepared from heptafluoro-*n*-propyl iodide.[45c]

**1,1,1,2-Tetrafluoro-2-trifluoromethyl-3-pentanol from 2-Hydroheptafluoropropane.**—In a manner similar to that described in the previous experiment, methyllithium and propionaldehyde were added to 2-hydroheptafluoropropane in ether at −70°. After the usual work-up, 13 g., b.p. 88–115°, containing *ca.* 15% of the fluorinated hexanol and 85% 2-butanol was obtained. The hexanol was isolated by preparative vapor phase chromatography[46] as above (23.0-min. peak) and found to be identical in the infrared spectrum, boiling point, and v.p.c. retention time with an authentic sample prepared from heptafluoroisopropyl iodide.[45c]

**Acknowledgment.**—Helpful discussions with Professors C. G. Swain, A. Streitwieser, Jr., and J. D. Roberts are gratefully acknowledged.

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

# Chemistry of Aliphatic Disulfides. VI. Effect of α-Alkylation on the Cyanide Cleavage of Unsymmetrical Disulfides[1,2]

BY RICHARD G. HISKEY, WILLIAM H. BOWERS,[3] AND DAVID N. HARPP

RECEIVED SEPTEMBER 25, 1963

The cyanide cleavage of several α-alkylated unsymmetrical disulfides of the type $RS\text{–}SCH_2CO_2CH_3$ have been studied to determine the nature of the equilibria between the disulfide and the primary cleavage products. Cyanide cleavage in the presence of N,N-diphenylcarbamyl chloride (DPCC) has been found to be a thermodynamically controlled reaction involving the unsymmetrical disulfide and the four primary cleavage products. The reactivity of the disulfide toward cyanide ion decreases as R is changed from isobutyl to isopropyl to *t*-butyl.

In previous experiments[4] the cyanide ion cleavage of methyl 4-phenyl-3,4-dithiabutanoate (I) was found to provide the four possible primary cleavage products II–IV as predicted[5] from the "$\Delta pK_a$" value of I (1.28). The more stable primary cleavage products sodium thiophenoxide (II) and methyl thiocyanoacetate (III) predominated over sodium carbomethoxymethyl mercaptide (IV) and phenyl thiocyanate (V). The cleavage of I was conducted in the presence of a single equivalent of N,N-diphenylcarbamyl chloride (DPCC) and the mercaptides were obtained as the N,N-diphenylcarbamate derivatives VI and VII.

(1) Supported by research grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, United States Public Health Service.

(2) Part V of this series R. G. Hiskey and W. P. Tucker, *J. Am. Chem. Soc.*, **84**, 4794 (1962).

(3) Abstracted in part from a thesis submitted by W. H. Bowers to the University of North Carolina in partial fulfillment of the requirements for the M.S. Degree, June, 1962.

(4) R. G. Hiskey and F. I. Carroll, *J. Am. Chem. Soc.*, **83**, 4647 (1961).

(5) R. G. Hiskey and F. I. Carroll, *ibid.*, **83**, 4644 (1961).

However, when either II and III or IV and V were allowed to react in the presence of DPCC the same mixture of products as that obtained from the cyanide cleavage of I resulted. Thus it was concluded[4] that the products obtained from the cleavage of I, as well as the products obtained from the previous cleavage reactions[5] involving DPCC, resulted from thermodynamic control of the cleavage reaction.

These results are consistent with at least two mechanisms. Attack of cyanide ion on I would provide the primary cleavage products in either case. The primary cleavage products could then equilibrate *via* either: (a) the unsymmetrical disulfide by attack of the mercaptide on the sulfur atom of the thiocyanate (Fig. 1), or (b) nucleophilic addition of the mercaptide to the carbon atom of the thiocyanate to yield the intermediate VIII (Fig. 2). Decomposition of VIII would be expected to provide an excess of the mercaptide of greater anionic stability, in this case II,

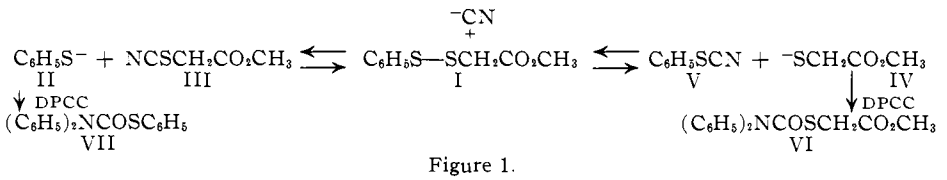



Figure 1.

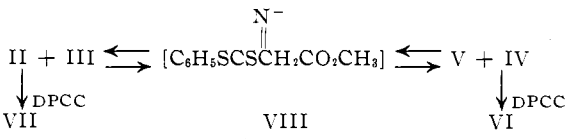
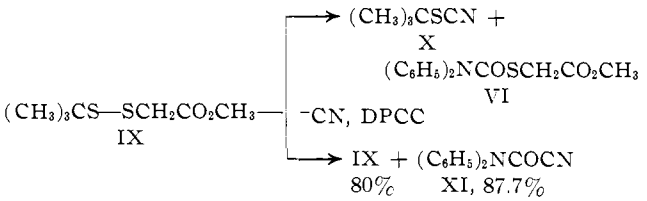
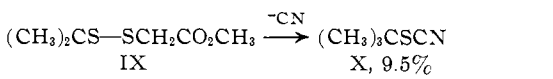



Figure 2.

and the corresponding thiocyanate III. Reaction of the equilibrium quantities of the mercaptides, produced by either path a or b, with DPCC would yield VI and VII.

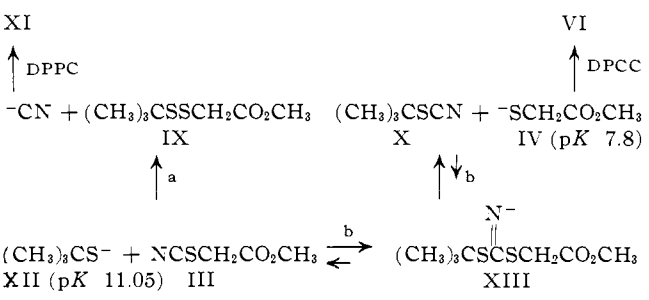
It appeared likely that a study of the recombination reactions of the primary cleavage products of methyl 5,5-dimethyl-3,4-dithiahexanoate (IX) could be utilized to distinguish between paths a and b (Fig. 1, 2). Despite the large "$\Delta pK_a$" value of IX (3.25), treatment with cyanide ion and DPCC provided only recovered IX and N,N-diphenylcarbamylnitrile (XI) rather than the anticipated products *t*-butyl thiocyanate (X) and VI. Presumably the lack of reactivity of IX is the result of a "neopentyl-type" steric effect which suppresses the rate of nucleophilic attack on the *t*-butyl sulfur atom to the point where the competing reaction of cyanide ion with DPCC is the more rapid reaction. Support for this suggestion was obtained by treatment of IX with cyanide in the absence of DPCC. A 9.5% yield of X was obtained under these conditions.[6]

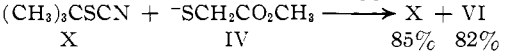


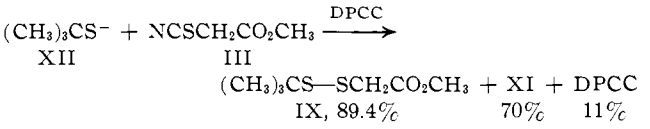

No attempt was made to isolate the mercaptide IV from the reaction mixture.

Since IX was recovered unchanged from the reaction with cyanide in the presence of DPCC, presumably IX could be isolated from a reaction between the least stable mercaptide, *t*-butylmercaptide (XII), and methyl thiocyanoacetate (III) if equilibria of the type shown in Fig. 1 (path a) represented the reaction mechanism. Alternatively, if the mechanism involved path b (Fig. 2) the reaction between XII and III should yield the more stable mercaptide, sodium carbomethoxymethyl mercaptide (IV), and *t*-butyl thiocyanate (X). The mercaptide IV would react with DPCC to provide the thiocarbamate derivative VI. That the reaction between X and IV would not be expected to provide IX in the presence of DPCC could be readily demonstrated. Incubation of X and IV with 1 equivalent of DPCC afforded an 85% yield of recovered X and 82% of VI. No trace of IX could be detected in the vapor fractogram of the reaction mixture.




The reaction between XII and III, however, would be expected to provide IX *via* path a or X and VI if the intermediate XIII were involved in the process (path b). When XII and III were allowed to react in the presence of 1 equivalent of DPCC, the unsymmetrical disulfide IX was obtained in 89.4% yield. A 70% yield of XI and 11% of recovered DPCC also resulted. The vapor fractogram of the reaction mixture exhibited no peaks corresponding to X or III. Distillation of the reaction mixture provided IX, identical in all respects to an authentic sample.




The formation of IX is consistent with path a and does not support path b. Thus the equilibration of the primary cleavage products obtained from I probably proceeds as shown in Fig. 1. These data indicate that the reaction of a mercaptide with a thiocyanate may proceed faster than the mercaptide–DPCC reaction. Therefore the nature of the cleavage products ultimately obtained does not necessarily reflect the initial site of nucleophilic attack on the unsymmetrical disulfide.[7]

The assumption that the low order of reactivity of the disulfide bond of IX was due to a "neopentyl-type" steric effect is supported by several earlier studies. Fava, *et al.*,[8] have investigated the effect of increasing $\alpha$-alkylation on the rate of nucleophilic attack on a sulfur atom. The reaction rates of several

(6) Unless otherwise noted all cleavage reactions were conducted in purified acetonitrile for 11 hr. at 50°. A single equivalent of cyanide ion and DPCC were utilized.

(7) The validity of this statement for nucleophiles and mercaptide scavengers other than cyanide ion and DPCC remains to be established although it might be anticipated.

(8) A. Fava and A. Iliceto, *J. Am. Chem. Soc.*, **80**, 3478 (1958); A. Fava, A. Iliceto, and E. Camera, *ibid.*, **79**, 833 (1957).

TABLE I

PRODUCTS FROM MERCAPTIDE–THIOCYANATE REACTIONS IN THE PRESENCE OF N,N-DIPHENYLCARBAMYL CHLORIDE

| Expt. | Reactants | RSCN | $RSSCH_2CO_2CH_3$ | $(C_6H_5)_2NCOSCH_2CO_2CH_3$ (VI) | $(C_6H_5)_2NCON$ | $(C_6H_5)_2NCOCl$ (DPCC) |
|---|---|---|---|---|---|---|
| A | $(CH_3)_3CSCN$ (X) + $^-SCH_2CO_2CH_3$ (IV) | 85.5 | 0 | 82 | 0 | 0 |
| B | $(CH_3)_3CS^-$ (XII) + $NCSCH_2CO_2CH_3$ (III) | 0 | 89.4 | 0 | 70 | 11.5 |
| C | $(CH_3)_2CHSCN$ (XVII) + $^-SCH_2CO_2CH_3$ (IV)[a] | 80.1 | 14.4 | 88.2 | 2.7 | 0 |
| D | $(CH_3)_2CHSCN$ (XVII) + $^-SCH_2CO_2CH_3$ (IV)[b] | 64.8 | 8.4 | 44.6 | 8.4 | 33.8 |
| E | $(CH_3)_2CHSCN$ (XVII) + $^-SCH_2CO_2CH_3$ (IV) | 70 | 14.2 | 63.6 | 5 | 16.9 |
| F | $(CH_3)_2CHS^-$ (XIX) + $NCSCH_2CO_2CH_3$ (III) | 65 | 8.2 | 27 | 22 | 33.9 |
| G | $(CH_3)_2CHCH_2S^-$ (XX) + $NCSCH_2CO_2CH_3$ (III) | 94 | 5.4 | 82 | | |

[a] 1.2 moles of mercaptide used. [b] 0.85 mole of mercaptide used.

sulfur-containing systems were compared with the corresponding carbon compounds and the SN2 rates were found to be similar. Thus the ratio of R = methyl to R = *t*-butyl in both systems was found to be about $10^5$. The ratio of rates of R = methyl to R = isopropyl was found to be 30 for the carbon system and 140 for sulfur. These data led to the proposal that nucleophilic attack on a bivalent sulfur atom occurs backside to the leaving group and along the axis of the sulfur–sulfur bond. Recently Pryor and Pickering[9] have observed similar rate profiles in the chain-transfer reaction of several symmetrical disulfides with polystyryl radicals.

$$SO_3^{-2} + RSSO_3^- \longrightarrow RS\text{-}SO_3^- + SO_3^{-2}$$

$$RS^- + RSSR \longrightarrow RSSR + RS^-$$

$$Y + RCH_2X \longrightarrow RCH_2Y + X^-$$

The single published example of the steric requirements of nucleophilic cleavage of an unsymmetrical disulfide appears to be that of McAllan, *et al.*[10] These workers noted that treatment of 3,4-dithiahexane (XIV) with *t*-butyl mercaptide (XII) provided the unsymmetrical disulfide XV, rather than di-*t*-butyl disulfide.

$$(CH_3)_3CS^- \text{ (XII)} + [CH_3CH_2S]_2 \text{ (XIV)} \longrightarrow (CH_3)_3CS\text{—}SCH_2CH_3 \text{ (XV)}$$

In view of the limited amount of information concerning the effect of increasing $\alpha$-alkylation on the nucleophilic cleavage of unsymmetrical disulfides, several disulfides and their primary cleavage products were studied. Initially the cyanide cleavage of methyl 5-methyl-3,4-dithiahexanoate (XVI) was compared with IX. Since the cyanide–DPCC reaction is more rapid than the reaction of cyanide ion with IX, the isopropyl disulfide (XVI) was also cleaved in the absence of DPCC. Analysis of the reaction mixture in the vapor fractometer indicated the presence of 52.8% isopropyl thiocyanate (XVII), 5.7% dimethyl 3-thiaglutarate (XVIII), and 11.9% of recovered XVI.

$$(CH_3)_2CHS\text{—}SCH_2CO_2CH_3 \text{ (XVI)} \xrightarrow{^-CN} (CH_3)_2CHCCN \text{ (XVII, 52.8\%)} + [CH_3O_2CCH_2\text{—}]_2S \text{ (XVIII, 11.4\%)} + \text{XVI (11.9\%)}$$

Similar results were obtained when either XVII and IV or sodium isopropyl mercaptide (XIX) and III were allowed to react. As previously stated, the cyanide cleavage of IX provided 9.5% of *t*-butyl thiocyanate (X). However, the reaction of X with IV

$$(CH_3)_2CHSCN \text{ (XVII)} + {}^-SCH_2CO_2CH_3 \text{ (IV)} \longrightarrow \text{XVII (53.8\%)} + \text{XVIII (31.8\%)} + \text{XVI (8.5\%)}$$

$$(CH_3)_2CHS^- \text{ (XIX)} + NCSCH_2CO_3CH_3 \text{ (III)} \longrightarrow \text{XVII (47.8\%)} + \text{XVIII (36.2\%)} + \text{XVI (9.4\%)}$$

$$(CH_3)_3CS\text{—}SCH_2CO_2CH_3 \text{ (IX)} \xrightarrow{^-CN} (CH_3)_3CSCN \text{ (X, 9.5\%)}$$

$$(C_3H)_3CSCN \text{ (X)} + {}^-SCH_2CO_2CH_3 \text{ (IV)} \longrightarrow \text{IX (35\%)} + \text{X (45\%)}$$

provided 35% of the unsymmetrical disulfide IX. The increased amount of attack on the *t*-butyl sulfur atom in X in these cases may reflect the greater "S-nucleophilicity" of a mercaptide as compared to cyanide ion.

An indication of the relative reactivity of several $\alpha$-alkylated unsymmetrical disulfides toward cyanide ion could be obtained by a comparison of the amount of unsymmetrical disulfide produced by the reaction of the primary cleavage products in the presence of DPCC. The reactions and products are given in Table I. Qualitatively it is apparent from these data that the amount of unreacted unsymmetrical disulfide produced increases with increasing $\alpha$-alkylation (expt. G, E, B). Presumably this reflects a decrease in the reactivity of the unsymmetrical disulfide caused by increasing $\alpha$-substitution. Thus the data are in qualitative agreement with the steric requirements previously observed[8,9] in other molecules containing sulfur.

$$RS^- + NCSCH_2CO_2CH_3 \rightleftharpoons RS\text{—}SCH_2CO_2CH_3 \rightleftharpoons \overset{+}{} \; ^-CN$$

$$RSCN + {}^-SCH_2CO_2CH_3 \xrightarrow{DPCC} \text{VI}$$

The formation of the symmetrical sulfide XVIII in the absence of DPCC was somewhat unexpected. Although XVIII was produced in 77% yield by incubation of III and IV, XVIII could also have conceivably been formed by attack of IV on the unsymmetrical disulfide XVI. The latter possibility could be eliminated since the treatment of XVI with IV under the

(9) W. A. Pryor and T. L. Pickering, *J. Am. Chem. Soc.*, **84**, 2705 (1962).
(10) D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *ibid.*, **73**, 3627 (1951).

$$CH_3O_2CCH_2SCN + {}^-SCH_2CO_2CH_3 \longrightarrow [CH_3O_2CCH_2\!\rightarrow\!{}_2S + {}^-SCN$$
III IV XVIII, 77%

$$(CH_3)_2CHS{-}SCH_2CO_2CH_3 + IV \longrightarrow XVIII$$
XVI <2%

cleavage conditions provided only trace amounts of XVIII. Thus the symmetrical sulfide probably arises from the reaction of III and IV.

From the difference in stability of the sodium isopropyl mercaptide (XIX) and sodium carbomethoxymethyl mercaptide (IV), the unsymmetrical disulfide XVI would be expected to provide only IV and XVII if the cleavage yielded the more stable products. Therefore the thiocyanate III should not be present. Thus the formation of XVIII is inconsistent with initial attack of cyanide ion on the more negatively polarized sulfur atom of XVI to afford the more stable mercaptide IV. However, the formation of XVIII is readily rationalized by the assumption that initial nucleophilic attack occurs on the more positively polarized sulfur atom of XVI to provide initially the more basic mercaptide XIX and the thiocyanate III. Recombination and subsequent cleavage to provide the more stable mercaptide IV would ultimately produce an equilibrium mixture of XVI and the four possible primary cleavage products. Competition between XIX and IV for III would lead to the observed products.

$$(CH_3)_2CHSCN + {}^-SCH_2CO_2CH_3 \rightleftharpoons (CH_3)_2CHS{-}SCH_2CO_2CH_3 \rightleftharpoons (CH_3)_2CHS^- + NCSCH_2CO_2CH_3$$
XVII IV XVI XIX III

$$\xrightarrow{{}^-CN} [CH_3O_2CCH_2\!\rightarrow\!{}_2S + {}^-SCN$$
XVIII

Nucleophilic attack on the more positively polarized sulfur atom of an unsymmetrical disulfide to provide initially the least stable mercaptide may also occur in cleavage reactions utilizing mercaptide scavengers. Since the reaction of alkyl mercaptides with III were shown to proceed in the presence of DPCC (expt. B, F, G, Table I), the alkyl mercaptides would not have been detected even if produced by cyanide cleavage. Experiments involving more efficient mercaptide scavengers are reported in the accompanying manuscript.[11]

## Experimental[12]

**Methyl 5,5-dimethyl-3,4-dithiahexanoate (IX)** was prepared as previously described[13] in 60% yield, b.p. 39° at 0.06 mm., $n^{25}D$ 1.4980, $d^{25}$ 1.0963; MR calcd. 52.21, found 52.00.

**Methyl 5-methyl-3,4-dithiahexanoate(XVI)** was prepared in 61% yield by the sulfenyl thiocyanate method[13]; b.p. 39° at 0.02 mm., $n^{25}D$ 1.5027, $d^{25}$ 1.1206; MR calcd. 47.40, found 47.40.

*Anal.* Calcd. for $C_6H_{12}O_2S_2$: C, 39.96; H, 6.70; S, 35.50. Found: C, 39.87; H, 6.53; S, 35.06.

**Methyl 6-methyl-3,4-dithiaheptanoate** was prepared in 76.5% yield by the sulfenylthiocyanate method[13]; b.p. 50° at 0.5 mm., $n^{25}D$ 1.4972, $d^{25}$ 1.0836; MR calcd. 52.02, found 52.05.

*Anal.* Calcd. for $C_7H_{14}O_2S_2$: C, 43.26; H, 7.26; S, 33.00. Found: C, 43.08; H, 7.03; S, 33.43.

***t*-Butyl thiocyanate (X)** was prepared in 80% yield from *t*-butyl chloride and ammonium thiocyanate by the procedure of Schmidt, *et al.*[14] The product contained 73.5% *t*-butyl thiocyanate and 26.5% *t*-butyl isothiocyanate as determined by the vapor fractometer. The mixture boiled at 30° at 20 mm., reported[13] b.p. 31° at 10–30 mm.

**Isobutyl thiocyanate** was prepared in 55.4% yield from isobutyl bromide and potassium thiocyanate according to the procedure of Terent'ev and Gershenovich.[15] The product was collected at 57–58.8° (8 mm.); reported[14] b.p. 58° at 8 mm.

**Reaction of Potassium *t*-Butyl Mercaptide (XII) with Methyl Thiocyanoacetate (III) in the Presence of N,N-Diphenylcarbamyl Chloride (DPCC).**—The mercaptide was prepared by dispersing 0.79 g. (0.02 g.-atom) of potassium in 100 ml. of dry xylene at 70°, followed by the dropwise addition of 1.804 g. (0.02 mole) of *t*-butyl mercaptan over a 3-hr. period. A 0.5-g. excess of mercaptan was required to consume the potassium. The xylene was decanted, the mercaptide washed by decantation with ether and suspended in 50 ml. of acetonitrile. The mercaptide suspension was added directly to a solution containing 2.62 g. (0.02 mole) of methyl thiocyanoacetate and 4.63 g. (0.02 mole) of N,N-diphenylcarbamyl chloride in 200 ml. of acetonitrile. The solution immediately turned yellow and a fine suspension separated. The mixture was stirred 11 hr. at 50°, the potassium chloride removed, and the solution evaporated. Trituration of the remaining solid with ether afforded 3.04 g. (70%) of N,N-diphenylcarbamyl nitrile, m.p. 121–126°. Removal of the ether *in vacuo* gave a clear oil which was dried and analyzed on the vapor fractometer. The determination indicated the presence of 3.47 g. (89.4%) of IX. Distillation of the oil afforded 2.14 g. (54.8%) of disulfide, $n^{25}D$ 1.4990. An infrared spectrum of the distillate was identical with that of an authentic sample. An additional 0.53 g. (11.6%) of N,N-diphenylcarbamyl chloride was isolated from the pot residue.

**Reaction of Sodium Carbomethoxymethyl Mercaptide (IV) with *t*-Butyl Thiocyanate (X) in the Presence of N,N-Diphenyl-**

TABLE II

VAPOR CHROMATOGRAPHY CONDITIONS FOR CALIBRATION CURVES[a]

| Compound | Standard | Column temp., °C. | Flow rate, ml. He/min. | Retention time,[b] sec. |
|---|---|---|---|---|
| $CH_3O_2CCH_2SCN$[c] | $C_6H_5CH_2CO_2C_2H_5$ | 150 | 40 | 170 |
| $(CH_3)_3CSCN$[c] | $C_6H_5CH_3$ | 50 | 12 | 39[d] |
| $(CH_3)_3CNCS$[c] | $C_6H_5CH_3$ | 50 | 12 | 72[d] |
| $(CH_3)_3CSSCH_2CO_2CH_3$[c] | $C_6H_5CH_3$ | 140 | 12 | 39[d] |
| $(CH_3)_2CHSCN$ | $C_6H_5CH_3$ | 75 | 24 | 180 |
| | $C_6H_5CO_2C_2H_5$ | 95 | 60 | 87 |
| $(CH_3)_2CHCH_2SCN$ | $C_6H_5CH_3$ | 80 | 30 | 170 |
| $(CH_3)_2CHSSCH_2CO_2CH_3$ | $C_6H_5CO_2C_2H_5$ | 150 | 30 | 140 |
| | $C_6H_5CO_2C_2H_5$ | 125 | 60 | 418 |
| $(CH_3)_2CHCH_2SSCH_2CO_2CH_3$ | $C_6H_5CO_2C_2H_5$ | 150 | 30 | 140 |
| $CH_3O_2CCH_2SCH_2CO_2CH_3$ | $C_6H_5CO_2C_2H_5$ | 135 | 60 | 636 |

[a] Calibration curves were obtained on an F and M Model 500 vapor fractometer using a detector flow rate of 18–24 ml./min. unless otherwise noted. [b] The retention times given were obtained from the calibration solution of the particular compound. The retention times were found to vary from run to run; however, the times were internally consistent relative to the pure component. [c] A column of 4.0% Carbowax 400 on Chromosorb P (30/60 mesh) was used. In all other experiments reported in Table I a column of 4.0% Carbowax 400 on Chromosorb P (60/80) mesh was employed. [d] Perkin–Elmer Model 154C vapor fractometer with Brown recorder.

(11) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, **86**, 2014 (1964).

(12) Boiling points are uncorrected. Elemental analyses by Micro-Tech Laboratories, Skokie, Ill.

(13) 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).

(14) E. Schmidt, W. Striewsky, M. Seefelder, and F. Hitzer, *Ann.*, **568**, 192 (1950).

(15) A. P. Terent'ev and A. I. Gershenovich, *Zh. Obshch. Khim.*, **23**, 204 (1953).

**carbamyl Chloride.**—The mercaptide was prepared by addition of 2.44 g. (0.02 mole) of methyl mercaptoacetate to 0.460 g. (0.02 g.-atom) of sodium in 4 ml. of absolute methanol. The solution was added to 100 ml. of anhydrous ether and the solid washed by decantation with ether. The mercaptide IV was suspended in 60 ml. of acetonitrile and added to a solution containing 2.32 g. (0.02 mole) of *t*-butyl thiocyanate (X, present as 3.17 g. of an oil containing 73.3% thiocyanate and 26.7% isothiocyanate) and 4.63 g. (0.02 mole) of N,N-diphenylcarbamyl chloride in 200 ml. of acetonitrile. The reaction mixture was stirred 10 hr. at 45–50° under nitrogen.

Isolation of the products in the manner previously described afforded 4.92 g. (82%) of the N,N-diphenylthiocarbamate derivative of methyl mercaptoacetate (VI), m.p. 113–114°. Analysis of the liquid portion in the vapor fractometer indicated 1.98 g. (85.5%) of *t*-butyl thiocyanate (X); 0.8 g. (94%) of *t*-butyl isothiocyanate was recovered unchanged. No other peaks were noted using either the thiocyanate or methyl 5,5-dimethyl-3,4-dithiahexanoate calibration conditions.

**General Conditions for Cyanide Cleavage and Recombination Reactions.**—The cyanide cleavage and recombination reactions were carried out in purified acetonitrile using the conditions previously described.[5] Sodium isopropyl mercaptide (XIX) and sodium isobutyl mercaptide (XX) were prepared by the method previously described for sodium carbomethoxymethyl mercaptide (IV).[5] In reactions involving DPCC a single equivalent was used. Analysis of the reaction mixtures were performed using either an F and M Model 500 vapor fractometer with a Honeywell recorder or a Perkin–Elmer Model 154C vapor fractometer with a Brown recorder. Glass columns (4 mm., 22 in.) were packed with 4.0% Carbowax 400 on Chromosorb P (60/80 mesh) or in some cases 30/60 mesh. Yields of the volatile products were obtained from standard calibration curves of each pure component. Ethyl benzoate and toluene were used as internal standards. The calibration conditions and retention times of the various components are shown in Table II. The nonvolatile reaction products were isolated by crystallization and compared with authentic samples.

**Formation of Dimethyl 3-Thiaglutarate (XVIII) from III and IV.**—A suspension of 0.640 g. (0.005 mole) of freshly prepared mercaptide IV in 25 ml. of acetonitrile was treated with 0.656 g. (0.005 mole) of III. The suspension was stirred under a nitrogen atmosphere for 12 hr. at 50°. The brown solid (0.250 g.) was filtered and the acetonitrile removed *in vacuo*. Analysis of the remaining oil (0.766 g.) in the vapor fractometer indicated the presence of 77.8% of XVIII. An infrared spectrum of the oil was identical with that of an authentic sample.[11]

**Reaction of Methyl 5-Methyl-3,4-dithiahexanoate (XVI) with Sodium Carbomethoxymethyl Mercaptide (IV).**—A solution containing 0.450 g. (0.0025 mole) of XVI in 75 ml. of acetonitrile was treated with a suspension of 0.320 g. (0.0025 mole) of IV in 75 ml. of acetonitrile. After 12 hr. at 50° the vapor fractogram of the reaction mixture showed the presence of 28.4% XVI, 2.0% XVIII, as well as considerable amounts of dimethyl 3,4-dithiaadapate (XXI). The symmetrical disulfide XXI was identified by comparison of the retention time with that of an authentic sample.

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

# Chemistry of Aliphatic Disulfides: VII. Cyanide Cleavage in the Presence of Thiocyanates[1,2]

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RECEIVED SEPTEMBER 25, 1963

Cleavage of several unsymmetrical disulfides containing a *t*-butyl group was conducted in the presence of phenyl or benzyl thiocyanate. In the examples studied cyanide ion was found to attack the more positively polarized sulfur atom and displace *t*-butyl mercaptide. The mercaptide was scavenged by the added thiocyanate and was obtained as a new unsymmetrical disulfide.

In the preceding paper[2] the equilibria established during cleavage of an unsymmetrical disulfide with cyanide ion was shown to involve the primary cleavage products and the unsymmetrical disulfide (eq. 1) rather than another type of adduct formed by recombination of the primary cleavage products.

$$R'S^- + RSCN \rightleftharpoons \underset{\displaystyle +\ {}^-CN}{R'S{-}SR} \rightleftharpoons R'SCN + RS^- \qquad (1)$$

Earlier experiments on the cleavage of unsymmetrical aryl alkyl[3] and dialkyl[4] disulfides in the presence of a mercaptide scavenger suggested that cyanide cleavage gave the more stable mercaptide (the mercaptan of lower $pK_a$) and the corresponding thiocyanate as the predominant products. The extent of selective attack appeared to depend on the relative anionic stability of the two mercaptans comprising the disulfide. For example, methyl 5-phenyl-3,4-dithiapentanoate (I), "$\Delta pK_a$" 1.63,[5] provided a 53.8% yield of the more stable mercaptide, sodium carbomethoxymethyl mercaptide (III) (isolated as the N,N-diphenylthiocarbamate derivative IV), 43.7% of the corresponding thiocyanate II, and 4.2% of methyl thiocyanoacetate (V). A similar cleavage of methyl 3,4-dithiadecanoate

$$\underset{\text{I}}{C_6H_5CH_2S{-}SCH_2CO_2CH_3} \xrightarrow[(C_6H_5)_2NCOCl]{{}^-CN} \underset{\text{II}}{C_6H_5CH_2SCN} + \underset{\text{V}}{CH_3O_2CCH_2SCN} + \underset{\text{IV}}{(C_6H_5)_2NCOSCH_2CO_2CH_3}$$

(VI), "$\Delta pK_a$" 2.86, gave only the more stable mercaptide III (also isolated as IV) and *n*-hexyl thiocyanate.

$$\underset{\text{VI}}{CH_3(CH_2)_5S{-}SCH_2CO_2CH_3} \xrightarrow[(C_6H_5)_2NCOCl]{{}^-CN} CH_3(CH_2)_5SCN + \underset{83.2\%}{\text{IV}}\ (68\%)$$

The results[4] obtained from the cyanide cleavage reactions using N,N-diphenylcarbamyl chloride (DPCC) were in agreement with the previous[3,6] conclusion that the bond-breaking step in nucleophilic cleavage of the sulfur–sulfur bond, rather than the bond-forming step, is of major importance. Since the scavengers used were presumably efficient mercaptide traps, these results implied that initial nucleophilic attack on an unsymmetrical disulfide occurred on the more electron-dense sulfur. Thus the more stable mercaptide ion was displaced. However, several

(1) Supported by research grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, United States Public Health Service.

(2) Part VI of this series: R. G. Hiskey, W. H. Bowers, and D. N. Harpp, *J. Am. Chem. Soc.*, **86**, 2010 (1964).

(3) A. J. Parker and N. Kharasch, *ibid.*, **82**, 3071 (1960).

(4) R. G. Hiskey and F. I. Carroll, *ibid.*, **83**, 4644 (1961).

(5) The "$\Delta pK_a$" value of a symmetrical disulfide is zero.

(6) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).