R-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.54° (neat), were mixed with 15 ml of dry ether and 0.25 ml (0.55 g, 0.0029 mol) of 1,2-dibromoethane was added to start the reaction. After 1.5 hr of reflux, dry CO_2 gas was bubbled through the mixture for 10 min, HCl (10% solution) was added, and the aqueous layer was extracted with ether. The ether extracts were then extracted with 10% NaOH. Acidification of the aqueous layer, extraction with ether, and removal of solvent under vacuum after drying (Na_2SO_4) gave 0.072 g (12%) of crude acid. Sublimation at 85° (0.6 mm) yielded (*R*)-(+)-β-phenyl-β-*t*-butylpropionic acid (**17**), $[\alpha]^{25}D$ +1.74° ($CHCl_3$, *c* 3.16), mp 110–112.5°, reported[22] 114–116°. The nmr spectrum of this material was compatible with the assigned structure.

Registry No.—**2**, 23406-51-1; **5**, 23406-52-2; **6**, 23406-53-3; **7**, 23439-89-6; **8**, 23406-54-4; **9**, 13491-16-2; **11**, 23406-56-6; **12**, 23406-57-7; **14**, 23406-58-8; **15**, 23439-90-9; **16**, 23439-91-0; **17**, 23406-59-9; (*R*)-(−)-3-methyl-2-phenyl-1-butanol, 23406-60-2; (*R*)-(−)-3-methyl-2-phenyl-1-chlorobutane, 23406-61-3.

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Sulfur-Containing Polypeptides. XII. Studies on the Scope and Limitations of the Sulfenylthiocyanate Method as a Route to Cystine Peptides[1,2]

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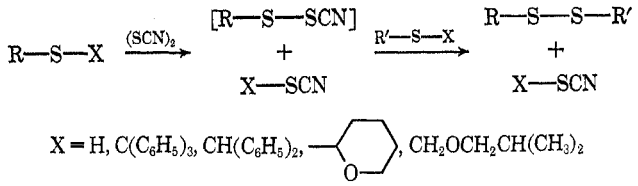
The sulfenylthiocyanate method of disulfide synthesis has been applied to the preparation of 13 cystine peptides containing various amino acid residues. In general no significant side reactions were observed; however, acidic solvents were required for a histidine-containing cystine peptide, and the ω-nitro protective group was necessary for an arginylcystine derivative.

Among the remaining obstacles to the unambiguous synthesis of complex polypeptides is the problem of the "correct pairing" of the sulfur–sulfur bonds of the cystine residues in synthetic polypeptides. At present the final stage of all synthetic routes to polypeptides containing several cystine residues has involved the simultaneous removal of S-protecting groups from cysteine residues and subsequent one-step oxidation. This approach appears to lead to complex mixtures and diminished biological activity.

Several years ago we reported[5] that cystine derivatives could be prepared by employing the sulfenylthiocyanate method discovered by Lecher and Wittwer.[6] These workers had used thiocyanogen to oxidize thiols, and the subsequent recognition that the oxidation could also be performed on appropriate thio ethers[5,7-10] and hemithioacetals[5,11] greatly enhanced the flexibility and apparent applicability of the method to the synthesis of polypeptides containing several cystine residues.



Although these experiments suggest that certain open-chain and cyclic cystine peptides can be prepared *via* the sulfenylthiocyanate method, no information was available on the compatibility of thiocyanogen or the sulfenylthiocyanates of cysteine derivatives with other amino acids. For example, thiocyanogen is known to decompose slowly in the presence of water or alcohols;[12,13] thiocyanogen[14] and sulfenylthiocyanates[15] are also known to react with aliphatic amines to yield amine thiocyanates. In addition, *para*-substituted aromatic amines and phenols undergo ring substitution with thiocyanogen and provide the corresponding 2-iminobenzoazoxoles or 2-iminobenzothioxoles.[12] Although the hydroxyl, phenolic, and amine side chains could always be protected during the preparation of a polypeptide, ring substitution and possible subsequent reactions in tyrosine, tryptophan, and histidine side chains would be a definite possibility. For example, tyrosine, tryptophan, and histidine peptides are cleaved by electrophiles, particularly bromine, N-bromosuccinimide, and cyanogen bromide.[16] Various sulfenyl halides react at the indole 2 position of tryptophan in peptides and proteins but not with the side chains of other amino acids.[17] Finally, methionine is known[16] to suffer cleavage by certain electrophiles, notably cyanogen bromide, and this possibility also warranted examination using thiocyanogen and sulfenylthiocyanates.

In order to evaluate the effects of side chains on the formation of cystine peptides with sulfenylthiocyanates or thiocyanogen, a series of 13 cystine derivatives were prepared; with two exceptions these were of the general structure IV (Table I). The sulfenylthiocyanates II

(1) Preceding paper: R. G. Hiskey, A. M. Thomas, R. L. Smith, and W. C. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 7525 (1969).

(2) Supported by Research Grants GM-07966 and AM-03416 from the Institute of General Medical Science and the Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) Abstracted in part from the Ph.D. dissertation of B. F. Ward, Jr., submitted in partial fulfillment of the requirements for the Ph.D. degree to the University of North Carolina, June 1969.

(4) Ethyl Corp. Fellow, 1968–1969.

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TABLE I
CONDITIONS FOR SYNTHESIS AND PROPERTIES OF UNSYMMETRICAL CYSTINE PEPTIDE DERIVATIVES

Z·CysOMe | Z·Cys·(AA)OR, (AA)OR	Concn, *M*	Time, hr	Purification[b]	Yield, %	Mp, °C	$[\alpha]^{21}D$, deg	Calcd, %				Found, %			
							C	H	N	S	C	H	N	S
GlyOEt (IVa)	0.3	22	F	58	123–124	−106.4 (*c* 0.5, MeOH)	53.27	5.63	6.90	10.53	53.39	5.69	6.84	10.58
SerOCH$_3$ (IVb)	0.08	5	F	84, 71[c]	100–101	+42.7 (*c* 1.0, $CHCl_3$)	51.99	5.33	6.73	10.28	51.95	5.42	6.68	10.21
AsnOEt (IVc)	0.07	9	A	74, 80[c]	161–162	−93.6 (*c* 0.5, MeOH)	52.54	5.46	8.43	9.65	52.36	5.46	8.24	9.49
AlaOEt (IVd)	0.06	12	G[d]	70	85–86	+35.7 (*c* 1.0, $CHCl_3$)	54.09	5.68	6.76	10.31	54.19	5.65	6.67	10.49
PheOEt (IVe)	0.08	11	D[d]	66	131–132	+43.6 (*c* 1.0, $CHCl_3$)	58.52	5.69	6.02	9.19	58.48	5.56	5.87	9.36
TyrOEt (IVf)	0.08	11	G[d]	77, 70[c]	81–83	+25.5 (*c* 1.0, $CHCl_3$)	57.21	5.51	5.88	8.98	57.01	5.50	5.87	9.02
MetOEt (IVg)	0.10	12	H[d]	75, 72[c]	83–85	+32.8 (*c* 1.0, $CHCl_3$)	52.84	5.76	6.16	14.11	53.00	5.77	6.21	14.09
HisOCH$_3$ (IVh)	0.10	12	I[e]	82, 68[c]	115–116	−67.9 (*c* 1.0, acetone)	53.47	5.24	10.40	9.52	53.24	5.22	10.28	9.66
TrpOEt (IVi)	0.15	12	J[d]	54, 62[c]	78–80	−46.4 (*c* 1.0, acetone)	58.68	5.47	7.60	8.70	58.57	5.32	7.40	8.89
ThrOCH$_3$ (IVj)	0.08	10	K[f]	61	51–53	+25.2 (*c* 0.5, $CHCl_3$)	52.73	5.53	6.59	10.06	52.90	5.47	6.54	10.32
NO$_2$ | ArgOEt (IVk)	0.10	8	L[g]	74, 75[c]	152–154	+12.6 (*c* 0.5, $CHCl_3$)	48.83	5.33	13.29	8.69	49.18	5.37	13.17	8.47
VI	0.05	15	F	31	70–72	−52.0 (*c* 1.0, acetone)	49.41	5.67	11.52	8.78	49.24	5.72	11.59	8.89
VII	0.14	8	M	70	167–168	−87.4 (*c* 0.5, MeOH)	54.37	5.99	7.93	9.07	54.41	6.09	8.18	9.00

[a] Solvents for IVh, VI, and VII were ethyl acetate–trifluoroacetic acid (1:1, v/v); all other reactions were conducted in ethyl acetate. [b] F = acetone–ether; A = ethyl acetate; G = ethyl acetate–ether; D = chloroform–ether (3:2, v/v); H = acetone–ether–hexane; I = ethyl acetate–hexane; J = acetone–cyclohexane; K = ether–hexane; L = ethyl acetate–ether–hexane; M = methanol. [c] Yield of disulfide *via* V. [d] Chromatographed prior to recrystallization using chloroform–ether (3:2, v/v). [e] Using chloroform–methanol (9:1, v/v). [f] Using ether. [g] Using ethyl acetate.

were generated by the action of thiocyanogen on I; the S-trityl component III (Table II) was then added to II in a suitable solvent. Alternatively the S-trityl peptide III could be treated with thiocyanogen to generate

the sulfenylthiocyanate V, which could then be treated with I to produce IV. Both reactions in either sequence could be monitored by tlc, and the products were isolated by column chromatography and/or crystallization.

The anticipated products, IV, were obtained in reasonable yield from II and derivatives of III containing glycine (a), serine (b), asparagine (c), alanine (d), phenylalanine (e), tyrosine (f), methionine (g), tryptophan (i), and threonine (j) (Table I). The reactions were performed in ethyl acetate. The cystine derivatives IVb, IVc, IVg, and IVi were prepared in similar yield by the reverse process (Table I). The nmr spectra of all cystine derivatives were in agreement with the indicated structures. These results suggest that the reaction of thiocyanogen or a sulfenylthiocyanate with these S-trityl thioethers proceeds rapidly and cleanly without detectable side reactions involving the other side chains. When the tyrosyl peptide IVf was prepared by the reverse process, tlc of the reaction mixture indicated the presence of the corresponding symmetrical disulfide; however, no product owing to ring substitution of thiocyanogen was evident.

The preparation of the histidine-containing peptide IVh led to somewhat different results. When the reaction between II and IIIh was carried out in ethyl acetate, no reaction occurred and IIIh was recovered unchanged after work-up of the reaction mixture. However, when the reaction was carried in ethyl acetate–acetic acid (1:1, v/v) a 24% yield of IVh was obtained; the presence of IIIh was noted in the reaction mixture. Assuming that a reaction of II and the basic nitrogen atoms of IIIh was responsible for the lowered yield, the reaction was repeated in ethyl acetate–trifluoroacetic acid (1:1, v/v); under these conditions IVh was obtained in 82% yield and no IIIh could be detected.

The effect of a basic side chain was also noted in the preparation of the arginyl cystine peptide VI. When methyl N-carbobenzoxy-L-arginyl-S-benzhydryl-L-cysteinate (VII) was allowed to react with II in ethyl acetate–trifluoroacetic acid (1:1, v/v), a low yield (31%) of VI resulted and VII was not completely consumed. However, when the ω-nitro protective group was employed for the guanidino side chain, IVk was obtained in 74% yield; IVk could also be obtained in good yield *via* the reverse reaction.

The production of IVb from II and IIIb was used to determine which types of polar solvents might be used

TABLE II

CONDITIONS FOR SYNTHESIS AND PROPERTIES OF VARIOUS CYSTEINE PEPTIDE DERIVATIVES

Tr | Z-Cys-AAOR, AAOR	Reaction solvent[a]	Crystallization solvent[b]	Yield, %	Mp, °C	$[\alpha]_D$, deg	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
GlyOEt (IIIa)[c]													
SerOCH$_3$ (IIIb)[d]	L	O[e]	76	62–66	+24.0[f]	68.22	5.72	4.68	5.35	68.03	5.79	4.62	5.32
AsnOEt (IIIc)[d]	N	Q[e]	43	103–105	+36.6[f]	67.58	5.83	6.57	5.01	67.84	5.89	6.37	4.94
AlaOEt (IIId)[d]	N	O[e]	72	46–50	+21.8[f]	70.44	6.08	4.70	5.37	70.46	6.24	4.67	5.33
PheOEt (IIIe)[d]	L	O[e]	71	47–50	+29.4[f]	73.18	5.99	4.16	4.77	73.04	5.91	4.17	4.76
TyrOEt (IIIf)[d]	N	P[e]	84	68–71	+33.1[g]	71.50	5.87	4.07	4.65	71.54	5.96	4.18	4.35
MetOEt (IIIg)[d]	L	O[e]	92	110–111	+28.4[f]	67.65	6.14	4.27	9.93	67.68	6.16	4.29	9.77
HisOCH$_3$ (IIIh)[h]	M	R	67	152–154	+58.7[g]	68.49	5.59	8.64	4.94	68.32	5.83	8.40	4.98
TrpOEt (IIIi)[d]	M	S[e]	62	65–70	+13.1[g]	72.55	5.81	5.90	4.50	72.79	6.10	5.73	4.04
ThrOCH$_3$ (IIIj)[d] NO$_2$ |	N	T[e]	68	60	+ 6.2[i]	68.60	5.92	4.57	5.23	68.88	6.26	4.41	4.93
ArgOEt (IIIk)[d] Bzh |	N	U[e]	61	91–95	+ 6.4[j]	62.34	5.66	11.76	4.50	62.52	5.71	11.72	4.63
Z-Arg-CysOCH$_3$ (VII)[k] ·HCl Bzh |	N	V[e]	22	97–99	−10.7[i]	57.63	6.29	11.20	5.13	57.93	6.44	10.96	5.18
Z-Val-Cys-GlyOEt (IX)[l]	L	W	82	165–167	−13.1[i]	65.43	6.49	6.94	5.29	65.32	6.44	7.03	5.50

[a] L = methylene chloride; M = methylene chloride–methanol (1:1, v/v); N = methylene chloride–DMF (2:1, v/v). [b] O = ether–cyclohexane; P = ethyl acetate; Q = ethyl acetate–ether; R = acetone; S = ether–hexane; T = acetone–ether–cyclohexane; U = chloroform–hexane; V = methanol–ether; W = ethyl acetate–hexane. [c] L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962). [d] Coupled to Z·(Tr)Cys⁻ DEA⁺ using 1-ethyl-3-(3′-*N*,*N*-dimethylaminopropyl)carbodiimide hydrochloride. [e] Chromatographed using ethyl acetate prior to crystallization. [f] $[\alpha]^{25}D$ (*c* 1, $CHCl_3$). [g] $[\alpha]^{21}D$ (*c* 1, $CHCl_3$). [h] Coupled to Z·(Tr)CysOSu. [i] $[\alpha]^{22}D$ (*c* 1, acetone). [j] $[\alpha]^{22}D$ (*c* 0.5, $CHCl_3$). [k] Prepared from H·(Bzh)Cys·OCH$_3$ by coupling with DCC. [l] Prepared from H·(Bzh)Cys·GlyOEt by coupling with 1-ethyl-3(3′-N,N-dimethylaminopropyl)carbodiimide hydrochloride.

TABLE III

SYNTHESIS OF Z·CysOCH$_3$ Z·Cys·SerOCH$_3$ (IVb) IN VARIOUS SOLVENTS

$(SCN)_2$ Prepd in[a]	II added in	III added in	Yield, %
A	A	A	84
A	A	CH_2Cl_2	82
A	AcOH	AcOH	76
A	TFA	TFA	73
A	MeOH	MeOH–H_2O	67
A	TFE	TFE	75
A	MeOH–H_2O	MeOH	0
A	NaOMe–MeOH	MeOH	0
MeOH	MeOH	MeOH	0
A	A	C_5H_5N	0
A	A	B	0
A	HMPA	HMPA	0
A	A	HMPA	5

[a] A = ethyl acetate; B = pyridine–acetic acid, pH 6.3; TFE = β,β,β-trifluoroethanol; HMPA = hexamethylenephosphoramide.

for the sulfenyl thiocyanate method (Table III). Ethyl acetate appears to be the solvent of choice for the generation of thiocyanogen; acetic acid can also be used, but the formation of thiocyanogen is much slower; water or alcohols cannot be employed. Sulfenylthiocyanates appear to be more stable to water and alcohols; these intermediates are decomposed by amines and apparently some amides, since reactions of sulfenylthiocyanates in hexamethylenephosphoramide (HMPA), DMF, DMAc, and N-methylpyrrolidone have not been successful.

Thus the sulfenylthiocyanate method of disulfide synthesis may be applicable to the synthesis of large polypeptides containing several cystine residues. The advantages of the method appear to lie in the high degree of reactivity of thiols and certain thio ethers toward thiocyanogen and sulfenylthiocyanates. The disadvantages of this approach involve the thermal lability of the intermediate sulfenylthiocyanates and their reactivity with basic nitrogen atoms. The actual application of this system to an appropriate biologically active polypeptide containing several cystine residues should establish whether the problem of the "correct pairing" of cystine residues can be overcome by this route.

Experimental Section[18]

Methyl N-carbobenzoyl-S-trityl-L-cysteinylglycinate (IIIa) was prepared by the procedure of Zervas and Photaki.[19]

General Procedure for the Preparation of N,O,S-Protected Di- and Tripeptides.—To a solution of 10 mmol of the appropriate cysteine derivative in 30 ml of methylene chloride was added 10 mmol of the appropriate protected amino acid in 20 ml of the indicated solvent. The solution was cooled to −10° and treated with 10.8 mmol of the indicated coupling reagent. The reaction mixture was allowed to stir at −10° for 2 hr, warmed to room temperature, and stirred for 12–15 hr. The reaction mixture was then diluted to 200 ml with methylene chloride and washed with 2 *N* sulfuric acid, water, and saturated brine. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to an oil which was purified by column chromatography and/or crystallization (Table II).

General Method of Preparation of Cystine Peptide Derivatives. A. In Ethyl Acetate.—A solution of 9 mmol of thio-

(18) Melting points are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The optical rotations were measured with 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 G coated microscope slides. The amino acid ester hydrochlorides used to prepare the various dipeptides were purchased from the Sigma Chemical Co. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 spectrometer.

(19) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

cyanogen in 35 ml of ethyl acetate was prepared in the usual manner in the dark at 0°. To this cold solution was added 7.2 mmol of I in 20 ml of ethyl acetate over at 15-min period. At this point tlc indicated that no thiol remained. The appropriate thioether (7.2 mmol) was dissolved in 25 ml of ethyl acetate and added in one portion to the reaction mixture. The solution was stirred in the dark for 2 hr at 0°, allowed to warm to room temperature, and stirred for an additional period of time (3–33 hr depending on the reaction progress as demonstrated by tlc). After reaction was complete the solution was diluted to 200 ml with ethyl acetate and washed with 5% sodium bicarbonate solution, water, and saturated brine. The organic extract was dried and evaporated *in vacuo*, and the residue was triturated with hexane to remove the trityl thiocyanate. The resulting powder was purified by recrystallization or chromatography followed by recrystallization. The reported yields (Table I) are based on the amount of purified product.

B. Acidic Solvents.—To a cold, stirred solution containing 9 mmol of thiocyanogen in 35 ml of ethyl acetate was added 7.2 mmol of I in 20 ml of trifluoroacetic acid (TFA). After 10 min, 7.2 mmol of the appropriate thio ether in 15 ml of TFA was added and the mixture was stirred at 0° for 3 hr and at room temperature for 5–12 hr. The reaction mixture was poured into 1200 ml of cold 5% sodium bicarbonate and the mixture was extracted with ethyl acetate. The organic layer was washed, dried, and evaporated *in vacuo*. Trituration with hexane afforded a powder which was purified by recrystallization.

Registry No.—IIIb, 23465-05-6; IIIc, 23465-06-7; IIId, 23465-07-8; IIIe, 23465-08-9; IIIf, 23465-09-0; IIIg, 23435-44-1; IIIh, 23435-45-2; IIIi, 23435-46-3; IIIj, 23435-47-4; IIIk, 23465-10-3; IVa, 23465-11-4; IVb, 23435-52-1; IVc, 23435-53-2; IVd, 23435-54-3; IVe, 23435-55-4; IVf, 23465-12-5; IVg, 23500-37-0; IVh, 23435-56-5; IVi, 23500-38-1; IVj, 23435-57-6; IVk, 23435-58-7; VI, 23435-48-5; VII, 23435-49-6; VII (HCl), 23435-50-9; IX, 23435-51-0.

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The Photodimerization of Substituted Stilbenes

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Stilbenes with electron-donating groups on either of the aromatic moieties undergo rapid photodimerization. With dissimilar phenyl groups, two photodimers are obtained, and their structures have been elucidated by nmr and mass spectral studies. The extent of dimerization was measured by gel-permeation chromatography and a singlet mechanism is proposed for the photodimerization process.

The photochemistry of stilbene is well known and the three photochemical reactions are *cis–trans* isomerization, cyclization, and dimerization. Although the dimerization of stilbene has been discovered at the beginning of this century by Ciamician and Silber,[1] it is the least understood of the three reactions. Shechter and coworkers[2] have isolated two photodimers from *trans*-stilbene (27% conversion upon irradiation for 2 months) and their structures were assigned on the basis of nmr data. In our study directed toward the use of stilbene derivatives for photocross-linking of polymers,[3] we noticed considerable enhancement of dimerization if electron-donating groups are attached to the aryl groups.[4] The quantum yield of dimerization of **5** was found to be *ca.* 0.06. In Table I the previously unreported stilbene derivatives used in this study are listed. The photodimerization was conducted on the mono- and bismethyl carbamates of the mono- and diisocyanates in order to approximate the bonding generated in polymer systems. As ultraviolet sources a 100- and a 450-W mercury lamp have been used and benzene, ethyl acetate, and tetrahydrofuran were the solvents employed in the photodimerization experiments. The quantitative determination of dimerization was achieved using gel permeation chromatography (gpc) and the monomer was used for calibration. The dimer yields were verified by column chromatography, which also allowed separation of the isomeric photodimers.

The gpc method is accurate, nondestructive (room temperature assay), and convenient, *i.e.*, the reaction mixture can be directly injected into the chromatograph. For example, the rate of photodimerization can be followed, and a first-order rate law is observed in the photodimerization of **5** (10% concentration) up to *ca.* 70% conversion. The results of the photodimerization experiments are listed in Table II.

The results obtained in the photodimerization experiments (irradiation for 4 hr in ethyl acetate) show that electronic effects as well as steric effects are operative. For example, electron-donating groups, such as OCH_3, $NHCOCH_3$, and $NHCOOCH_3$, enhance dimerization (compare *trans*-stilbene with **14**, **2**, **3**, and **5**). The steric effects are also quite pronounced, as shown by the comparison of **15** (4,4′ substituted) with **9** (2,4′ substituted) and **12** (2,2′ substituted). Comparable yields were obtained using benzene, ethyl acetate, and tetrahydrofuran. However, highly polar solvents, such as N,N-dimethylformamide, lower the extent of dimerization. For example, irradiation of **5** in DMF for 4 hr, using a 450-W source, gave 68% photodimerization, while in tetrahydrofuran, under similar conditions, 91.3% dimerization was obtained. The extent of dimerization was not affected when the reaction was conducted in a nitrogen atmosphere.

No *cis*-stilbene or phenanthrene could be isolated, suggesting that, at the concentrations studied, only photodimerization is the major pathway. The extent of dimerization decreases with dilution (see compound **5** in Table II), meaning that at higher dilution isomeri-

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(2) H. Shechter, W. J. Link, and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **85**, 1601 (1963).

(3) F. A. Stuber, H. Ulrich, D. V. Rao, and A. A. R. Sayigh, *J. Appl. Polym. Sci.*, **13**, 2247 (1969).

(4) This phenomenon appears to be general because we observed a similar effect in the photodimerization of coumarins and cinnamates: D. V. Rao, F. A. Stuber, H. Ulrich, and A. A. R. Sayigh, in press.