nature of the product are consistent with such a mechanism.

### Experimental Section

The *tert*-butyl amidosulfite 2 prepared by the method of Deyrup and Moyer[2] had bp 60–62° (0.4 mm) [lit.[2] bp 70–75° (0.3 mm)]. Kinetics were followed at 276 nm using a Durham-Gibson stopped-flow spectrophotometer. Optical densities were measured on the photograph of the oscilloscope trace and rate constants determined graphically. The values of $k_\psi$ in Table I are the average of several runs at each acid concentration. Average deviation from the mean is less than 5%. Initial concentration of amidosulfite in kinetic runs was ca. $10^{-3}$ *M*.

**Registry No.**—**2,** 18366-45-5.

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## Sulfur-Containing Polypeptides XVII. The S-Carbomethoxysulfenyl Derivative as a Protective Group for Cysteine[1,2]

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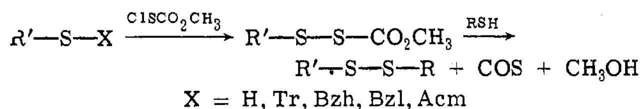
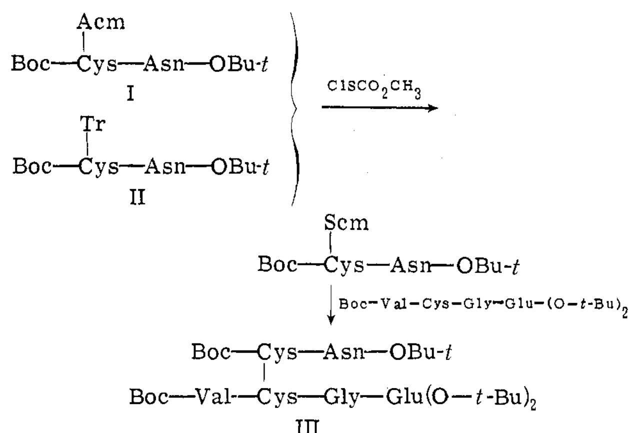
The synthesis of unsymmetrical disulfides via sulfenylthiocarbonates has been reported by Brois et al.[4] In comparison to sulfenyl thiocyanates or sulfenyl iodides, these derivatives of thiols offer the advantage of often being crystalline, stable molecules that yield carbonyl sulfide, methanol, and the disulfide when treated with thiols. Recently,



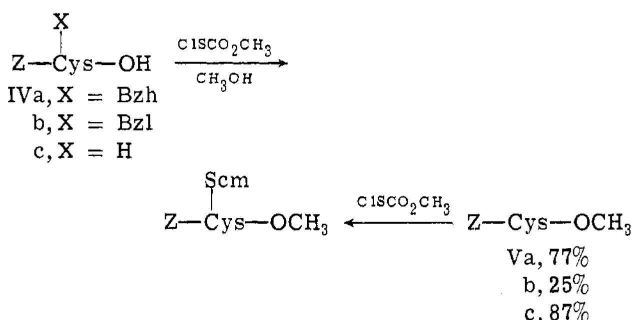
Kamber[5] has shown not only that carbomethoxysulfenyl chloride can be utilized to convert cysteine to the intermediate *S*-carbomethoxysulfenyl derivative[6] but also that the *S*-trityl and *S*-acetamidomethyl derivatives are cleaved by the sulfenyl chloride. Kamber also utilized the method to prepare fully protected open-chain cystine derivatives as illustrated by the conversion of I or II to III.

The present report concerns our studies with the *S*-carbomethoxysulfenyl (Scm) group; these experiments establish that the group is stable to many of the conditions employed for deblocking and coupling operations used in peptide synthesis. Thus, the Scm group can serve as an S-protective group as well as a labile intermediate useful for the selective conversion of a cysteine residue to cystine in the late stage of a synthesis.

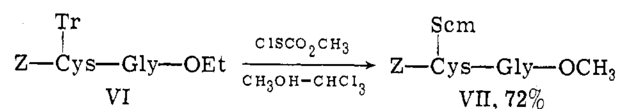
Our preliminary experiments established that the *S*-benzhydryl, *S*-trityl, and (in low yield) the *S*-benzyl



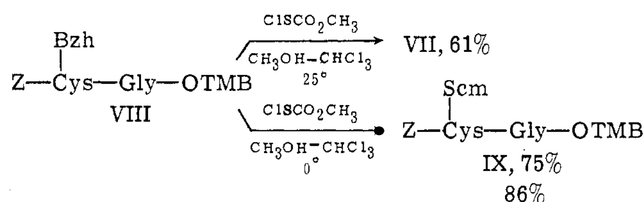
thioethers of cysteine could be converted to the corresponding Scm derivative. However, these experiments also

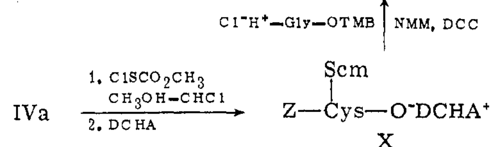


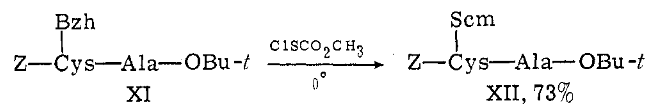
indicated that esterification of free carboxyl groups or transesterification were potential problems. A study of conditions designed to circumvent this problem indicated that esterification or ester interchange could be avoided by conducting the reaction at 0° or by the addition of calcium carbonate to the reaction mixture.[7] The preparation of the di-



peptides IX and XII (both containing acid-labile ester groups) as well as the salt of the carboxylic acid, X, indicated that the undesirable reactions could be suppressed. The

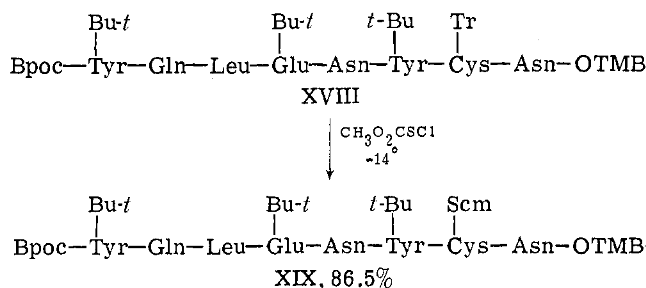




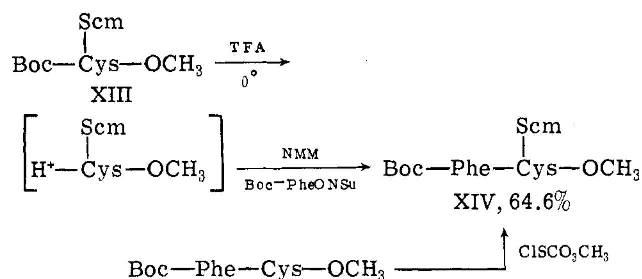


stability of other acid-labile protective groups, used to block certain side-chain functionalities in peptides, toward carbomethoxysulfenyl chloride was indicated by the conversion of the octapeptide derivative (XVIII) to the corresponding Scm peptide (XIX).

The fact that coupling reactions could be successfully conducted in the presence of the Scm group without cleav-

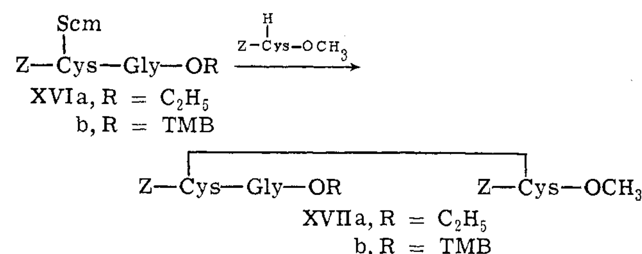


age of the sulfur–sulfur bond was established by the preparation of IX from X and 2,4,6-trimethylbenzyl glycinate. The conversion of XIII to XIV by coupling with *N-tert*-butyloxycarbonyl-L-phenylalanine *N*-hydroxysuccinimide ester indicated that the amino group of *S*-carbomethoxysulfenyl-L-cysteine could also be acylated without loss of the Scm group.



Although intermediate sulfenyl iodides[8] or sulfenyl thiocyanates[9] generated from cysteine derivatives react readily with various thioether, hemithioacetal, and *S*-acetamidomethyl derivatives of cysteine, as well as with cysteine itself, the *S*-carbomethoxysulfenyl derivatives are converted to unsymmetrical disulfides only when treated with thiols. Thus the Scm derivatives are considerably more selective in their reactivity with sulfur nucleophiles than sulfenyl thiocyanates or sulfenyl iodides.

The preparation of the unsymmetrical cystine derivative, XVII, from XVI and methyl *N*-carbobenzoxy-L-cysteinate was also studied in various solvents. In chloroform–metha-



nol (1:1) solvent a 79% yield of XVIIb was obtained in 4 hr; using pyridine 50% of XVIIa resulted in 24 hr together with some *N*-carbobenzoxy-L-cystine methyl ester. Similar results were obtained in trifluoroacetic acid–acetic acid (1:1). When the reaction was conducted in *N,N*-dimethylacetamide for 30 hr a 50% yield of XVIIb was obtained together with a 40% recovery of unreacted XVIb; in DMF only a small amount of XVIIb was produced with substantial amounts of symmetrical disulfide.

## Experimental Section

Melting points are uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Optical rotations were measured using a Perkin-Elmer Model 141 polarimeter. Column chromatography was performed on 0.05–0.20 mm silica gel. Thin layer chromatography was conducted on silica gel GF 254 using the following solvent systems: (A) chloroform–methanol, 9:1; (B) 9.5:0.5; (C) 9.8:0.2; (D) 9.9:0.1. Unless otherwise stated products were dried in vacuo over phosphorus pentoxide.

**Methyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinate (V). A. From Methyl *N*-Benzyloxycarbonyl-L-cysteinate.** A solution of 2.69 g (0.01 mol) of IVc[10] in 50 ml of absolute methanol was treated with 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride[11] in one portion at room temperature and the reaction mixture was stirred for 2 hr. The solvent was removed in vacuo and the residue was triturated with hexane. The hexane was decanted and the resulting gum recrystallized from ethyl acetate–hexane to provide 2.98 g (83%) of V: mp 61°; homogeneous system A, $R_f$ 0.66; $[\alpha]^{25}\text{D} + 17.6°$ (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{14}H_{17}NO_6S_2$: C, 46.78; H, 4.70; N, 17.84. Found: C, 46.90; H, 4.80; N, 17.70.

**B. From *N*-Benzyloxycarbonyl-L-cysteine.** To a solution of 2.55 g (0.01 mol) of *N*-benzyloxycarbonyl-L-cysteine[12] in 50 ml of absolute methanol was added 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride in one portion at room temperature. The reaction mixture was stirred for 3 hr and worked up as described above to yield 3.12 g (87%) of V, identical in all respects with the material produced in A.

**C. From *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteine (IVa).** A suspension of 3.01 g (5.0 mmol) of *N*-benzyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylamine salt[13] in 100 ml of ethyl acetate was converted to the free acid by washing with 100 ml of 10% citric acid. The oily acid was dissolved in 50 ml of absolute methanol and treated with 0.69 g (5.5 mmol) of carbomethoxysulfenyl chloride in one portion. After 3 hr the reaction mixture was worked up in the manner described above to yield 2.76 g (77%) of V, identical with the material obtained in A.

**D. From *N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteine (IVb).** To a solution of 1.7 g (5.0 mmol) of IVb[14] in 100 ml of 2,2,2-trifluoroethanol–methanol (25:5) solvent was added 0.69 g (5.5 mmol) of carbomethoxysulfenyl chloride in one portion. The reaction mixture was stirred at 25° for 4 days; work-up in the usual manner provided 0.43 g (25%) of product identical with that obtained in A.

**Methyl *N-tert*-Butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinate.** A suspension of *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt[15] in 200 ml of ethyl acetate was converted to the free acid with 100 ml of 10% citric acid solution. The resulting gum was dissolved in 50 ml of chloroform–methanol (1:1) and treated with 1.38 g (0.011 mol) of carbomethoxysulfenyl chloride in one portion at 0°. The reaction mixture was stirred for 6 hr and worked up in the usual manner and the solid recrystallized from hexane to yield 2.1 g (66%) of the ester: mp 78°; $[\alpha]^{25}\text{D} +27.7°$ (*c* 1, $CHCl_3$); homogeneous system D.

Anal. Calcd for $C_{11}H_{19}NO_6S_2$: C, 46.60; H, 5.89; N, 4.30; S, 19.70. Found: C, 46.70; H, 5.89; N, 4.20; S, 19.50.

**2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate (VIII).** A suspension of 6.02 g (0.01 mol) of *N*-benzyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylamine salt and 2.44 g (0.01 mol) of 2,4,6-trimethylbenzyl glycinate hydrochloride[16] in 100 ml of a chloroform–1,2-dimethoxyethane (1:1) solvent was cooled to −10° and treated with 1.15 g (0.01 mol) of *N*-hydroxysuccinimide and 2.1 g (0.01 mol) of DCC. The stirred suspension was allowed to warm to room temperature and stirred for 2 hr. The suspension was filtered, the filtrate evaporated in vacuo, and the residue dissolved in ethyl acetate and washed with cold solutions of 10% citric acid, 1 *M* sodium bicarbonate, and saturated sodium chloride solution. The dried organic layer was evaporated; chromatography of the crude product (4.5 g) on silica gel using chloroform as the eluent provided 4.0 g of solid. Recrystallization from chloroform–hexane provided 3.9 g (64%) of the dipeptide derivative: mp 126°; homogeneous, system B, $R_f$ 0.5; $[\alpha]^{25}\text{D} -22.4°$ (*c* 1, DMF).

Anal. Calcd for $C_{36}H_{38}N_2O_5S$: C, 70.78; H, 6.22; N, 4.58; S, 5.25. Found: C, 70.88; H, 6.22; N, 4.64; S, 5.11.

**Methyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinylglycinate (VII). A. From 2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate.** To a solution of 1.5 g (2.5 mmol) of VIII in 50 ml of chloroform–methanol (1:1) was added 0.37 g (2.75 mmol) of carbomethoxysulfenyl chloride. The reaction mixture was stirred at 25° for 48 hr; the solvent was removed in vacuo and the residue triturated with hot hexane. The residue was chromatographed on silica gel using chloroform as the eluent. The solid was recrystallized from a chloroform–hexane mixture to yield 0.8 g (61%) of the dipeptide derivative: mp 109°; homogeneous, system A, $R_f$ 0.8; $[\alpha]^{25}\text{D} -92.6°$ (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{16}H_{20}N_2O_7S_2$: C, 46.14; H, 4.84; N, 6.72; S, 15.40. Found: C, 46.11; H, 4.87; N, 6.63; S, 15.50.

**B. From Ethyl *N*-Benzyloxycarbonyl-*S*-trityl-L-cysteinyl-**

**glycinate (VI).** A solution of 2.9 g (5 mmol) of VI was treated with 0.69 g (0.011 mol) of carbomethoxysulfenyl chloride under the conditions described above. After 6 hr removal of the solvent and chromatography of the residue provided 1.5 g (72%) of VII identical with the material obtained in A.

**2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinylglycinate (IX). A. From 2,4,6-Trimethylbenzyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycinate.** To a solution of 1.5 g (2.5 mmol) of VIII in 50 ml of chloroform-methanol (1:1) at 0° was added 0.37 g (2.75 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 6 hr. The solvent was removed and the residue worked up in the manner previously described. Recrystallization of the solid from petroleum ether (bp 30–60°) provided 0.98 (75%) of IX: mp 144–146°; homogeneous, system B; $[\alpha]^{25}D$ −69.9° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{30}N_2O_7S_2$: C, 56.15; H, 5.66; N, 5.24; S, 11.99. Found: C, 55.88; H, 5.71; N, 5.13; S, 12.14.

**B. From *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteine (IVa). *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteine Dicyclohexylamine Salt (X).** A suspension of 5.9 g (0.01 mol) of the dicyclohexylamine salt of IVa in 100 ml of ethyl acetate was washed with 100 ml of 10% citric acid solution. The dried oily acid was dissolved in 50 ml of chloroform–methanol (1:1) solution containing 1.1 g (0.011 mol) of calcium carbonate and treated with 1.38 g (0.011 ml) of the sulfenyl chloride at 0°. The reaction mixture was stirred for 3 hr and worked up in the usual manner to provide a gum which was treated with 1.83 g (0.01 mol) of dicyclohexylamine. Recrystallization of the precipitated solid from chloroform–petroleum ether provided 4.29 g (77.7%) of X as a white solid: mp 139–140; $[\alpha]^{22}D$ −30.1° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{25}H_{38}N_2O_6S_2$: C, 57.00; H, 7.27;N, 5.32; S, 12.81. Found: C, 56.73; H, 7.23; N, 5.34; S, 12.20.

**Coupling of X with 2,4,6-Trimethylbenzyl Glycinate.** A suspension of 2.9 g (5.5 mmol) of X was converted to the free acid as previously described. The acid was suspended in 50 ml of chloroform–methylene chloride (1:1) solution, cooled to 0°, and treated with 1.22 g (5.0 mmol) of 2,4,6-trimethylbenzyl glycinate hydrochloride, 0.51 g (5.0 mmol) of *N*-methylmorpholine, and 1.11 g (5.5 mmol) of DCC. The solution was stirred at 0° for 12 hr and for 6 hr at room temperature. The reaction mixture was filtered and the filtrate evaporated. A solution of the residue in ethyl acetate was washed with 10% citric acid solution and water. Evaporation of the organic layer and recrystallization of the residue from ethyl acetate provided 2.29 g (86%) of IX: mp 142°; $[\alpha]^{22}D$ −71.4° (*c*, 1, $CHCl_3$).

Anal. Found: C, 56.39; H, 5.79; N, 5.34; S, 11.89.

***tert*-Butyl *N*-Benzyloxycarbonyl-*S*-benzhydryl-L-cysteinyl-L-alaninate (XI).** A suspension of 6.02 g (0.01 mol) of the dicyclohexylamine salt of IVa and 1.8 g (0.01 mol) of *tert*-butyl L-alaninate hydrochloride in 50 ml of methylene chloride was cooled to −10° and treated with 1.15 g (0.01 mol) of *N*-hydroxysuccinimide and 2.1 g (0.01 mol) of DCC. The stirred suspension was allowed to warm to 25° and stirred for 2 hr. Work-up in the manner previously described provided a gum which was recrystallized from chloroform–hexane to yield the desired ester: mp 73°; homogeneous, system B; $[\alpha]^{25}D$ +9.0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{31}H_{36}N_2O_5S$: C, 67.86; H, 6.70; N, 5.10; S, 5.84. Found: C, 67.93; H, 6.76; N, 5.08; S, 5.93.

***tert*-Butyl *N*-Benzyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-alaninate (XII).** To a solution of 1.36 g (2.5 mmol) of XI in 50 ml of chloroform–methanol at 0° was added 0.37 g (2.7 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 6 hr and worked up in the usual manner to provide a gum. The gum was chromatographed on silica gel using chloroform as eluent. Recrystallization of the resulting solid from chloroform–petroleum ether yielded 0.86 g (73%) of XII: mp 70°; homogeneous, system C, $R_f$ 0.6; $[\alpha]^{25}D$ −75.2° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}N_2O_7S_2$: C, 50.83; H, 5.97; N, 5.92; S, 13.51. Found: C, 50.80; H, 5.97; N, 5.81; S, 13.42.

**Methyl *N*-*tert*-Butyloxycarbonyl-L-phenylalaninyl-*S*-carbomethoxysulfenyl-L-cysteinate (XIV). A. From Methyl *S*-Carbomethoxysulfenyl-l-cysteinate.** A solution of 0.715 g (2.2 mmol) of XIII in 2 ml of cold methylene chloride was treated with 1 ml of cold trifluoroacetic acid. After 30 min the reaction mixture was evaporated to dryness; the last traces of acid were removed by the addition of toluene and evaporation. The resulting gum was dried, dissolved in 5 ml of methylene chloride, cooled to 0°, and treated with 0.242 g of *N*-methylmorpholine and 0.724 g (2.0 mmol) of the *N*-hydroxysuccinimide ester of *N*-*tert*-butyloxycarbonyl-L-phenylalanine. The reaction mixture was stirred for 24 hr at 0° and 2 hr at 25° and filtered and the filtrate was evaporated in vacuo. The product was extracted from the resulting gum with hot hexane and obtained as 0.61 g (64.6%) of white solid: mp 112–113°; homogeneous, system C; $[\alpha]^{26}D$ +5.0° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{20}H_{28}N_2O_7S_2$: C, 50.82; H, 5.97; N, 5.93; S, 13.57. Found: C, 50.96; H, 5.98; N, 6.03; S, 13.58.

**B. From Methyl *N*-*tert*-Butyoxycarbonyl-L-phenylalaninyl-*S*-benzhydryl-L-cysteinate (XV).** To 0.549 g (1.0 mmol) of XV in 2.5 ml of chloroform–methanol (1:1) was added 0.14 g (1.1 mmol) of the sulfenyl chloride. The reaction was conducted at 0°. Work-up in the usual manner provided 0.354 g (75%) of XIV: mp 113°; $[\alpha]^{26}D$ +4.6° (*c* 1, $CHCl_3$).

Anal. Found: C, 50.83; H, 6.03; N, 5.96; S, 13.64.

***N*-*tert*-Butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester.** To a solution of 0.710 g (1 mmol) of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (17) in 4 ml of chloroform–methanol (2:1) at 0° was added 0.176 (2 mmol) of the sulfenyl chloride. The reaction mixture was stirred at 0° for 50 min and then treated with 2.2 ml of 1 *N* aqueous diethylamine followed by 100 ml of chloroform. The chloroform solution was washed with 10% citric acid and twice with water. After drying over sodium sulfate, the solvent was concentrated to 3 ml, and the product was precipitated with petroleum ether. Recrystallization from chloroform–petroleum ether (30–60°) provided 0.46 g (82.5%) of product: homogeneous, system A, $R_f$ 0.56; mp 125–127°; $[\alpha]^{25}D$ −50.0° (*c* 0.5, methanol).

Anal. Calcd for $C_{24}H_{35}O_8N_3S_2$: C, 51.68; H, 6.32; N, 7.53; S, 11.49. Found: C, 51.60; H, 6.33; N, 7.47; S, 11.42.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-tert-butyl-L-tyrosyl-L-glutaminyl-L-leucyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-carbomethoxysulfenylcysteinyl-L-asparaginyl 2,4,6-Trimethylbenzyl Ester (XIX).** To a solution of 0.183 g (0.1 mmol) of the protected octapeptide XVIII[17] in 4 ml of chloroform–methanol (2:1) at −14° was added 17.6 μl of the sulfenyl chloride and the reaction mixture was stirred at −10° for 28 min. The reaction mixture was then stirred with 0.22 ml of 1 *N* aqueous diethylamine for 5 min below 0°. The solvent was evaporated and the residue was triturated with cold 10% citric acid. The solid was filtered, washed with water, and dried. Recrystallization of the solid from chloroform containing a few drops of methanol–petroleum ether provided 145 mg (86.5%) of product: mp 235–238°; homogeneous system A, $R_f$ 0.4; $[\alpha]^{23}D$ −44.4° (*c* 0.5, chloroform–methanol, 9:1).

Anal. Calcd for $C_{85}H_{116}O_{20}N_{11}S_2$: C, 60.85; H, 6.97; N, 9.18; S, 3.82. Found: C, 60.62; H, 6.93; N, 9.19; S, 3.95.

**Registry No.**—IVa, 53957-20-3; IVa dicyclohexylamine salt, 54062-81-6; IVb, 3257-18-9; IVc, 53907-29-2; V, 53907-34-9; VI, 3695-78-1; VII, 53907-35-0; VIII, 53907-17-8; IX, 53907-18-9; X, 53907-20-3; XI, 53907-21-4; XII, 53907-22-5; XIII, 53907-23-6; XIV, 53907-24-7; XV, 53907-25-8; XVIII, 53907-26-9; XIX, 53907-27-0; methyl *N*-benzyloxycarbonyl-L-cysteinate, 53907-28-1; carbomethoxysulfenyl chloride, 26555-40-8; *N*-benzyloxycarbonyl-L-cysteine, 53907-29-2; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt, 26988-59-0; 2,4,6-trimethylbenzyl glycinate hydrochloride, 6645-08-5; *tert*-butyl-L-alaninate hydrochloride, 13404-22-3; *N*-*tert*-butyloxycarbonyl-L-phenylalanine, 13734-34-4; *N*-*tert*-butyloxycarbonyl-*S*-carbomethoxysulfenyl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester, 53907-30-5; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester, 30806-18-9.

## References and Notes

(1) Supported by Grants GM-07966 and AM-03416, National Institutes of Health, U.S. Public Health Service.

(2) The following abbreviations have been utilized in the text: Bu-t = *tert*-butyl; Tr = trityl; Bzh = benzhydryl; Bzl = benzyl; Acm = acetamidomethyl; Z = benzyloxycarbonyl; Boc = *tert*-butylcarbonyl; TMB = 2,4,6-trimethylbenzyl; Scm = carbomethoxysulfenyl; DCHA = *N,N*-dicyclohexylamine; NSu = hydroxysuccinimide; DCC = *N,N*-dicyclohexylcarbodiimide.

(3) On leave from Presidency College, Madras, India.

(4) S. J. Brois, J. F. Pilot, and H. W. Barnum, *J. Am. Chem. Soc.*, **92**, 7629 (1970).

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(6) Following Kamer's suggestion we have utilized the abbreviation Scm to designate the $-SCO_2CH_3$ group.

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## Studies with α-Methyl Amino Acids. Resolution and Amino Protection[1a]

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We have prepared derivatives of α-methyl amino acids that are suitable for use in peptide synthesis because it appears that peptide hormone analogs containing them might be of special interest. Marshall and Bosshard[2a] and Marshall et al.[2b] have shown by theoretical studies on the allowed dihedral angles of model peptides that the replacement of the α proton of an amino acid residue with a methyl group results in a dramatic reduction of the conformational space available to the backbone of the peptide chain at the position where that residue occurs. These calculations have subsequently been confirmed by others.[3,4] Peptide hormone analogs containing α-methyl amino acid residues should therefore have a sterically rigid backbone conformation at those positions and would correspond closely to "conformational analogs" of the hormone, i.e., analogs which have a primary structure essentially identical with that of the native hormone but which are capable of adopting conformations that would comprise only a small subset of the total set available to the parent molecule.

Should such an analog be biologically active, important constraints might thereby be placed on evolving models of the conformation assumed by the hormone as it interacts with its receptor. In addition, if side-chain interactions were essential for binding, such analogs, which retain all of the native hormone's side chains, might offer a route to inhibitors which bind to the receptor but which are not capable of inducing subsequent events necessary to activity owing to their conformational inflexibility. This sort of inhibitor might be missed by schemes of analog generation which involve varying only the character or position of side chains.

Analogs bearing α-methyl groups would also be expected to be metabolized slowly, since model compounds containing α-methyl amino acids are known to be resistant to chemical hydrolysis[5,6] and to enzymatic attack by both endopeptidases[7] and exopeptidases.[8,9] The synthesis of such analogs might therefore result in the generation of either long-acting agonists or antagonists or of peptides which lack either property but which nonetheless potentiate the effect of endogenous hormone by interfering with its degradation.

We chose to resolve and protect α-methylphenylalanine (2-amino-2-methyl-3-phenylpropionic acid) and α-methylvaline (2-amino-2,3-dimethylbutyric acid) because both phenylalanine and valine occur in angiotensin II, a molecule of current interest. In achieving optical resolution of amino acids, enzymatic digestion of their acylated derivatives is often the method of choice, since it is less tedious and more rapid than many chemical resolution procedures. Since it is known that one enzyme commonly used for such purposes, hog renal acylase I, is unable to catalyze the hydrolysis of *N*-acetyl-α-methylphenylalanine,[7] we decided to use commercially available bovine carboxypeptidase A (CPA). We prepared the *N*-trifluoroacetyl derivatives of the amino acids because they are generally far superior substrates for CPA when compared to the *N*-acetyl derivatives[10] and because such a procedure had proven convenient for the resolution of other amino acids in our laboratory.[11]

We followed described procedures in synthesizing α-methylphenylalanine (**1**) and α-methylvaline (**2**) (Scheme I) from the corresponding ketones, phenylacetone and 2-methyl-3-butanone, respectively.[12,13] These amino acids can be trifluoroacetylated readily with trifluoroacetic anhydride in trifluoroacetic acid by the method of Weygand and Geiger,[14] though not by the milder method of Schallenberg and Calvin[15] which employs *S*-ethylthiol trifluoroacetate in aqueous solution and is an excellent procedure for many amino acids.

Both *N*-trifluoroacetyl-α-methylphenylalanine (**3**) and *N*-trifluoroacetyl-α-methylvaline (**4**) are digested stereospecifically by CPA, releasing the L isomers of **1** and **2** and leaving the D isomers of **3** and **4** intact. The protected derivatives can easily be separated from the amino acids by a simple extraction procedure and the D isomers of **1** and **2** can be generated from D isomers of **3** and **4** by mild saponification. The absolute configuration of α-methylphenylalanine has been determined previously,[16,17] and the direction and magnitude of the optical rotation of the free amino

**Scheme I**