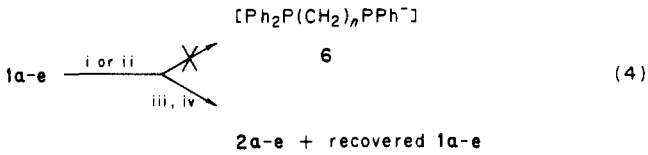
nature of this type of reactions. Because of the heterogeneity, once the monophosphide anion was formed, it became the species that was closest to the Li metal. Therefore, the second P–Ph bond on the same molecule would be cleaved faster than that of another molecule. Therefore, the diphosphines **1a–e** were either doubly cleaved or unreacted (eq 4).



(4)

(i) 2 equiv of Li, ultrasound irradiation; (ii) 2 equiv of K, -78 °C; (iii) *t*-BuCl; (iv) MeI.

In conclusion, the double reductive cleavage of the P–Ph bond of a diphosphine can normally be achieved under mild conditions such as with K at −78 °C or with the less reactive Li at 0 °C at extremely slow rate. Subsequent alkylation gives the disubstituted diphosphine with contamination. Attempted rate enhancement by increasing the reaction temperature is unsatisfactory while ultrasonic irradiation not only accelerates the reaction but also eliminates the formation of side products. The reason why ultrasonic irradiation selectively increases only the rate of the main reaction and not that of the side reactions is still unclear. It is suspected, however, that the main product is derived from a heterogeneous reaction on whose rate the ultrasound irradiation normally has significant influence[10] and that the side reactions may be derived from some type of homogeneous reactions on whose rate the ultrasound has little or no influence.

(10) Suslick, K. S.; Johnson, R. E. *J. Am. Chem. Soc.* **1984**, *106*, 6856 and references cited therein.

Experimental Section

All reactions and workup procedures were manipulated under anhydrous nitrogen atmosphere. All solvents were dried and deoxygenated before use. NMR spectra were recorded on a JEOL C-60-HL NMR spectrophotometer. IR spectra were recorded on a Perkin-Elmer 297 infrared spectrophotometer. MS spectra were taken on a HP 5990B gas chromatograph/mass spectrometer. Elemental analyses were taken at National Taiwan University.

Preparations of the Diphosphines 2a–e and 4a–e. Since the procedures are similar, **2b** is used here as a typical example. To a vial containing finely chopped metal Li (50 mg, 7.2 mmol) in THF (3 mL) cooled at −10 °C was added dropwise bis(diphenylphosphino)propane (dppp) (**1b**) (300 mg, 1.2 mmol) in THF (2 mL). The colorless reaction mixture was put into an ultrasound cleaner kept at 0 °C and irradiated. The reaction was followed by TLC (alumina, hexane/EtOAc) until the starting material was consumed (less than 10 min). The dark red solution was separated from the excess of Li metal, and *t*-BuCl (220 mg, 2.4 mmol) in THF (1 mL) was added immediately at room temperature. No color change was observed at this stage. The resulting solution was again cooled to 0 °C, and as MeI (340 mg, 2.4 mmol) was added, the color faded instantaneously. After the mixture was stirred for another 60 min, water (8 mL) was added, and the layers were separated. The aqueous layer was extracted with benzene (4 × 10 mL). The combined organic layers were dried (Na_2CO_3), concentrated under reduced pressure and purified by flash column chromatography (alumina, benzene), giving the diphosphine **2b**.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support (NSC73-0201-M001C-04).

Registry No. **1a**, 1663-45-2; **1b**, 6737-42-4; **1c**, 7688-25-7; **1d**, 27721-02-4; **1e**, 19845-69-3; **2a**, 23808-01-7; **2b**, 98170-68-4; **2c**, 98170-69-5; **2d**, 98170-70-8; **2e**, 98170-71-9; **4a**, 98170-72-0; **4b**, 98170-73-1; **4c**, 72144-83-3; **4d**, 90116-42-0; **4e**, 98170-74-2; MeI, 74-88-4; $C_6H_{11}Br$, 108-85-0.

Conversion of Thiosulfinate Derivatives of Cystine to Unsymmetrical Cystines and Lanthionines by Reaction with Tris(dialkylamino)phosphines

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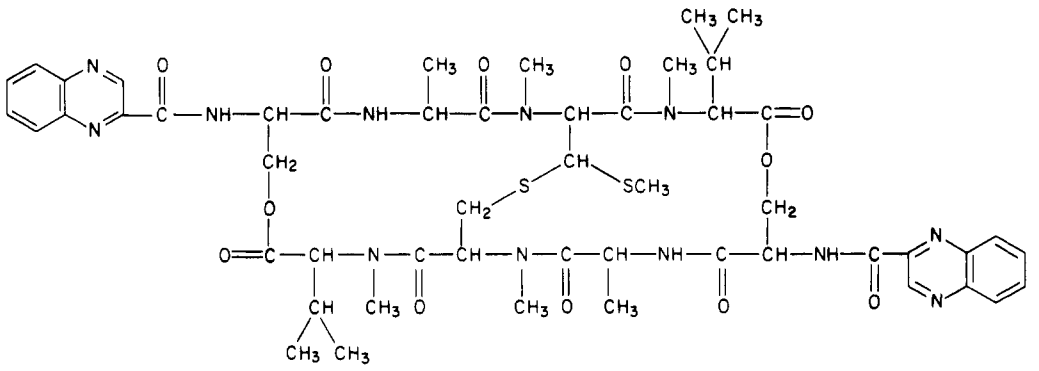
Synthetic routes to the unsymmetrical lanthionines **2** and **3** have been developed. Reaction of a thiosulfinate, derived by oxidation of the corresponding symmetrical cystine with *m*-chloroperbenzoic acid, with a protected cysteine in the presence of a tris(dialkylamino)phosphine, hexaethylphosphorus triamide, yielded an unsymmetrical or mixed cystine. Contraction of the disulfide linkage in the appropriate mixed cystine by reaction with hexaethylphosphorus triamide provided the unsymmetrical lanthionines **2** and **3**. A second route to unsymmetrical lanthionines was investigated that involved the attempted displacement of sulfonate leaving groups from di- or tripeptides containing a serylvaline residue. The sulfonate ester function was observed to be very unreactive toward displacement by mercaptide anion in these peptides, a fact that may be due to steric or conformational effects originating from the adjacent valine residue.

The quinomycin antibiotics[1] are a structurally unique group of cyclic depsipeptides that contain a novel β-methylthiolanthionine as a constituent of the peptide. Echinomycin (**1**), the most prominent of the quinomycins, is known to bind to deoxyribonucleic acids by bifunctional intercalation and to thereby function as a potent inhibitor of RNA synthesis.[2] The antibiotics are known to possess

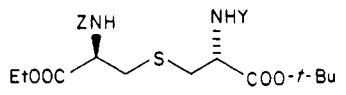
(1) Dell, A.; Williams, D. H.; Morris, H. R.; Smith, G. A.; Feeney, J.; Roberts, G. C. K. *J. Am. Chem. Soc.* **1975**, *97*, 2497. Martin, D. G.; Mizsak, S. A.; Biles, C.; Stewart, J. L.; Baczynskyj, L.; Meulman, P. A. *J. Antibiot.* **1975**, *28*, 332.

(2) Waring, M. J. In "Antibiotics V Part 2: Mechanism of Action of Antileukaryotic and Antiviral Compounds"; Hahn, F. E., Ed.; Springer-Verlag: Heidelberg, 1979; pp 173–194.

0022-3263/85/1950-4332$01.50/0



1, echinomycin

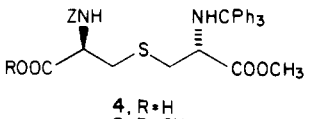


2, Y = COO-t-Bu
3, Y = $COOCH_2CCl_3$

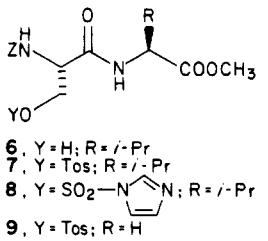
important biological activities, including cytotoxic activity.[3] Pursuant to our interest in the total synthesis of echinomycin, we envisioned beginning the peptide synthesis from an appropriate lanthionine derivative and to couple other peptide fragments to this unit, followed by cyclization and quinoxalation. Earlier studies[4] have established that this approach, starting from a symmetrically substituted lanthionine in which the equivalent pair of amino or carboxyl groups cannot be differentiated, is beset with certain difficulties. We, therefore, desired to have available an appropriate unsymmetrical lanthionine having four different protecting groups on the amino and carboxyl functions so as to allow differentiation in the incorporation of the peptide units and in the subsequent cyclization reactions leading to the bicyclic quinomycin ring system. We report in this paper the synthesis of unsymmetrical lanthionines **2** and **3**, both of which are functionally adapted for use in the above described approach to the quinomycins.

There are no general routes presently available for the preparation of chiral, unsymmetrical substituted lanthionines. Displacement reactions by sulfur nucleophiles on *O*-tosyl-L-serine or β-chloro-L-alanine derivatives have been studied;[5,6] these reactions are often complicated by the formation of racemic products, which are apparently formed by elimination and conjugate addition processes. Attempted disulfide contraction of unsymmetrical cystine derivatives by reaction with tris(dialkylamino)phosphine has been reported[7] to yield symmetrical cystines. This rather surprising result apparently arises as a consequence of the various equilibria attendent with the reaction, which allow equilibration of the alkylthiol groups and, in one case, because of the low solubility, resulted in the precipitation of the symmetrical cystine from the reaction mixture. Subsequent to these studies, the preparation of symmetrical lanthionines by ring opening of chiral aziridines has been reported,[8] though the yields were rather low. This method should be applicable to the synthesis of unsymmetrical lanthionines.

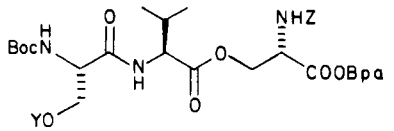
The unsymmetrical lanthionine **4** is a known compound.[9]



4, R = H
5, R = CH_3



6, Y = H; R = *i*-Pr
7, Y = Tos; R = *i*-Pr
8, Y = SO_2—imidazolyl; R = *i*-Pr
9, Y = Tos; R = H



10, Y = H
11, Y = SO_2CH_3

We attempted to prepare **4** to use in our studies; however, in our hands the reported selective saponification of the diester **5** was not successful and a mixture of products was obtained. We therefore decided to investigate other routes to the desired unsymmetrical lanthionines.

We have studied the displacement reactions of the seryl sulfonate esters **7**, **8**, and **11**, which were derived from the di- and tripeptides **6** and **10**. The choice of these peptide derivatives was dictated by the reported[6] lack of elimination and conjugate addition reactions with seryl amide derivatives as compared with the corresponding esters. We therefore desired to have the carboxyl group of serine functionalized as an amide which, because of their respective positions in the quinomycins, would necessitate that valine be attached at the carboxyl group of serine. Dipeptide **6** was prepared by condensation of *N*-(benzyloxycarbonyl)-L-serine with L-valine methyl ester. The corresponding tosylate **7** and imidazolyl sulfonate **8**[10] were prepared by standard procedures. Attempted displacement of the sulfonate group in either **7** or **8** with benzyl mercaptide in dimethylformamide resulted in no reaction occurring and in the recovery, in good yield, of the *O*-sulfonyl dipeptide. We attribute this lack of reactivity in

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(4) Olsen, R. K.; Kini, G. D., unpublished results.
(5) Zioudrou, C.; Wilchek, M.; Patchornik, A. *J. Org. Chem.* **1966**, *31*, 2865.
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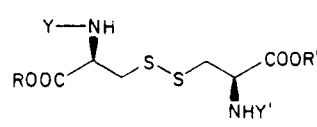
(7) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 73.
(8) Nakajima, K.; Oda, H.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 520.
(9) Photaki, I.; Samouilidis, I.; Caranikas, S.; Zervas, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2599.
(10) Hanessian, S.; Vatele, J. M. *Tetrahedron Lett.* **1981**, *22*, 3579.

peptides 7 and 8 to a steric or conformational effect due to the isopropyl group of the valine residue. Support for this hypothesis is the fact that the *O*-tosyl derivative **9** of (*Z*)-Ser-Gly-OMe readily undergoes displacement by benzyl mercaptide under the same conditions as used above.[6] Examination of space-filling molecular models of the above dipeptide indicates that conformations exist in which the isopropyl group of the valine residue does sterically hinder nucleophilic displacement of the serine tosylate.

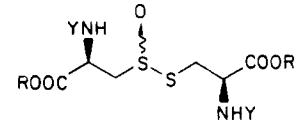
Tridepsipeptide **10** was obtained by coupling the known didepsipeptide *N*-(benzyloxycarbonyl)-*O*-[*N*-(butyloxycarbonyl)-L-valyl]-D-serine *p*-bromophenacyl ester[11] with *N*-(*tert*-butyloxycarbonyl)-L-serine. Similar steric or conformation crowding of the seryl hydroxyl function also was observed for **10**. Attempts to prepare the tosylate derivative of **10** were not successful and lead to recovered tridepsipeptide. The less sterically demanding mesylate derivative **11** could be prepared. However, attempts to effect substitution of the mesylate by benzyl mercaptide failed and mesylate **11** was recovered in good yield.

We now turned our attention to the possibility of preparing unsymmetrical lanthionines by phosphine-mediated disulfide contraction on suitable thiosulfinates derived from cystine derivatives. Thiosulfinates are readily prepared by oxidation of disulfides.[12,13] Reaction of thiosulfinates with alkyl thiols is known to furnish an unsymmetrical disulfide.[13] Our rationale for studying the sulfur contraction of thiosulfinates was that attack at the sulfenyl sulfur by the phosphine would liberate a weak nucleophile, a sulfenic acid, and at that point in the reaction the only other reactive nucleophile present would be the added cysteine. Nucleophilic displacement by the cysteinyl sulfur at carbon of the intermediate phosphonium ion would provide the desired unsymmetrical lanthionine, while displacement at the sulfur atom of the phosphonium ion would give the unsymmetrical cystine. An alternative sequence of reactions is possible, however, in which an acid–base reaction between the phosphine and the cysteine sulfhydryl group would generate a mercaptide ion, which then effects nucleophilic displacement at the sulfenyl sulfur of the thiosulfinate to yield an unsymmetrical cystine. That such a pathway is plausible is supported by the known reactivity of mercaptide nucleophiles toward thiosulfinates. The anion of thiophenyl has been reported to react 2.1×10^6 times faster than the secondary amine, piperidine, in displacement reactions on thiosulfinates.[14] Comparable data for tris(dialkylamino)phosphines is, to our knowledge, not available.

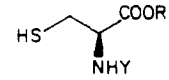
Cystine **12**, upon oxidation with *m*-chloroperbenzoic acid (MCPBA), furnished the corresponding thiolsulfinate **17** in good yield. Reaction of **17** with 1 equiv of the tris(dialkylamino)phosphine hexaethylphosphorus triamide and cysteine **19** in benzene at room temperature gave the corresponding unsymmetrical cystine **14**. None of the desired lanthionine **2** was formed as shown by lack of any absorption in the ^{1}H NMR at δ 3.0 due to the methylene hydrogens adjacent to sulfur; the analogous hydrogens in the corresponding cystine are deshielded slightly and occur at 3.2 ppm. To the best of our knowledge, this is the first example of the use of a thiosulfinate in the synthesis of an unsymmetrical cystine.



12, R = R' = Et; Y = Y' = Z
13, R = R' = *t*-Bu; Y = Y' = Toc
14, R = Et, Y = Z, R' = *t*-Bu; Y' = Boc
15, R = Et; Y = Z, R' = *t*-Bu; Y' = Toc
16, R = R' = *t*-Bu; Y = Y' = Boc



17, R = Et; Y = Z
18, R = *t*-Bu; Y = Toc



19, Y = Boc; R = *t*-Bu
20, Y = Z; R = Et
21, Y = Toc; R = *t*-Bu

Use of an excess of the tris(dialkylamino)phosphine was studied with the expectation that, in a one-pot reaction, the initially formed cystine would undergo contraction to the desired unsymmetrical lanthionine. Rather surprisingly, reaction of thiosulfinate **17** with 3 equiv of the phosphine gave only the unsymmetrical cystine in reduced yields of 15–22%. None of the lanthionine was isolated, nor was likely formed, since we have observed the cystine and lanthionine to coelute in all chromatographic systems we have used.

We have found the most satisfactory procedure for preparation of the unsymmetrical lanthionines **2** and **3** is by a two-step sequence involving first the formation of the unsymmetrical cystine by reaction of the thiolsulfinate with 1.1 equiv of phosphine and cysteine, followed, in a second reaction, by contraction of the cystine to the unsymmetrical lanthionine using 1.1–2.5 equiv of phosphine in benzene. Thus, reaction of thiolsulfinate **17** and cysteine **19** provided cystine **14** in 43–55% yields, which, upon contraction, gave lanthionine **2** in yields of 25–52%. In the above reactions, small amounts of the symmetrical cystines **12** and **16** were isolated and identified by TLC and NMR analysis.

Lanthionine **3** was prepared in a similar fashion. Thiolsulfinate **18** was transformed in a yield of 54% to the unsymmetrical cystine **15** by treatment with the above tris(dialkylamino)phosphine and cysteine **20** in benzene. A more convenient route to cystine **15** involved reaction of the cysteine **21** with thiosulfinate **17** in the presence of the phosphine, in which a 65% yield of **15** was obtained. In a second reaction, **15** underwent disulfide contraction using 2.5 equiv of the tris(dialkylamino)phosphine to provide lanthionine **3** in a yield of 58%. Use of only 1.1 equiv of phosphine reagent resulted in an incomplete reaction to furnish in a mixture of **15** and **3**.

The cysteine derivatives **19** and **20** employed in the above studies were prepared by reduction of the corresponding cystines with zinc in 5% acetic acid in ether. In each case, the cysteine was obtained in nearly quantitative yields and was used as such without further purification. For the preparation of cysteine **21**, attempted reduction of the disulfide bond in **13** with zinc in 5% acetic acid in ether, conditions which should leave the 2,2,2-trichloroethoxycarbonyl (Toc) group intact, resulted in no reaction occurring. Cysteine **21** was obtained, however, in quantitative yield by reduction of cystine **13** with tri-*n*-butylphosphine in aqueous methanol.[15]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were

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(12) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3921.
(13) Schoberl, A.; Tausent, H.; Grafje, H. *Angew. Chem.* **1956**, *68*, 213. Small, L. D.; Bartey, J. H.; Cavallito, C. J. *J. Am. Chem. Soc.* **1947**, *69*, 1710.
(14) Kice, J. L.; Liu, C.-C. A. *J. Org. Chem.* **1979**, *44*, 1918.
(15) Erickson, B. W.; Khan, S. A. *J. Am. Chem. Soc.* **1981**, *103*, 7374.

recorded on a Varian EM-360 or JEOL FX-90 spectrometer. Satisfactory NMR data were obtained for all compounds and data for selected intermediates are reported. The format of the data report is: chemical shift (in δ units), multiplicity (s = single, d = doublet, t = triplet, m = multiplet), integral intensity, and source. Solvents were removed in vacuo on a Buchler rotary evaporator. Thin-layer chromatography was performed on commercially available silica gel plates; Whatman MK6F-1 × 3", silica gel 40 Å, with fluorescent indicator; components were located under ultraviolet irradiation and with iodine vapors. The solvent systems used were (A) hexane–acetone, 8:2, (B) hexane–acetone, 7:3, and (C) hexane–acetone, 6:4. Medium-pressure liquid chromatography (MPLC) was performed on columns packed with silica gel 60 (0.040–0.064 mm).

The amino acids, their derivatives, coupling reagents, and other chemicals used were obtained from commercial sources. The THF used was distilled from sodium benzophenone ketyl. DMF was distilled over CaH_2 and stored over appropriate molecular sieves. CH_2Cl_2 was distilled over P_2O_5. All other solvents used were distilled in glass prior to use.

Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

***N,N'*-Bis(benzyloxycarbonyl)-L-cystine Diethyl Ester (12).** To L-cystine diethyl ester dihydrochloride (7.38 g, 20 mmol) dissolved in H_2O (400 mL) and cooled to 0 °C in ice–salt bath was added $NaHCO_3$ (6.72 g, 80 mmol) slowly, with stirring. To the cold solution was added benzyl chloroformate (8.6 mL, 60 mmol) dropwise and the reaction mixture stirred at 0 °C for 1 h followed by stirring at room temperature for 5 h. The reaction mixture was saturated with NaCl and extracted with ethyl acetate (4 × 100 mL). The combined organic phase was washed with H_2O (100 mL) and dried over Na_2SO_4. Removal of solvent in vacuo resulted in a white solid, which was crystallized from ethyl acetate–petroleum ether to yield 9.8 g (88%) of **12**: mp 81–83 °C; reported mp 86 °C;[16] TLC (solvent $CHCl_3$) R_f 0.21.

***N,N'*-Bis[[(2,2,2-trichloroethyl)oxy]carbonyl]-L-cystine Di-*tert*-butyl Ester (13).** To L-cystine di-*tert*-butyl ester dihydrochloride[17] (1.28 g, 3.0 mmol) in H_2O (100 mL), cooled to 0 °C in ice–salt bath, was added $NaHCO_3$ (1.01 g, 12 mmol) and the mixture stirred for 5 min. 2,2,2-Trichloroethyl chloroformate (1.91 g, 9.0 mmol) was added dropwise to the cold mixture, which was stirred at 0 °C for 2 h and room temperature for 5 h. The reaction mixture was acidified in cold with 6 N HCl, saturated with NaCl, and extracted with ethyl acetate (4 × 25 mL). The combined organic phase was washed with H_2O, saturated aqueous NaCl and dried over Na_2SO_4. Removal of solvent led to an oil, which was purified on MPLC to yield 1.76 g (84%) of **13**: TLC (solvent B) R_f 0.56, $[\alpha]^{25}_D$ +5.46° (*c* 2.2, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.5 (s, 18 H, *tert*-butyl ester Me's), 3.2 (d, 4 H, cystine methylenes), 4.6 (m, 2 H, α-H's), 4.8 (s, 4 H, (trichloroethyl)oxycarbonyl methylenes), 6.0 (d, 2 H, NH's). Anal. Calcd for $C_{20}H_{30}N_2S_2Cl_6O_8$: C, 34.14; H, 4.27; N, 3.98; S, 9.10. Found: C, 34.27; H, 4.38; N, 3.85; S, 9.03.

***N*¹-(Benzyloxycarbonyl)-*N*²-(*tert*-butyloxycarbonyl)-L-cystine Ethyl *tert*-Butyl Diester (14).** To the thiolsulfinate **17** (2.31 g, 4.0 mmol) in benzene (40 mL) was added hexaethylphosphorus triamide (0.99 g, 4.0 mmol) under an atmosphere of nitrogen. *N*-(*tert*-Butyloxycarbonyl)-L-cysteine *tert*-butyl ester (1.11 g, 4.0 mmol) was added and the mixture stirred under an atmosphere of nitrogen for 5 h. Solvent was removed in vacuo and the resulting oil purified on the MPLC with 10% acetone in hexane as eluant to give 1.23 g (55%) of **14** as an oil: TLC (solvent B) R_f 0.31; $[\alpha]^{25}_D$ +20.4° (*c* 3, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.3 (t, 3 H, ethyl ester methyl), 1.5 (s, 18 H, Boc and *t*-Bu Me's), 3.2 (t, 4 H, cystine methylenes), 4.3 (q, 2 H, ester methylenes), 4.6 (m, 2 H, α-H), 5.1 (s, 2 H, benzyloxycarbonyl methylenes), 5.4–5.8 (d, 2 H, NH), 7.4 (s, 5 H, benzyloxycarbonyl aromatics). Anal. Calcd for $C_{25}H_{38}O_8N_2S_2$: C, 53.76; H, 6.81; N, 5.02; S, 11.47. Found: C, 54.00; H, 7.00; N, 5.05; S, 11.57.

***N*¹-(Benzyloxycarbonyl)-*N*²-[[(2,2,2-trichloroethyl)oxy]carbonyl]-L-cystine Ethyl *tert*-Butyl Diester (15).** To a solution of thiol sulfinate **18** (2.01 g, 2.8 mmol) in benzene (40 mL), through which nitrogen gas had been bubbled for 5 min, was added hexaethylphosphorus triamide (0.72 g, 3.0 mmol) at room temperature under nitrogen, followed by *N*-(benzyloxycarbonyl)-L-cysteine ethyl ester (0.84 g, 4.0 mmol), and the mixture stirred at room temperature for 8 h. The solvent was removed in vacuo and the resulting oil purified on the MPLC with 10% acetone in hexane as eluant to yield 0.90 g (54%) of **15** as an oil: TLC (solvent hexane–acetone, 9:1) R_f 0.2; $[\alpha]^{25}_D$ +19.4° (*c* 3, $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$) δ 1.3 (t, 3 H, ethyl ester Me), 1.5 (s, 9 H, *tert*-butyl ester Me), 3.2 (d, 4 H, cystine methylenes), 4.3 (q, 2 H, ethyl ester methylenes), 4.6 (m, 2 H, α-H's), 4.8 (s, 2 H, ((trichloroethyl)oxy)carbonyl methylenes), 5.2 (s, 2 H, benzyloxycarbonyl methylenes), 5.9 (dd, 2 H, NH's), 7.4 (s, 5 H, benzyloxycarbonyl aromatics). Anal. Calcd for $C_{23}H_{31}N_2O_8Cl_3S_2$: C, 43.57; H, 4.89; N, 4.42; S, 10.10. Found: C, 43.25; H, 4.96; N, 4.54; S, 9.63.

Alternate Method of Synthesis of 15. To thiolsulfinate **17** (1.03 g, 1.78 mmol) in benzene (20 mL) was added hexaethylphosphorus triamide (0.44 g, 1.78 mmol) under nitrogen. *N*-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-L-cysteine *tert*-butyl ester **21** was added and the mixture stirred under N_2 for 6 h. Solvent was removed in vacuo and the resulting oil purified by MPLC with 10% acetone in hexane to yield 0.70 g (65%) of **15** as an oil. This oil was identical with the one prepared by the previous method.

***N,N'*-Bis(*tert*-butyloxycarbonyl)-L-cystine Di-*tert*-butyl Ester (16).** To a suspension of L-cystine di-*tert*-butyl ester dihydrochloride[17] (1.28, g, 3.0 mmol) in dimethyl formamide (30 mL) was added triethylamine (0.84 mL, 6.0 mmol) and the mixture stirred for 5 min. Di-*tert*-butyl dicarbonate (1.46 g, 6.6 mmol) was added and the reaction mixture stirred at room temperature for 5 h. Solvent was removed in vacuo and the residue partitioned between 1 N HCl (50 mL) and ethyl acetate (75 mL). The organic phase was washed with 1 N HCl (2 × 25 mL), H_2O (25 mL), and brine and dried over Na_2SO_4. Removal of solvent led to an oil which was purified on MPLC with 10% acetone in hexane as the eluting solvent to yield 1.52 g (91%) of **16** as a white solid: mp 97–99 °C; TLC (solvent B) R_f 0.69; $[\alpha]^{25}_D$ +7.49 (*c* 0.85, $CHCl_3$); ^1H NMR (60 MHz, $CDCl_3$) δ 1.5 (s, 36 H, Boc and *t*-Bu Me's), 3.2 (d, 4 H, cystine methylenes), 4.5 (m, 2 H, α-H's), 5.5 (br d, 2 H, NH).

Synthesis of Thiolsulfinate 17. To *N,N'*-bis(benzyloxycarbonyl)-L-cystine diethyl ester (5.04 g, 9.0 mmol) in CH_2Cl_2 (150 mL) cooled to 0 °C in an ice–salt bath was added *m*-chloroperbenzoic acid (1.71 g, 9.9 mmol) slowly with stirring, whereupon the solution turned turbid. The reaction mixture was allowed to warm up to room temperature, upon which a clear solution resulted, and to stand overnight at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and saturated aqueous NaCl (50 mL) and dried over anhydrous Na_2SO_4. Removal of solvent resulted in 5.2 g (100%) of **17** as an oil, which was used for subsequent reaction without purification; TLC (solvent B) R_f 0.15.

Synthesis of Thiolsulfinate 18. To 1.27 g (1.8 mmol) of **13** dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C in an ice–salt bath was added *m*-chloroperbenzoic acid (0.44 g, 2.16 mmol) slowly in portions. The reaction mixture was allowed to warm up to room temperature and to stand at room temperature overnight. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 × 25 mL). The combined organic phase was washed with brine and dried over Na_2SO_4 and the solvent was removed in vacuo to yield 1.12 g (85%) of **18** as an oil. This oil was used without further purification for subsequent reactions; TLC (solvent B) R_f 0.24.

***N*-(*tert*-Butyloxycarbonyl)-L-cysteine *tert*-Butyl Ester (19).** To **16** (2.5 g, 4.65 mmol) in 5% acetic acid in ether (65 mL) cooled to 0 °C in an ice–salt bath was added zinc dust (18.34 g, 282 mmol) slowly in portions over a period of 20 min, after which the mixture was stirred at 0 °C for 2 h. The mixture was filtered and the precipitate washed well with acetic acid. The combined filtrate and washings were concentrated in vacuo and the residue was taken up in 1 N HCl (75 mL). The aqueous phase was extracted with ethyl acetate (75 mL) and the organic phase washed with saturated aqueous NaCl (50 mL). Upon drying over Na_2SO_4 and removal of solvent, 2.51 g (100%) of **19** was obtained as an oil: TLC (solvent $CHCl_3$) R_f 0.7; ^1H NMR (60 MHz, $CDCl_3$) δ 1.5 (s, 18 H, Boc and *t*-Bu Me's), 1.9 (d, 1 H, SH), 3.0 (dd, 2 H,

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cysteine methylenes), 4.5 (m, 1 H, α-H), 5.5 (br d, 1 H, NH). The oil was used in subsequent reactions without further purification.

N-(Benzyloxycarbonyl)-L-cysteine Ethyl Ester (20). To N,N'-bis(benzyloxycarbonyl)-L-cystine diethyl ester (1.69 g, 3.0 mmol) dissolved in a 5% solution of acetic acid in diethyl ether (100 mL), and cooled to 0 °C in an ice–salt bath, was added zinc dust (5.81 g, 180 mmol) slowly, in portions, over a period of 15 min. The mixture was stirred at 0 °C for 2 h and at room temperature for 1 h. The reaction mixture was filtered and the precipitate washed well with acetic acid–ether. The combined filtrate and washings were concentrated in vacuo, and the residue was dissolved in 1 N HCl (50 mL). The aqueous solution was saturated with NaCl and extracted with ethyl acetate (3 × 25 mL). The organic phase was dried over Na_2SO_4 to yield 1.69 g (100%) of title compound as an oil. This oil was used without further purification for subsequent reactions: TLC (solvent A) R_f 0.3; ^{1}H NMR (60 MHz, $CDCl_3$) 1.3 (t, 3 H, ethyl ester Me), 1.9 (d, 1 H, SH), 3.1 (dd, 2 H, cysteine methylenes), 4.3 (q, 2 H, ester methylenes), 4.8 (m, 1 H, α-H), 5.2 (s, 2 H, benzyloxycarbonyl methylenes), 5.9 (br d, 1 H, NH), 7.4 (s, 5 H, benzyloxycarbonyl aromatic).

N-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-L-cysteine *tert*-Butyl Ester (21). To **13** (0.37 g, 0.53 mmol) in 90% aqueous methanol (5 mL) was added tri-*n*-butylphosphine (0.312 g, 1.05 mmol) and the reaction mixture was stirred at room temperature for 5 h. The solvent was removed in vacuo and the residue triturated with ether (10 mL). Removal of ether led to an oil which was purified on a silica gel gravity column with 5% acetone in hexane as the elutant. Compound **21** was obtained, 0.33 g (89%), as an oil: TLC (solvent hexane–acetone, 9:1) R_f 0.3; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.5 (s, 9 H, *tert*-butyl ester Me's), 1.9 (d, 1 H, SH), 3.2 (dd, 2 H, cysteine methylenes), 4.8 (s, 2 H, trichloroethyloxycarbonyl methylenes).

N^1-(Benzyloxycarbonyl)-N^2-(*tert*-butoxycarbonyl)-L,L-lanthionine Ethyl *tert*-Butyl Diester (2). Cystine **14** (0.96 g, 1.74 mmol) and hexaethylphosphorus triamide (0.47 g, 1.91 mmol) in 25 mL of benzene were stirred at room temperature under an atmosphere of nitrogen for 5 h. The solvent was removed in vacuo and the product mixture was purified by MPLC with hexane as the eluting solvent to yield 0.47 g (52%) of lanthionine **2** as an oil: TLC (solvent B) R_f 0.31; $[\alpha]^{25}_D$ +2.3° (*c* 7.9, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.3 (t, 3 H, ethyl ester methyl), 1.5 (s, 18 H, Boc and *t*-Bu Me's), 3.0 (t, 4 H, lanthionine methylenes), 4.3 (q, 2 H, ethyl ester methylenes), 5.2 (s, 2 H, benzyloxycarbonyl methylenes), 5.4–5.8 (d, 2 H, NH), 7.4 (s, 5 H, benzyloxycarbonyl aromatics). Anal. Calcd for $C_{25}H_{38}O_8N_2S$: C, 57.03; H, 7.22; N, 5.32; S, 6.08. Found: C, 56.90; H, 7.31; N, 5.30; S, 6.09.

N^1-(Benzyloxycarbonyl)-N^2-[[(2,2,2-trichloroethyl)oxy]carbonyl]-L,L-lanthionine Ethyl *tert*-Butyl Diester (3). To a solution of **15** (0.33 g, 0.54 mmol) in benzene (15 mL) was added hexaethylphosphorus triamide (0.34 g, 1.36 mmol) dropwise, with stirring, under nitrogen. The reaction mixture was stirred at room temperature overnight, and the solvent was evaporated in vacuo. The oil obtained was purified by MPLC, with 10% acetone in hexane as the eluting solvent, to yield 0.18 g (58%) of **3** as an oil: TLC (solvent hexane–acetone, 9:1) R_f 0.22; $[\alpha]^{25}_D$ +2.4° (*c* 5.7, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.3 (t, 3 H, ethyl ester Me), 1.5 (s, 9 H, *tert*-butyl ester Me), 3.0 (d, 2 H, lanthionine methylenes), 4.2 (q, 2 H, ethyl ester methylenes), 4.6 (m, 2 H, α-H's), 4.8 (s, 2 H, [(trichloroethyl)oxy]carbonyl methylenes), 5.2 (s, 2 H, benzyloxycarbonyl methylenes), 5.9 (dd, 2 H, NH's), 7.4 (s, 5 H, benzyloxycarbonyl aromatics). Anal. Calcd for $C_{23}H_{31}N_2O_8Cl_3S$: C, 45.88; H, 5.15; N, 4.66; S, 5.32. Found: C, 47.16; H, 5.27; N, 4.75; S, 5.59. Two attempts to obtain satisfactory analysis for **3** resulted in % C found to be higher than the calculated value.

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A Theoretical Study of the Homolytic Abstraction of Benzylic Hydrogen

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The activation energies for the abstraction of a hydrogen atom from toluene, 4-chlorotoluene, and *p*-xylene by chlorine and bromine atoms and a methyl radical from toluene have been calculated with the MNDO approximation of molecular orbital theory with complete geometric optimization of both the reactants and the transition states. The results indicate that electron transfer to the attacking radical occurs but that the usual explanation of the polar effect in radical abstraction reactions is not complete.

The most common reaction of free radicals is the abstraction of hydrogen.[1] This reaction has been widely studied. When toluenes serve as the hydrogen donors in this reaction a Hammett correlation is observed.[1] While some radicals give better correlations with σ and others with σ^+, the interpretation of the "polar effect" as generally accepted was first given by Russell.[2] This explanation of the polar effect rests upon the idea of stabilization of the transition-state structure by a polar canonical structure

$$ArCH_3 + \dot{X} \rightarrow \underset{\text{I}}{[Ar\dot{C}H_2\dot{H}\ \dot{X}} \leftrightarrow \underset{\text{II}}{ArC^+H_2\ \dot{H}:X^-}] \rightarrow Ar\dot{C}H_2 + HX$$

This interpretation was based upon the observation that most abstracting radicals correlate with a negative value for ρ in Hammett-type plots; i.e. electron-withdrawing substituents slow the reaction.[3] This polar interpretation of substituent effects seemed strengthened by the discovery that radicals of low electronegativity, *tert*-butyl,[4] 3-heptyl,[5] and undecyl,[6] afforded Hammett correlations with a positive ρ value.

Zavitsas and Pinto[7] proposed that charge separation in the transition state either does not occur or is an unnecessary assumption. These workers argued that the differences in reactivities of a series of substituted toluenes

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