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Synthesis of Nucleophilic Adducts of Thiols(XI). Addition of L-Cysteine to β,β-Dinitrostyrene Derivatives

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The addition of L-cysteine without blocking amino and carboxyl groups to β,β-dinitrostyrene derivatives(11a-e) were investigated. β,β-Dinitrostyrene derivatives(11a-e) easily undergo addition reactions with L-cysteine to from s-(2,2-dinitro-1-phenylethyl)-L-cysteine(12a), s-[2,2-dinitro-1-(p-methyl)phenylethyl]-L-cysteine(12b), s-[2,2-dinitro-1-(p-methoxy)phenyl-eyhyl]-L-cysteine(12c), s-[2,2-dinitro-1-(p-chloro)phenylethyl]-L-cysteine (12d) and s-[2,2-dinitro-1-(p-nitro)phenyl-ethyl] -L-cysteine(12a), respectively. The structure of adducts were confirmed by means of spectral data, molecular weight measurement and elemental analysis.

Introduction

There have been growing interests in synthesis of cysteinyl peptide derivatives with biological activities.[1-5]

In the previous papers, we reported the synthesis of s-(2-nitro-1-phenylethyl)-L-cysteine,[6] s-(2-nitro-1-phenylethyl)-L-glutathione[7] and s-(2,2-diethoxycarbonyl-1-phenylethyl)-L-cysteine derivatives.[8]

In each case, the product was obtained in excellent yields from β-nitrostyrene and β,β-diethoxycarbonylstyrene with L-cysteine or glutathione under mild condition. The major advantage of this synthesis is that biologically important[9-11] products can be obtained in good yields by simple addition reactions without protecting the functional groups.[12,13]

In this work, we have synthesized a series of s-(2,2-dinitro-1-phenylethyl)-L-cysteine derivatives from the reaction of β,β-dinitrostyrene derivatives with L-cysteine.

Experimental

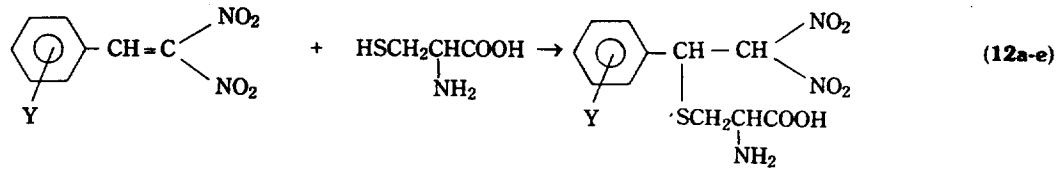
General. Melting point was determined on a Fisher Johns melting point apparatus. Infrared spectra was obtained with a JASCO A-102 IR spectrophotometer. UV-spectra was recorded on a JASCO UNIDEC-430B UV-spectrophotometer. Proton NMR spectra was obtained with a Varian Model EM-360 spectrometer in DMSO-d_6. Elemental analyses were conducted with MOO-1106 Model Carlo Erba, Italy. Optical rotation was measured with a JASCO DIP-181 polarimeter. All of the reagents were commercially available and used without further purification.

Synthesis of β,β-Dinitrostyrene. β,β-Dinitrostyrene derivatives were prepared from β-nitrostyrene[14] and nitrogen oxide by the well-known method.[15]

Synthesis of s-(2,2-Dinitro-1-phenylethyl)-L-cysteine Derivatives. L-Cysteine hydrochloride monohydrate, 0.91g. (0.005 mole) and N-methylmorphorine, 0.81g. (0.008 mole) were dissolved in 5m*l*. of water and 12m*l*. of acetonitrile. β,β-Dinitrostyrene(**11a**), 1.0g. (0.005 mole) was added to the solution and the mixture was adjusted to pH 5.0~6.0 with ammonia water and was stirred for 12 hours until the product was competely precipitated. The product was collected by filtration, washed with 1:1 aqueous methanol, and dried (The yield was 1.14g., 72.4%). The maximum yields, melting point, result of the elemental analysis and the UV, IR and NMR spectral data are recorded in Table 1, 2 and 3, respectively.

Determination of Molecular Weight and Optical Rotation of s-(2,2-Dinitro-1-phenyl)-L-cysteine Derivatives. Sixty four point three mg. of s-(2,2-dinitro-1-phenylethyl)-L-cysteine was dissolved in the mixture of glacial acetic acid(50.00m*l*.) and formic acid(1m*l*.). The solution was treated with crystal violet indicator, and titrated with 0.1N $HClO_4$. Since 1.0 m*l*. of 0.1N $HClO_4$ is equivalent to 0.031537g. of s-(2,2-dinitro-1-phenylethyl)-L-cysteine, the molecular weight of the adduct was calculated from the volume of $HClO_4$ solution added to reach the end point. Op-

Table 1. Yield, Melting Point and Analytical Data of s-[2,2-Dinitro-1-(substituent) phenylethyl]-L-cysteine Derivatives



(12a-e)

Y	Yield, %	mp., °C	Analytical Data of Element, wt., %							
			Calcd.				Found.			
			C	H	N	S	C	H	N	S
H (**12a**)	72.4	190-192	41.30	4.16	13.33	10.17	41.85	4.21	13.45	10.35
p-CH_3 (**12b**)	65.3	228-230	43.75	4.59	12.76	9.74	43.93	4.65	12.78	9.77
p-OCH_3(**12c**)	60.2	188-190	41.74	4.38	12.17	9.29	41.80	4.33	12.21	9.35
p-Cl (**12d**)	75.4	200-203	37.37	3.46	12.02	9.17	37.69	3.49	12.11	9.13
p-NO_2 (**12e**)	62.4	210-212	36.67	3.36	15.55	9.08	36.73	3.42	15.86	9.10

Table 2. Characteristic UV and IR Absorption of β,β-Dinitrostyrene and s-(2,2-Dinitro-1-phenylethyl)-L-cysteine Derivatives

Compds.	UV, nm.	IR-band, cm^{-1}, KBr pellet
11a	316	1620 (C = C), 1510, 1320 (-NO_2)
11b	334	1640 (C = C), 1540, 1330 (-NO_2)
11c	312	1600 (C = C), 1500, 1310 (-NO_2)
11d	329	1620 (C = C), 1500, 1320 (-NO_2)
11e	312	1600 (C = C), 1500, 1320 (-NO_2)
12a	250	3300-2400(-OH), 3400(-NH_2), 164(C = C), 1580, 1330(-NO_2)
12b	243	3420(-NH_2), 3300-2400(-OH), 1640(C = C), 1580, 1320(-NO_2)
12c	275	3450(-NH_2), 3350-2400(-OH), 1640(C = C), 1580, 1320(-NO_2)
12d	247	3400(-NH_2), 3300-2400(-OH), 1630(C = C), 1580, 1320(-NO_2)
12e	262	3400(-NH_2), 3300-2400(-OH), 1640(C = C), 1580, 1320(-NO_2)

Table 3. NMR Spectra of s-(2,2-Dinitro-1-phenylethy)-L-cysteine Derivatives

Compds.	Chemical shift in ppm (DMSO-d_6)
12a	2.3(m,2H:NH_2), 3.5(d,2H:CH_2), 3.9(t,1H:CH), 6.2(D,1H:CH), 7.6(S,5H:phenyl), 8.2(d,1H:CH)
12b	1.9(m,2H:NH_2), 2.8(s,3H:CH_3), 3.4(d,2H:CH_3), 3.9(d,2H:CH_2), 3.9(t,1H:CH), 6.1(d,1H:CH), 6.8-7.2(q,4H:phenyl), 8.0(d,1H:CH)
12c	1.9(m,2H:NH_2), 2.9(d,2H:CH_2), 3.6(s,3H:OCH_3), 4.0(t,1H:CH), 6.0(d,1H:CH), 8.1(d,1H:CH), 7.8-8.0(q,4H:phenyl)
12d	2.1(m,2H:NH_2), 2.9(d,2H:CH_2), 3.6(t,1H:CH), 6.5(d,1HCH), 7.8(s,4H:phenyl), 8.0(d,1H:CH)
12e	2.4(m,2H:NH_2), 3.1(d,2H:CH_2), 3.9(m, 1H:CH), 6.3(d,1H:CH), 8.0(s,5H:phenyl, CH)

tical Rotation of the adducts(5% solution) was determined in 0.1N hydrochloric acid. The results of optical rotation and molecular weight are recorded in Table 4.

Table 4. Optical Rotation and Molecular Weight of s-(2,2-Dinitro-1-phenylethyl)-L-cysteine Derivatives

Compds.	$[\alpha]_D$	Amine content,%	Molecular weight	
			Calcd.	Found.
12a	+24.1	100.50	315.31	316.80
12b	+36.4	99.79	329.34	328.64
12c	+13.2	99.30	345.34	342.92
12d	+15.4	100.30	349.76	350.81
12e	+21.4	99.40	360.32	358.16

[a] Determined in 1.0N-HCl solution.

Result and Discussion

A series of s-(2,2-dinitro-1-phenylethyl)-L-cysteine derivatives were obtained in excellent yields from the reaction of the β,β-dinitrostyrene with L-cysteine under mild condition. The yields and physical constants of the products are recorded in 1,2,3,4 and 5.

The structure of the adducts was characterized by the analytical and spectral data. The results of elemental analyses and molecular weight determination (Table 1) were consistent with those expected from the adducts. The infrared spectra (Table 2) showed characteristic peaks correspond to OH and NH stretching vibration 3400cm^{-1}, 3300-2400cm^{-1}, respectively; COO^-, 1640cm^{-1}; NO_2, 1580 and 1330cm^{-1}. The stretching vibration of conjugated carbon-carbon double bond at 1600-1640 cm^{-1} disappeared. The UV-

Table 5. The yield of s-(2,2-Dinitro-1-phenylethyl)-L-cysteine Derivatives with the Various pH

pH	Yield of adducts(**12a-e**), wt., %				
	12a	**12b**	**12c**	**12d**	**12e**
3.0-3.7	32.5	58.2	72.3	56.3	28.2
4.3-4.5	52.8	65.8	79.2	73.0	36.6
5.8-6.8	72.4	90.8	85.0	90.2	48.6
7.2-7.9	72.4	95.7	85.0	93.5	43.6
8.2-8.9	29.8	78.2	69.8	67.5	8.6
9.4-9.5	small	16.4	43.2	32.8	nothing
9.7-9.8	small	nothing	22.5	12.4	nothing

spectra in dioxane (Table 2) showed marked decrease in absorptions at λ_{max} of corresponding β,β-dinitrostyrene derivatives, indicating again the absense of carbon-carbon double bond in the adducts. The NMR spectra (Table 3) are in good agreement with the proposed structure (Table 1).

The yields of the products the dependence between β,β-dinitrostyrene and L-cysteine upon pH were experimented (Table 5). The lower yields observed at lower pH may be ascribed to the decreased concentration of reactive thiolate anion. At higher pH, the competing hydrolysis of β,β-dinitrostyrene may be predominent, thus decrease the yields.

In spite of many applications of nucleophilic addition reaction, the number of qualitative observations suggest a quite plausible mechanism, it has been the subject of only a few kinetic studies. Thus, attempts have to be made to reveal the exact reaction mechanism[7] of the L-cysteine addition to β,β-dinitrostyrene in future.

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The Terminal-Phosphinidene Complexes. Bonding, Geometrical Optimization, and Electronic Considerations

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The molecular interaction and geometrical optimization of $Cr(CO)_5$ and $Ni(CO)_3$ units have been studied for phosphinidene complex by means of extended Hückel calculations. The results were compared with those of *ab initio* calculations and found to be in qualitative agreement. Geometrical optimization of $HPCr(CO)_5$ (1) and $HPNi(CO)_3$ (2) gave the values R = 2.36 Å, θ = 111.5°, and ϕ = 45° for 1, and R = 2.37 Å, θ = 120°, and ϕ = 58° for 2. It is found that the low rotational barriers for 1(0.46 kcal mol^{-1}) and 2(0.12 kcal mol^{-1}) would be accompanied by the free rotation, in spite of the fact that both 1 and 2 adopt staggered conformations.

Introduction

Metal carbene complexes of the type R_2CML_n are of considerable importance as intermediates of many organometallic reactions.[1] Terminal-phosphinidene complexes of the type $RPML_n$ which are closely related to metal carbene complexes are of interest as one of the special bonding modes in organometallic chemistry. Recently, such complexes of the transition metals, Cr, Mo, W[2], and Fe[3], have been reported and known as short-lived species. So far, no crystal structures have yet been reported. As we are interested in the nature of the M=P bond, and the origin of the reactivity of the phosphinidene complexes, we have chosen the hypothetical terminalphosphinidene complexes $HPCr(CO)_5$ (1) and $HPNi(CO)_3$ (2).