R. Stewart and L. J. Muenster, *Chem. and Ind.*, 1906 (1961).
(10) K. Kim, S. R. Mani and H. J. Shine, *J. Org. Chem.*, **40**, 3857 (1975).
(11) E. Bergman and M. Tschudnowshy, *Ber.*, **65**, 457 (1932).
(12) E. S. Huyser, in Free-Radical Chain Reactions, wiley-Interscience, New York, p. 287, 1970.
(13) J. A. Howard and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 1056 (1968).
(14) K. Tokumaru and O. Simmamura, *Bull. Chem. Soc. Jap.*, **36**, 333 (1963).
(15) H. Tsubomura and R. P. Lang, *J. Amer. Chem. Soc.*, **83**, 2085 (1961).
(16) H. J. Shine, in The Chemistry of the Sulphonium Group, (Ed C. J. M. Stirling), Part 2, Chap. 14, Interscience, New York, p. 523, 1981.
(17) C. S. Foote and J. W. Peters *J. Amer. Chem. Soc.*, **93**, 3795 (1971).
(18) K. F. Purcell and J. R. Berschied, *Jr., J. Amer. Chem. Soc.*, **89**, 1579 (1967).
(19) W. Ando, Y. Kabe, S. Kobayashi, C. Takyu, A Yamagishi, and H. Inaba, *J. Amer. Chem. Soc.*, **102**, 4526 (1980).

Synthesis of Nuclophilic Adducts of Thiols (VI). Addition of L-Cystein to β, β-Diethoxycarbonylstyrene Derivatives

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A series of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine derivatives (10a-e) were synthesized from the reaction of β, β-diethoxycarbonylstyrene with L-cysteine in 1:1 aqueous methanol. Thus, S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine(10a), S-[2,2-diethoxycarbonyl-1-(3′,4′-methylendioxyp) phenylethyl]-L-cysteine (10b), S-[2,2-diethoxycarbonyl-1-(3′,4′,5′-trimethoxy)phenylethyl]-L-cyseine (10c), S-[2,2-diethoxycarbonyl-1-(*p*-hydroxy) phenylethyl]-L-cysteine (10d), S-[2,2-diethoxycarbonyl-1-(*p*-methoxy) phenylethyl]-L-cysteine (10e) were obtained in moderate to excellent yields. The structure of the adducts was characterized by analytical and spectral data. The effects of pH upon the product yields were also briefly examined.

Introduction

There have been growing interests in the synthesis of cysteinyl peptide derivatives with biological activities.[1-5] We reported the synthesis of S-(2-nitro-1-phenylethyl)-L-cysteine[6] and S-(2-nitro-1-phenylethyl)-L-glutathione derivatives.[7] In each case, the product was obtained in excellent yields from the reaction of β-nitrostyrene[8-10] with cysteine or glutathione under mild condition. The major advantage of this synthesis is that biologically important products can be obtainde in good yields by simple addition reactions without protecting the functional groups.[11-15]

In this work, we have synthesixed a series of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine derivatives from the reaction of β, β-diethoxycarbonylstyrene derivatives with L-cysteine. The effects of pH upon the product yields were also briefly examined.

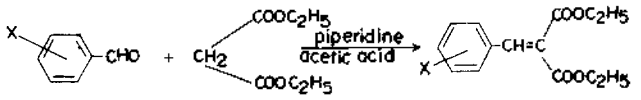
Experimental

General. Melting points were determined on a Fisher Johns melting point apparatus. Infrared spectra were obtained with a JASCO IRA-2 spectrophotometer. UV spectra were recored on a Beckman Model 26 spectrophotometer. Proton nmr spectra were obtained with a Varian Model EM-360 spectrometer in DMSO-d_6. Elemental analyses were conducted with MOO-1106 Model Carlo Erba, Italy. All of the reagents were commercially available and used without further purification.

Synthesis of β, β-Diethoxycarbonylstyrene. β, β-Diethoxycarbonylstyrene derivatives were prepared from substituted

benzaldehydes and diethylmalonate by the known method.[16] The yields, melting points, and the elemental analyses data are recorded in Table 1.

TABLE 1: Yields, Melting Points and Analytical Data of β,β-Diethoxycarbonylstyrene Derivatives (9a-e)



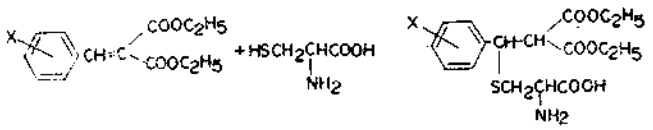
(9a-9e)

X	Yield(%)	mp (°C)	Analytical data of elements(%) Calcd. C	Calcd. H	Found C	Found H
H(9a)	88.7	31	67.74	6.45	67.70	6.65
3,4-methylene-dioxy(9b)	86.4	53–55	62.06	4.83	61.88	4.65
3,4,5-trimethoxy (9c)	86.0	70–71	60.35	6.51	60.54	6.30
4-hydroxy(9d)	72.4	92–92	63.63	6.06	63.88	6.13
4-methoxy(9e)	70.8	37	64.74	6.47	64.67	6.54

Synthesis of S-(2,2-Diethoxycarbonyl-1-phenylethyl)-L-cysteine Derivatives. L-Cysteine·HCl·H_2O (3.51g, 0.02 mole) and N-methylmorpholine (2.02g, 0.02 mole) were dissolved in 200 m*l* of 1:1 aqueous methanol. β,β-Diethoxycarbonylstyrene (9a: 4.69g, 0.02 mole) was added to the solution and the mixture was heated to 55°C to get a clear solution. The solution was cooled to room temperature and stirred for about 12 hours until the product was completely precipitated. The product was collected by filteration, washed with methanol, and dried (The yield was 2.6g, 52.8%). The maximum yields, melting points, and the elemental analyses data were summarized in Table 2. The UV, IR and umr spectral data are recorded in Table 3 and 4, respectively. The product yields determined at various pH are summarized in Table 6.

Determination of Optical Rotations, R_f Values, and Molecular weight of S-(2,2-Diethoxycarbonyl-1-phenylethyl)-L-cysteine Derivatives. Optical rotations of the adducts were determined in 1.0N HCl (aq). The R_f values of the products were determined on a TLC plate (silica gel) using a mixture of ethyl acetate/acetic acid/water(v/v; 3/1/1) as a developing siovent. The molecular weight of the adducts were determined by

TABLE 2: Yields, Melting Points, and Analytical Data of S-[2,2-di-ethoxycarbonyl-1-(substituted)phenylethyl]-L-cysteine Derivatives (10a-e)



(9a-e) (10a-e)

X	Yield (%)	mp (°C)	Analytical data of elements (%) Calcd C	Calcd H	Calcd N	Calcd S	Found C	Found H	Found N	Found S
N (10a)	52.8	163–164	55.20	6.23	3.79	8.67	55.18	6.13	3.85	8.70
3,4-methylene-dioxy (10b)	96.8	162–163	53.30	5.57	3.38	7.75	53.26	5.54	3.25	7.64
3,4,5-trimethoxy	85.0	164–165	52.28	6.31	3.05	6.97	52.11	6.55	3.20	7.10
4-hydroxy (10d)	93.5	173–174	52.99	5.97	3.64	8.13	52.94	6.71	3.50	8.60
4-methoxy (10e)	42.6	157–158	54.13	6.26	3.50	8.20	54.01	6.01	3.70	8.31

TABLE 3: Characteristic UV and IR Absorptions of β,β-Diethoxycarbonylstyrenes (9a-e) and S-(2, 2-Diethoxycarbonyl-1-phenylethyl)-L-Cysteine Derivatives (10a-e)

Compds.	UV absorptions nm(ε)	IR-bands (cm^{-1}) (KBr pellet)
9a	217(15400)[a] 279(7700)	2975. 2930. 2890. 1720. 1630. 1575. 1495. 1365. 1200–690.
9b	218(17100)[a] 295(550) 311(7000)	2950. 2900. 1720. 1625. 1600. 1490. 1365. 1220. 810–750.
9c	229(16300)[a] 311(7000)	2980. 2960. 2900. 2840. 1725. 1690. 1625. 1580. 1505. 1220. 830.
9d	217(17700)[a] 314(12000)	3300. 2980. 2840. 2900. 1720. 1690. 1625. 1590. 1525. 1220. 770–735
9e	215(15000)[a] 313(9500)	2980. 2940. 2840. 1720. 1675. 1605. 1570. 1515. 1210. 760.
10a	222(15450)[b] 279(0)	3410. 3210. 3200–2800. 1750. 1620. 1490. 1450. 1425. 1200–1100. 770–735. 700.

10b	218(19100)[b] 294(1600) 330(500)	3410. 1620. 810–750.	3210. 1500.	3200–2850. 1455. 1420.	1745. 1200–1100.
10c	223(15700)[b] 310(0)	3420. 1625. 880–860.	3210. 1500.	3200–2800. 1455. 1420.	2840. 1740. 1200–1100.
10d	219(15200)[b] 314(450)	3420. 1620. 770–735.	3200. 1510.	3200–2800. 1450. 1425.	1736. 1200–1100.
10e	219(15000)[b] 312(350)	4320. 1740. 1200–1100.	3210. 1610.	3200–2800. 1530. 1440. 770–730.	2830. 1420.

[a] in MeOH [b] in 0.1N NaOH

TABLE 4: Proton nmr Spectra of S-(2,2-Diethoxycarbonyl-1-phenylethyl)-L-cysteine Derivatives(10a-e)

Compds.	Chemical shifts in ppm (DMSO-d_6)		
10a	1.0(t, 6H, CH_3), 4.5(t, 2H, CH_2), 7.5(S, 5H, phenyl)	2.7(S, 2H, NH_2), 4.9(t, 1H, CH),	3.8(m, 5H, CH_2, CH) 5.8(d, 1H, CH)
10b	1.1(t, 5H, CH_3), 4.5(t, 2H, CH_2), 7.2-7.8(m, 3H, phenyl)	2.6(S, 2H, NH_2), 5.1(t, 1H, CH),	3.5-3.7(m, 5H, CH_2, CH) 5.9(d, 1H, CH), 6.4(S, 2H, CH_2)
10c	1.2(t, 6H, CH_3), 4.6(t, 2H, CH_2),	2.6(S, 2H, NH_2), 5.0(t, 1H, CH),	4.0(m, 14H, OCH_3, CH_2 CH) 5.8(d, 1H, CH), 6.8(S, 2H, phenyl)
10d	1.3(t, 6H, CH_3), 4.4(t, 2H, CH_2), 6.9-7.3(m, 4H, phenyl)	2.7(S, 2H, NH_2), 4.9(t, 1H, CH),	3.9(m, 5H, CH_2, CH), 5.6(S, 1H, OH), 5.9(d, 1H, CH)
10e	1.2(t, 6H, CH_3), 4.7(t, 2H, CH_2), 6.9-7.3(m, 4H, phenyl)	2.6(S, 2H, NH_2), 5.0(t, 1H, CH),	3.9(m, 8H, CH_2, CH, OCH_3) 5.8(d, 1H, CH)

TABLE 5: Optical Rotations, R_f Values, and Molecilar Weight of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine Derivatives (10a-e)

Compds.	$[\alpha]^{20}$[a]	R_f[b]	Amine content. (%)	Molecular weight	
				calcd	found
10a	−54°	0.71	101.9	369.43	362.54
10b	−65.4°	0.71	102.9	413.44	401.79
10c	−18.2°	0.61	102.4	459.51	448.65
10d	−36.2°	0.61	102.6	385.43	375.65
10e	−80.2°	0.67	102.8	399.46	388.58

[a] Determined in 1.0N HCl. [b] R_f-value of L-cysteine; 0.14 (Solvent: Ethyl acetate/acetic acid/water=v/v: 3/1/1).

nonaqueous amine titration. Since 1.0 m*l* 0.1*N* $HClO_4$ is equivalent to 0.036943g of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine, the molecular weight of the adduct was calculated from the volume of the $HClO_4$ solution added to reach the end point. The optical ortations, R_f values, and molecular weight of the adducts are recorded in Table 5.

Results and Discussion

A series of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine dervatives were obtained in moderate to excellent yields from the reactions of the β, β-diethoxycarbonylstyrene with L-cysteine under mild conditions. The yields and physical conatnts of the products are recorded in Table 2 and 5.

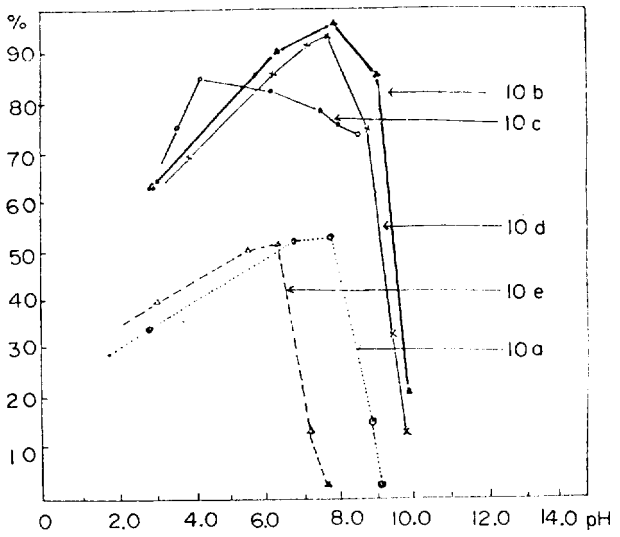


Figure 1. The dependence of the yields of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine derivatives (10a-e) upon the pH.

The structures of the adducts were characterized by the analytical and spectral dara. The results of elemental analyses (Table 2) and molecular weight determination (Table 5) are consis'en: with those expected from the adducts. The infrared spectra (Table 3) show characteristic peaks corres-

TABLE 6: The Yields of S-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine Derivatives(10a-e) at Various pH

Adducts	Base (equivalent amount)				pH	Yield
10a	N-methylmorpnoline (1)				3.2	35.2%
	N- 〃	(1) and triethylamine		(0.5)	7.2	52.8
	N- 〃	(1) and	〃	(1)	8.2	52.8
	〃	(1) and	〃	(1.5)	8.8	14%
	〃	(1) and	〃	(2)	9.4	trace
	〃	(1) and	〃	(2.5)	9.8	〃
10b	N-methylmorpholine (1)				3.0	62.9
	〃	(1) and triethylamine		(0.5)	6.9	90.8
	〃	(1) and	〃	(1)	8.4	96.85
	〃	(1) and	〃	(1.5)	9.3	79.9
	〃	(1) and	〃	(2)	9.5	27.54
	〃	(1) and	〃	(2.5)	9.8	0.0
10c	N-methylmorpholine (1)				3.7	80.6
	triethylamine (1)				4.3	85
	N-metyhlmorpholine (1) and TEN (1)				6.9	77.34
	〃	(1) and	〃	(1.5)	7.4	73.0
	〃	(1) and	〃	(2)	7.9	72.4
	〃	(1) and	〃	(2.5)	8.6	70.8
10d	N- 〃	(1)			6.4	83.0
	〃	(1) and	〃	(0.5)	7.0	92.2
	〃	(1) and	〃	(1)	7.8	93.5
	〃	(1) and	〃	(1.5)	8.9	67.5
	〃	(1) and	〃	(2.0)	9.5	33.8
	〃	)1) and	〃	(2.5)	9.7	10.4
10e	N- 〃	(1)			3.5	37.6
	〃	(1) and	〃	(0.5)	5.7	42.6
	〃	(1) and	〃	(1)	6.6	42.6
	〃	(1) and	〃	(1.5)	7.2	12.8
	〃	(1) and	〃	(2.0)	7.6	3.6
	〃	(1) and	〃	(2.5)	8.5	0.0

ponding to OH and NH stretching vibration at 3140cm^{-1}, $^{+}NH_3$ and $-CH_2$ stretching vibration of the cysteine moiety at 3200–2800cm^{-1},ester carbonyl at 1740cm^{-1}, assym. bending of $^{+}NH_3$ and assym. stretching vibration of COO–at 1620cm^{-1}, SCH_2 at 1420cm^{-1} and $-O-CH_2$ at 1250cm^{-1}. The stretching vibration of conjugated C=C at 1570–1600cm^{-1} disappeared. The UV spectra in methanol (Table 3) show marked decrease in absorptions at λ_{max} of the corresponding β,β-diethoxycarbonylstrene derivatives, indicating again the absence of C=C bond in the adduct. The nmr spectra also agree well with the proposed atructure (Table 5).

The yields of the reactions between β,β-diethoxycarbonylstyrenes and L-cysteine at various pH are summarized in Table 6.

In each case, an appropriate amount of triethylamine was added to adjust the pH. As may be seen, the yields are always higher at neutral pH than those at acidic or basic region (Figure 1).

The low yields observed at low pH may be ascribed to the low concentration of the reactive thiolate anion. At high pH, the competing hydrolysis of β,β-diethoxycarbonylstyrenes may become predomiant, decreasing the yields. The detailed mechanism of the rections between β,β-diethoxycarbonylstyrenes and L-cysteine over the entire range of pH will be the subject of our future investigation.

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References

(1) J. C. Sheehan and D. H. Yang, *J. Amer. Chem. Soc.*, **80**, 1158 (1958).
(2) G. E. Foley, E. F. Barell, R. A. Adams and H. Lazarus, *Exp. Cell. Res.*, **57**, 129 (1969).
(3) K. A. Harrap and D. E. M. Speed, *Br. J. Cancer Res.*, **18**, 809 (1964).
(4) K. Y. Zee-Cheng and C. C Cheng, *J. Med. Chem.*, **13**, 414 (1970).
(5) K. Y. Zee-Cheng and C. C Cheng, *J. Med. Chem.*, **15**, (1972).
(6) T. R. Kim and S. Y. Choi, *Bull. Korean Chem. Soc.*, **2**, 125 (1981).
(7) T. R. Kim, S. Y. Choi and W. S. Choi, *Bull. Korean Chem. Soc.*, **4**, 92 (1983).
(8) N. Runsch, *et al., FEBS Letters*, **30**, 286 (1976).
(9) M. Esterbauer, *Carbohydrate Res.*, **43**, 779 (1975).
(10) I. H. Hall, K. H. Lee, E. C. Mar and C. O. Starness, *J. Med. Chem.*, **20**, 333 (1977).
(11) H. Esterbauer ,A. Ertl and N. Soholz, *Tetrahedron*, **32**, 285 (1976).
(12) B. Paul and W. Korytnyk, *J. Med. Chem.*, **19**, 1002 (1976).
(13) N. Runsch, *et al., FEBS letters*, **30**, 286 (1976).
(14) M. Esterbauer, *Carbohydrart Res.*, **43**, 779 (1975).
(15) I. H. Hall, K. H. Lee, E. C. Mar and C. O. Starness, *J. Med. Chem.* **20**, 333 (1977).
(16) *Org. Synthesis Coll*, Vol. 3, 377 (1955).