Acknowledgment.—The author wishes to thank the National Science Foundation (GP-1704) and the National Institutes of Health (GM-14062) for supporting this research.

Chemistry of Aliphatic Disulfides. XIV. The Preparation of Disulfide Sulfoxides by Selective Oxidation[1-3]

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As part of an over-all program designed to produce and study unsymmetrical disulfides and related sulfur-containing peptide derivatives [1,6] it became desirable to investigate the selective oxidation of substrates containing a thio ether group and a disulfide bond. Although numerous examples of sulfoxide formation *via* oxidation of appropriate thioethers are found in the chemical literature [7-9] no report has appeared in which such an operation was successfully carried out in the presence of a disulfide bond within the same molecule.

Preliminary experiments indicated that chromium trioxide in acetic acid solution was satisfactory for the oxidization of simple diaryl thioethers such as benzhydryl phenyl sulfide (I) and benzhydryl benzyl sulfide[1] (II) to the corresponding sulfoxides, III and IV (eq 1). However, when N-(2-benzhydrylthio-

$$(C_6H_5)_2CHSC_6H_5 \xrightarrow[HOAc]{CrO_3} (C_6H_5)_2CH\overset{\uparrow O}{S}C_6H_5$$
I III, 68.5%

$$(C_6H_5)_2CHSCH_2C_6H_5 \xrightarrow[HOAc]{CrO_3} (C_6H_5)_2CH\overset{\uparrow O}{S}CH_2C_6H_5 \quad (1)$$
II IV, 58%

ethyl)-5-phenyl-4,5-dithiapentanoic amide[1] (V) was treated with this reagent, extensive decomposition occurred. Attempts to oxidize V with either hydrogen peroxide or *m*-chloroperbenzoic acid also resulted in decomposition of the starting material. N-(2-benzhydrylsulfinylethyl)-5-phenyl-4,5-dithiapentanoic amide (VI) was eventually prepared in 71% yield by treating a methanolic solution of V with an aqueous solution of sodium metaperiodate[10] (eq 2). The di-

$$C_6H_5SSCH_2CH_2CONHCH_2CH_2SCH(C_6H_5)_2 \xrightarrow[CH_3OH,\ 0°]{NaIO_4}$$
V

$$C_6H_5SSCH_2CH_2CONHCH_2CH_2\overset{\uparrow O}{S}CH(C_6H_5)_2 \quad (2)$$
VI, 71%

sulfide sulfoxide, VI, could also be prepared independently as outlined in eq 3 and 4. 2-Benzhydrylthioethylammonium chloride[1] (VII) was treated with so-

$$Cl^-H_3{}^+NCH_2CH_2SCH(C_6H_5)_2 \xrightarrow[\text{aqueous } CH_3OH]{NaIO_4}$$
VII

$$Cl^-H_3{}^+NCH_2CH_2\overset{\uparrow O}{S}CH(C_6H_5)_2 \quad (3)$$
VIII

$$C_6H_5SSCH_2CH_2CO_2H + \text{VIII} \xrightarrow[WSC]{Et_3N} \text{VI, 55\% (2 steps)} \quad (4)$$
IX

dium metaperiodate in aqueous methanol to produce 2-benzhydrylsulfinyl ethylammonium chloride (VIII). This chromatographically pure foam was coupled with 5-phenyl-4,5-dithiapentanoic acid[6] (IX) in the presence of 1 equiv of triethylamine and WSC to give a 55% yield of VI.

The application of this specific oxidative procedure to a bisdisulfide thioether was made possible by the availability of N-[N-carboxy-3-[[2-[3-(phenyldithio)-propionamido]ethyl]dithio]-L-alanyl]-DL-methionine N-benzyl ethyl ester (X).[11] The oxidation of X under conditions similar to those used to prepare VI yielded N-[N-carboxy-3-[[2-(3-(phenyldithio)propionamido]ethyl]dithio]-L-alanyl]-DL-methionine-*dl*-sulfoxide N-benzyl ethyl ester (XI). This reaction, as well as an alternate route to XI, is presented in Scheme I. Ethyl DL-methionate hydrochloride (XII) was prepared from DL-methionine by treatment with anhydrous hydrogen chloride in ethanol. The oxidation of XII with sodium metaperiodate was conducted in the usual manner, but the hydrochloride could not be isolated in a pure form. Consequently, the oxalate salt was prepared; ethyl DL-methionate-*dl*-sulfoxide oxalate (XIII) was isolated following treatment of the crude hydrochloride with triethylamine in ethyl acetate and addition of an equivalent of oxalic acid. Coupling N-carboxy-3-[[2-[3-(phenyldithio)propionamido]ethyl]dithio]-L-alanine N-benzyl ester[6] (XIV) and the free amine (which had been liberated from XIII by treatment with barium hydroxide solution) in the presence of WSC produced XI.

In addition to the novelty of the disulfide sulfoxides and the unique methods of preparation, the stability of VI and XI indicates that intramolecular interactions between sulfoxide and disulfide species are probably insignificant. This could not be firmly established prior to the synthesis of materials containing both functions.

The successful preparation of these sulfoxides stimulated an attempt to reverse the procedure and reproduce the starting thioethers, V and X, by a selective reduction process. Initial studies involving the established reduction methods disclosed no report of a sulfoxide which was selectively reduced in the presence of a disulfide bond. Although Iselin[12] had demonstrated

(1) Part XIII of this series: R. G. Hiskey and M. A. Harpold, *Tetrahedron*, in press.

(2) Supported by Research Grant RG-7966 from the National Institute of General Medical Sciences of the National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been incorporated into the text: WSC = 1-ethyl-3-(3-N,N-dimethylaminopropyl)carbodiimide hydrochloride, and Ox^- = oxalate.

(4) Abstracted in part from a dissertation submitted by M. A. Harpold to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, June 1967.

(5) National Science Foundation Cooperative Fellow, 1964–1966.

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

(7) R. Knoll, *J. Prakt. Chem.*, **113**, 40 (1926).

(8) S. Hünig and O. Boes, *Ann. Chem.*, **579**, 23 (1953).

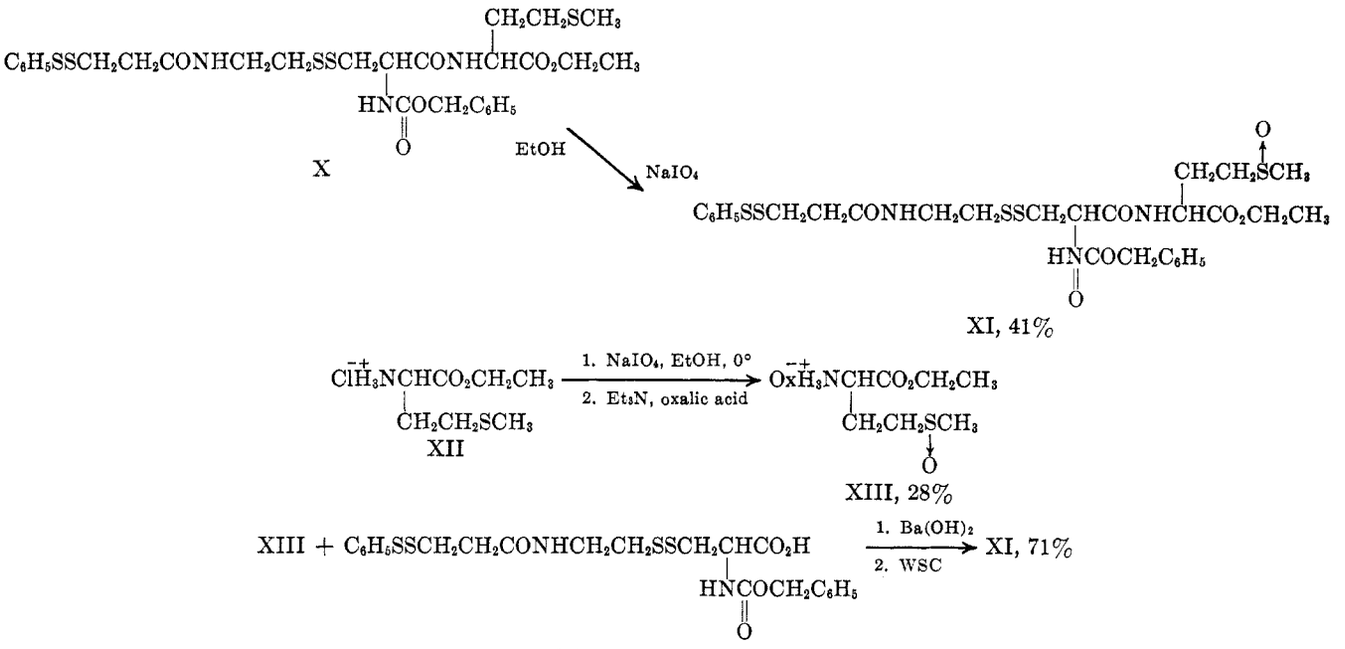
(9) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(10) Essentially the method previously used by Leonard and Johnson;[9] only slight modifications in this original procedure were required.

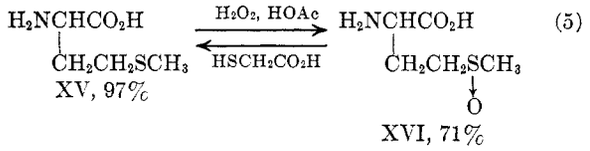
(11) R. G. Hiskey and M. A. Harpold, manuscript in preparation.

(12) B. M. Iselin, *Helv. Chim. Acta*, **44**, 61 (1961).

SCHEME I

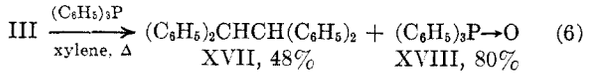


that L-methionine-*dl*-sulfoxide could be efficiently reduced with thioglycolic acid in aqueous medium, this method had not been extended to peptide derivatives containing disulfide bonds. The preparation of DL-methionine-*dl*-sulfoxide (XVI) and subsequent reduction to D,L-methionine (XV) (eq 5) corroborated



(5)

Iselin's results, but, when applied to XI, the thioglycolic acid reduction method resulted in complete decomposition of the starting material. Attempts to reduce the thioether function of VI by reaction with triphenylphosphine in chloroform[13] or by the thioglycolic acid procedure resulted in extensive decomposition. The former method produced a 6% yield of V, but apparently all of the starting material was destroyed. Attempts to modify the triphenylphosphine reduction procedure failed to give increased yields of the desired thioether. One such modification involved treatment of III with triphenylphosphine in refluxing xylene; no I was obtained, but 1,1,2,2,-tetraphenylethane (XVII) and triphenylphosphine oxide (XVIII) were isolated from the reaction mixture (eq 6).



(6)

Experimental Section[14]

Benzhydryl phenyl sulfoxide (III) was prepared in 68.5% yield by the procedure described by Knoll,[7] mp 122–123° (lit.[7] mp 139°).

Anal. Calcd for $C_{19}H_{16}OS$: C, 78.05; H, 5.52; S, 10.96. Found: C, 78.21; H, 5.47; S, 10.94.

Benzhydryl benzyl sulfoxide (IV) was prepared by the general procedure of Knoll.[7] A solution of 1.45 g (5 mmoles) of II in 24 ml of acetic acid was stirred at 75° and treated with a solution of 0.50 g (5 mmoles) of chromium trioxide in 6 ml of water. The heating was continued and the green solution was allowed to reflux; after 20-min total reaction time the reaction mixture was cooled and the crude product was precipitated by the addition of 100 ml of water. The precipitate was collected, dried *in vacuo*, and recrystallized from ethanol. The product appeared as 0.89 g (58%) of white solid: mp 125.5–126.5°; homogeneous on tlc (system A); ν_{max}^{KBr} 3050, 2950, 1600, 1480, 1440, 1060, 1020, 745, 690 cm^{-1}. An additional recrystallization failed to raise the melting point.

Anal. Calcd for $C_{20}H_{18}OS$: C, 78.39; H, 5.92; S, 10.46. Found: C, 78.46; H, 6.06; S, 10.52.

N-(2-Benzhydrylsulfinylethyl)-5-phenyl-4,5-dithiapentanoic amide (VI) was prepared by adding a solution of 4.50 g (0.021 mole) of sodium metaperiodate in 100 ml of water to a stirred mixture of 8.80 g (0.02 mole) of V in 300 ml of methanol The temperature was maintained at 0–5° throughout the 0.5-hr addition and for 3 hr following the addition. At this time, 100 ml of methanol was added and stirring was continued for 5 hr wihtout cooling. The yellow-white mixture was cooled and filtered, and the residue was washed with methanol. The combined filtrate was concentrated *in vacuo* and dried *in vacuo*, and the crude product was trituated with boiling chloroform, treated with decolorizing charcoal, and filtered. The filtrate was applied to a 2.5 × 80 cm column of silica gel (150 g, 0.05–0.2 mm). The chromatography was monitored by tlc and the desired material was eluted from the column with a gradient solvent system of ethyl acetate-chloroform (1:1) to ethyl acetate. After removal of the solvent *in vacuo*, the white solid residue was recrystallized from carbon tetrachloride–*n*-hexane. The product appeared as 6.48 g (71%) of white solid: mp 130–131°; homogeneous by tlc (system A); ν_{max}^{KBr} 3380, 1660, 1540, 1490, 1250, 1040, 1020, 755, 695 cm^{-1}; τ 2.80 (16.2 H, m), 5.15 (1.0 H, s), 6.45 (1.8 H, m), 7.42 (5.5 H, m).

(13) J. P. A. Castrillón and H. H. Szmant, *J. Org. Chem.*, **30**, 1338 (1965).

(14) Melting points are uncorrected and were obtained in capillary tubes or with a Kofler melting point apparatus when the range desired exceeded 200°. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Thin layer chromatograms were conducted on microscope slides and on 5 × 20 and 20 × 20 cm Pyrex plates using uniform coatings of silica gel GF_{254}. The chromatograms were developed with iodine vapor and/or viewed under ultraviolet light. Solvent systems for tlc were benzene–dioxane–acetic acid (90:25:4, system A), 1-butanol–acetic acid–water (4:1:5, system B), chloroform–methanol (9:1, system C), and chloroform–benzene (1:1, system D). Paper chromatography was ascending and employed Whatman No. 1 paper with solvent system B. Commercial reagents were of the highest quality available and were purified as necessary. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter, using a glass cell. Nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as the internal standard. Mass spectra were recorded on a Hitachi–Perkin-Elmer RMU-6E mass spectrometer.

Anal. Calcd for $C_{24}H_{25}NO_2S_3$: C, 63.26; H, 5.53; N, 3.07; S, 21.11. Found: C, 63.32; H, 5.70; N, 3.16; S, 20.97.

Material which is identical was prepared in 86% yield by allowing 592 mg (2 mmoles) of VIII, 0.28 ml (2 mmoles) of triethylamine, 420 mg (2.2 mmoles) of WSC, an 428 mg (2 mmoles) of IX to react at 0° in 10 ml of methylene chloride. After 1.5 hr at ice temperature, the reaction mixture was allowed to stir for 2 hr without cooling, diluted by addition of 100 ml of methylene chloride, and washed with 100-ml portions of water, 2 *N* sulfuric acid, water, 2% sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying, the solution was concentrated *in vacuo* to 10 ml and applied to a 1.5 × 40 cm column of silica gel (40 g, 0.05–0.2 mm). The chromatography was monitored as previously described and the identical purification process provided 785 mg, mp 129–130°. A mixture melting point was not depressed.

An attempt to prepare VI by the chromium trioxide–acetic acid method described previously for III and IV was successful, but inefficient; less than 5% of product, mp 131–132°, resulted.

2-Benzyhydrylsulfinylethylammonium chloride (VIII) was prepared by addition of a solution of 2.25 g (0.0105 mole) of sodium metaperiodate in 50 ml of water to a solution of 2.80 g (0.01 mole) of VII in 150 ml of ethanol at 0°. The addition required 15 min and stirring was continued for 12 hr while the reaction mixture was warming slowly to room temperature. The mixture was cooled and filtered, and the combined washings and filtrate were concentrated *in vacuo* to a white solid. The residue was triturated with boiling chloroform–ethyl acetate (3:1) and filtered, and the filtrate was diluted with *n*-hexane. The small amount of oily precipitate was discarded and the supernatant was concentrated *in vacuo* to a white foam. This material was dissolved in methanol and filtered, and the product was precipitated by the addition of ethyl ether. Trituration with ether yielded 1.9 g (64%) of hygroscopic white solid: mp 90–95°; homogeneous by tlc (system B); ν_{max}^{KBr} 3400–2400, 1980, 1602, 1490 1450, 1020, 745, 700 cm^{-1}. Two additional triturations failed to raise the melting point.

Anal. Calcd for $C_{15}H_{18}ClNOS$: C, 60.90; H, 6.13; N, 4.74; S, 10.84. Found: C, 59.92; H, 6.29; N, 4.74; S, 10.00.

Repeated attempts to improve the elemental analysis were unsuccessful although the melting point could be raised to 99–101° by dissolving the triturated product in tetrahydrofuran and precipitating the material with ethyl ether. This chromatographically pure material was used in the preparation of VI.

Preparation of N-[N-Carboxy-3-[[2-[3-(phenyldithio)propionamido]ethyl]dithio]-L-alanyl]-DL-methionine-*dl*-sulfoxide N-Benzyl Ethyl Ester (XI). A. *Via* Coupling.—To a stirred solution of 170 mg (0.6 mmole) of XIII in 2 ml of water was added sufficient saturated barium hydroxide solution to make the reaction mixture basic to phenolphthalein. After stirring for 2–3 min, the reaction mixture was filtered to remove the insoluble barium oxalate. The amine was partitioned between chloroform and saturated sodium chloride solution. Evaporation of the dried organic layer provided 63 mg of crude amine as an oil.

The crude amine was dissolved in 3 ml of methylene chloride and treated with a solution containing 132 mg (0.25 mmole) of XIV and 57.5 mg (0.3 mmole) of WSC in 2 ml of methylene chloride. The reaction mixture was stirred at 0° for 2.5 hr and at room temperature for an additional 2.5 hr. The reaction mixture was washed with 50-ml portions of water, 2 *N* sulfuric acid, water, and saturated sodium chloride solution. Evaporation of the dried organic extract provided a viscous oil which was dried and dissolved in ethyl acetate and precipitated with *n*-hexane. The oil was separated by decantation and triturated to obtain a tacky solid which was dried, redissolved in ethyl acetate, and reprecipitated with *n*-hexane. The oil was triturated with hot ethyl ether; addition of *n*-hexane to the ether supernatant provided 20 mg of solid, mp 78–81°. The ether-insoluble oil was dissolved in chloroform and applied to a 1.5 × 40 cm column of silica gel (40 g, 0.05–0.2 mm). The elution was monitored by tlc (system D) and the major component was removed with 10% methanol in chloroform. Removal of solvent provided an oil which was crystallized from a large volume of ether–*n*-hexane: 145 mg, mp 80–82°. The combined solids were recrystallized from ethyl acetate–*n*-hexane to yield 124 mg (71%) of product: mp 83–85°; ν_{max}^{KBr} 3370, 3050, 2950, 1730, 1650, 1530, 1400, 1245, 1050, 740, 695 cm^{-1}; $[\alpha]^{24}D$ −6.2° (*c* 0.5 chloroform).

Anal. Calcd for $C_{29}H_{33}N_3O_7S_5$: C, 49.62; H, 5.60; N, 5.99; S, 22.84. Found: C, 49.83; H, 5.67; N, 6.06; S, 22.74.

B. *Via* Oxidation.—A stirred mixture of 137 mg (0.2 mmole) of X in 20 ml of ethanol at 0° was treated with 1.1 ml (0.22 mmole) of 0.2 *M* sodium metaperiodate solution. The reaction mixture was stirred at 0–5° for 18 hr and filtered, and the filtrate was concentrated *in vacuo* to a yellow film. A chloroform solution of this material was applied to a 1.5 × 40 cm column of silica gel (40 g, 0.05–0.2 mm). The elution was monitored by tlc (system D) and the major product was obtained as an oil after removal of the solvent *in vacuo*. The oil was crystallized from ethyl acetate–*n*-hexane to yield 57.4 mg (41%) of white solid: mp 83.5–85°; homogeneous on tlc with mobility equal to product from the coupling route. A mixture melting point was not depressed.

Ethyl DL-methionate hydrochloride (XII) was prepared by the addition of 29.85 g (0.02 mole) of DL-methionine to a saturated solution of hydrogen chloride in 200 ml of anhydrous ethanol at ice temperature. The reaction mixture was allowed to warm slowly while stirring overnight and a clear solution was observed after 12 hr. The solution was refluxed for 1 hr and the solvent was removed *in vacuo* to yield a viscous yellow oil which solidified upon drying *in vacuo*. The solid was recrystallized from ethyl acetate to produce a white powder: mp 73–75°; ninhydrin positive, but tlc (system B) indicated a trace of sulfoxide. The yield of material of this purity was 39.2 g (92%). An analytical sample was prepared by two more recrystallizations from ethyl acetate: mp 79–81°; homogeneous on tlc (lit.[15] mp 56°).

Anal. Calcd for $C_7H_{16}ClNO_2S$: C, 39.33; H, 7.55. Found: C, 39.44; H, 7.70.

Ethyl DL-methionate-*dl*-sulfoxide oxalate (XIII) was prepared from 2.4 g (0.01 mole) of XII and 2.24 g (0.0105 mole) of sodium metaperiodate in aqueous ethanol by the general procedure. The free amine was generated by allowing the oily product from the standard work-up to react with 1.4 ml (0.01 mole) of triethylamine in 50 ml of ethyl acetate. After the mixture had stirred for 0.5 hr, 50 ml of methylene chloride was added and stirring was continued for 0.5 hr. The reaction mixture was filtered and evaporated to a viscous oil which was washed with *n*-hexane and dissolved in an ethyl acetate–methylene chloride mixture. A solution of 0.90 g (0.01 mole) of oxalic acid in methylene chloride–ethyl acetate (1:1) was added to the solution of the amine. The yellow oil which precipitated was triturated with *n*-hexane, dried *in vacuo*, and crystallized from chloroform–ethanol to yield 1.3 g of white solid: mp 102–105°. Two additional recrystallizations gave 0.8 g (28%) of product: mp 120–121°; homogeneous by paper chromatography; ν_{max}^{KBr} 3500, 3300–2400, 2010, 1720, 1230, 1000 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO_7S$: C, 38.15; H, 6.05; N, 4.95; S, 11.32. Found: C, 37.92; H, 6.18; N, 4.92; S, 11.47.

DL-Methionine-*dl*-sulfoxide (XVI) was prepared in 71% yield by the procedure of Lepp and Dunn,[16] with minor modification: mp 225–228°. The product was recrystallized twice from ethanol–water to give mp 231–236° (lit.[17] mp 220–230° dec).

Chemical Reduction of DL-Methionine-*dl*-sulfoxide.—An adaptation of the method of Iselin[12] was used to convert the sulfoxide into the analogous thio ether. A solution of 1.65 g (1 mmole) of XVI in 45 ml of water was treated with 4.6 g (50 mmoles) of thioglycolic acid[18] and the resultant solution was stirred at 50° (±1°) for 12 hr. The reaction mixture was diluted with 100 ml of ethanol and concentrated *in vacuo* below 40° to a viscous oil. The dried oil was treated with absolute ethanol to yield 1.45 g (97%) of product: mp 240–250° dec. A paper chromatogram indicated that the material was homogeneous and had a mobility equal to DL-methionine. One recrystallization from water–ethanol gave product with mp 241–243° dec. A mixture melting point with a freshly crystallized sample of authentic material (mp 250–255°) was 248–251° dec.

Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43. Found: C, 39.70; H, 7.40.

Atempted Reduction of XI.—When a solution of XI in ethanol was treated with thioglycolic acid in the general manner described for the reduction of XVI, tlc (system A) indicated at least three components. The mixture could not be resolved by column chromatography.

(15) F. Hoffmann-LaRoche and Co., A.-G., Swiss Patent 251,251 (July 16, 1948).

(16) A. Lepp and M. Dunn, "Biochemical Preparations," Vol. 4, New York, N. Y., John Wiley and Sons, Inc., 1955, p 80.

(17) G. Toennies, *Science*, **88**, 545 (1938).

(18) Freshly distilled, bp 148–150° (50 mm of Hg), and bottled under nitrogen.

Attempted Reduction of VI.—When VI was subjected to the conditions of Iselin[12] or Castrillón and Szmant,[13] decomposition of the substrate resulted. The former procedure provided 31% the starting material while the latter method produced a 6% yield of the desired thioether, mp 83–85°. A mixture melting point with authentic V was not depressed.

Attempted Reduction of III with Triphenylphosphine.—A mixture of 0.73 g (2.5 mmoles) of III and 0.78 g (3 mmoles) of triphenylphosphine in 75 ml of xylene was stirred under a gentle reflux for 0.5 hr, cooled, filtered, and concentrated *in vacuo* to 10 ml. The solution was applied to a 2.5 × 40 cm column of silica gel (100 g, 0.05–0.2 mm); elution was monitored by tlc (system D); and two major components were removed and purified. The higher mobility material was eluted from the column with chloroform and was recrystallized from ethanol to yield 100 mg (48%) of 1,1,2,2-tetraphenylethane: mp 210–212° (lit.[19] mp 210°). A mixture melting point with authentic material was not depressed and tlc (system D) mobility was identical. The mass spectra of both materials exhibited a parent ion at *m/e* 334 and successive fragments corroborated the assignment. The lower mobility component required ethyl acetate–chloroform (1:1) for elution and was recrystallized from *n*-hexane to produce 660 mg (80%) of triphenylphosphine oxide: mp 155–156° (lit.[20] mp 154°). Comparison of the infrared spectrum with a published spectrum of triphenylphosphine oxide[21] indicated that two materials were identical. No starting material or phenyl benzhydryl sulfide was observed.

Registry No.—IV, 13641-03-7; VI, 13641-04-8; VIII, 13641-05-9; XI, 13641-06-0; XII, 6297-53-6; XIII, 13698-40-3.

Acknowledgment.—We are indebted to Dr. Kurt L. Loening of the Chemical Abstracts Service for assistance in determining the nomenclature for the bisdisulfide derivatives.

(19) W. T. Nauta and D. Mulder, *Rec. Trav. Chim.*, **58**, 1070 (1939).
(20) H. Straudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
(21) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 835 (1951).

The Synthesis of a Series of 1,1a,3,3a,4,5,5,5a,5b,6-Decachlorooctahydro-4′-Substituted Spiro[1,3,4-metheno-2H-cyclobuta-[*c,d*]pentalene-2,2′-oxazolidin]-5′-ones

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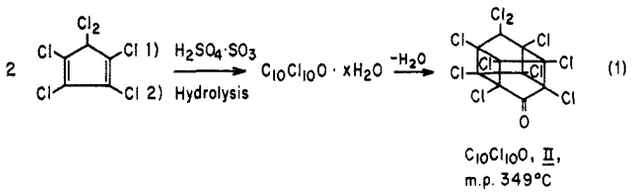
The reaction of hexachlorocyclopentadiene (I) with itself in the presence of fuming sulfuric acid or sulfur trioxide with subsequent hydrolysis gives $C_{10}Cl_{10}O$ (II)[1,2] (Kepone, Allied Chemical Corp; H-1 ketone, Hooker Chemical Corp.). The product is usually isolated as a hydrate with one to four associated water molecules. The parent ketone, mp 349°, can be obtained by azeotropic dehydration with toluene, xylene, etc. The chemistry of II has been reviewed recently[3]



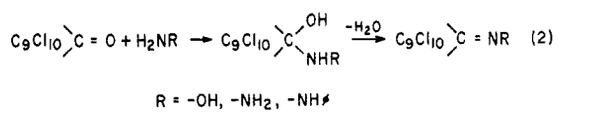
and the structure of the compound has been adequately proven[4,5]

Compound II is particularly effective against chewing insects (fire ants, roaches, soil insects in bait form, and chewing insects that prey ornamentals and potatoes)[6] with an LD_{50} of 126 mg/kg (rat).

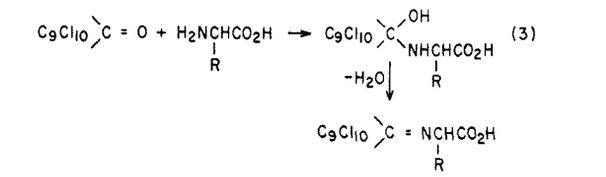
As in the case of many of the other highly chlorinated organic agricultural chemicals, II appears to have inherent residue and toxicity problems. That there is a high level of biological activity in the parent structure seems proven. That utilization of this activity may be of further interest seems apparent by the modifications of structure which have recently been described in the literature.[3,6]

Discussion

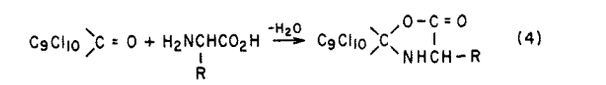
Attempts have been made to form typical ketone derivatives of $C_{10}Cl_{10}O$, oximes, hydrazones, phenylhydrazones, etc., and the initial addition to the carbonyl group takes place. Elimination of water to form the stable derivatives have, as presently known, required azeotropic distillation.[3]



We postulated that by using an amino group adjacent to a carboxyl group we might effect the dehydration to a stable imino structure, carrying also a solubilizing (salt-forming) carboxyl group. $C_{10}Cl_{10}O$ reacts under



azeotropic conditions with α-amino acids to give, with the loss of water, compounds of the type envisioned. However, structure determinations led us to the conclusion that, whereas the product isolated had indeed lost a molecule of water (from the original addition of the amino group to the carboxyl group), the actual loss had been from the reaction of the intermediate hydroxyl compound with the carboxyl group to form a lactone.



This oxazolidinone system appeared chemically stable but did release a free amino group on boiling in

(1) E. E. Gilbert and S. L. Giolito, U. S. Patent 2,616,928 (1952); see Reissue 24,435 (Feb 25, 1958) to Allied Chemical Corp.
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