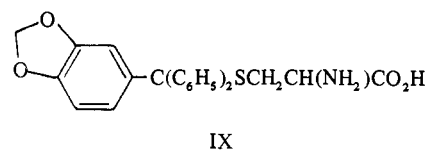
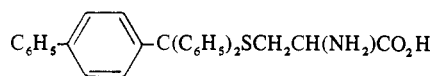


carboxy) analog of *S*-trityl-L-cysteine (VIIb) by condensation of the intermediate dicarboxylic acid VIb with L-cysteine was not realized.^{††}

For a comparison of activity with previously synthesized compounds, the *p*-phenyl derivative of *S*-trityl-L-cysteine (VIII) and the corresponding 3,4-methylenedioxyphenyl derivative IX were prepared from the appropriately substituted trityl alcohols by reported procedures.¹



Biological Activity and Discussion. Tables I and II list test results^{‡‡} of dipeptides of *S*-trityl-L-cysteine and *S*-(substituted trityl)-L-cysteines, respectively, against leukemic L-1210. Results are summarized as follows. (a) Activity of some *S*-trityl-L-cysteinyl amino acids (III-1, III-2, III-4, III-5) is observed but is of a lesser degree than that of the parent compound.¹ *N*-Substituted dipeptides and derivatives (III-7 to III-22) are inactive. (b) Monohydroxymethyl-substituted *S*-trityl-L-cysteine Ve still retains the original activity. However, the corresponding bis(hydroxymethyl) compd VIIa is devoid of activity. (c) Carboxy-substituted trityl-L-cysteine Va and its salts Vb and Vc are without activity. (d) Although the cation localization energy¹² of 4 position of biphenyl is closer to that of the 2 position rather than 1 position of the naphthalene ring, L-3-[[4-biphenyl]diphenylmethyl]thio]alanine (VIII), as in the case of *S*-(1-naphthyl)diphenylmethyl-L-cysteine,¹ possesses no activity, whereas *S*-(2-naphthyl)diphenylmethyl-L-cysteine is quite active.¹ This suggests that steric requirements of the trityl position are more important than considerations of electron localization,¹² acidity of hydrocarbon,¹³ or free

^{††}This may be due to (1) high acidity of VIb (the monocarboxylic acid IVb was sol in dil aq NaHCO₃, whereas the dicarboxylic acid VIb was sol in dil aq NaOAc), which hampers carbonium ion formation; the latter is necessary for the condensation reaction; or (2) the tritylcarbon-S bond, even if formed, is readily cleaved in acid medium stronger than AcOH.

^{‡‡}Test results were provided by contract screeners of CCNSC. Detailed interpretations of test data are provided in reference 11.

radical stability for antileukemic activity. (e) The activity of the 3,4-methylenedioxy derivative of *S*-trityl-L-cysteine (IX) is comparable to the corresponding *p*-methoxy¹ or bis(*p*-methoxy)¹ analogs. The methylenedioxy compound is slightly less toxic than the MeO compounds.

Experimental Section

All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus by a special method of determination.¹ Analyses (C, H, N) obtained for compds reported throughout this paper were within ±0.4% of the theoretical values.

For the prepn of dipeptides of *S*-trityl-L-cysteine, an example for the ditrityl derivative of L-cysteinyl-L-cysteine is given. Other peptides were prepd in a similar manner.

Diethylamine Salt of *N,S*-Ditrityl-L-cysteine (II). To a rapidly stirred cold mixt of 35.1 g (0.2 mole) of L-cysteine hydrochloride monohydrate in 600 ml of H₂O was added at 0° and under N₂, 102 ml of Et₃NH in 600 ml of Et₂O followed by 152 g (0.54 mole) of Ph₃CCl in small portions. The mixt was stirred in ice bath for 4 hr and extd with 3 × 800 ml of Et₂O. The Et₂O ext was washed (H₂O) and dried (Na₂SO₄). The solvent was removed and the residue recrystd from CHCl₃-EtOH to give 95 g (70% yield) of II, mp 205–207° (lit.⁶ no mp reported). *Anal.* (C₄₅H₄₆N₂O₂S) C, H, N.

Et Ester of *N,S,S'*-Trityl-L-cysteinyl-L-cysteine (III-18, See Table I). To a stirred mixt of 41 g (0.06 mole) of II in 110 ml of CH₂Cl₂ was added at 0° a soln of 30.5 g (0.07 mole) of Et ester of *S*-trityl-L-cysteine hydrochloride¹ in 100 ml of CH₂Cl₂ followed by 15 g (0.072 mole) of DCC. The mixt was stirred at room temp for 18 hr. The urea was sep'd by filtration and washed with CH₂Cl₂. The combined filtrate and washings were washed successively with H₂O, 0.4 N HCl, dil NaHCO₃, and H₂O, and dried (Na₂SO₄). The solvent was removed, and the residue was recrystd from CH₂Cl₂-EtOH to give 46 g (79% yield) of product, mp 171–173°.

Et Ester of *S,S'*-Ditrityl-L-cysteinyl-L-cysteine Hydrochloride (III-6, See Table I). To a soln of 24 g (0.024 mole) of the aforementioned ester in a mixt of 75 ml of CH₂Cl₂ and 120 ml of Me₂CO was added, with cooling, 1.8 g (0.049 mole) of HCl in Et₂O. The resulting mixt was allowed to stand at room temp for 30 min. The solvent was removed at room temp, and the residue was triturated repeatedly with anhyd Et₂O. The solid was collected by filtration and dried (70° at 0.5 mm) to give 13 g (70% yield) of product, mp 135° dec.

***S,S'*-Ditrityl-L-cysteinyl-L-cysteine (III-3, See Table I).** A mixt of 12 g (0.015 mole) of salt III-6 in 120 ml of 1 N KOH in MeOH was heated on a steam bath with stirring for 5 min and filtered. The filtrate was acidified with 10% AcOH to pH 6 and cooled. The solid was collected by filtration, washed (H₂O), and recrystd (MeOH-H₂O) to give 10 g (90% yield) of product, mp 158° dec.

Prepn of amino acid derivatives of *N,S* ditrityl-L-cysteine (IIIc) from the corresponding ester IIIa was carried out under similar base hydrolysis procedure.



Me esters of amino acids used for our peptide synthesis were prep'd by the 2,2-dimethoxypropane-aq HCl method.⁷ The following 2 compds were not included in the original report.⁷ Me ester of L-valine hydrochloride, mp 158–160° (lit.¹⁴ mp 170°; lit.¹⁵ mp 161–162°), from 42.2 g of L-valine hydrochloride, 600 ml of 2,2-dimethoxypropane, 54 ml of concd HCl, and 100 ml MeOH, 87% yield. Me ester of L-aspartic acid hydrochloride, mp 115–117° (lit.¹⁴ 116–117°), 93% yield.

α-Hydroxy-α,α-diphenyl-*p*-toluic Acid (IVb). A mixt of 8.3 g (0.03 mole) of *p*-tolylidiphenyl methanol, 14.4 g (0.09 mole) of KMnO₄, and 600 ml of H₂O was gently refluxed for 14 hr with stirring. The mixt was cooled and filtered. The cake was washed (3 × 150 ml of H₂O). The combined filtrate and washings were concd *in vacuo* to 250 ml and cautiously acidified at 0° with concd HCl to give pH 2. The pptd acid was collected by filtration and dried to give 4 g of IVb, mp 191–195°. Recrystn from EtOH-H₂O gave analytically pure sample, mp 206–208°. (Extn of the filtered cake with CHCl₃ recovered 3 g of starting material.) *Anal.* (C₂₀H₁₆O₃) C, H.

α-(*p*-Carboxyphenyl)-α-hydroxy-α-phenyl-*p*-toluic acid (Vib) was prep'd in a similar fashion from 8.7 g of bis(*p*-tolyl)phenyl-methanol and 39 g of KMnO₄ in 600 ml of H₂O. The yield of Vib, mp 198–200°, was 84%. *Anal.* (C₂₁H₁₆O₅) C, H.

(*p*-Hydroxymethylphenyl)diphenylmethanol (IVc). A soln of 18.6 g (0.06 mole) of IVb in 320 ml of THF was added dropwise, with cooling, into a mixt of 10 g (0.26 mole) of LAH in 150 ml of THF. The mixt was stirred overnight, refluxed for 1 hr, cooled, and

Table I. Dipeptides of S-Trityl-L-cysteine

Compd	R ₁	R ₂	Molecular formula ^a	Mp, °C	Yield, %	Antileukemic activity vs. L-1210			
						Dose, mg/kg	Survivors	Wt. diff, T/C	T/C, %
$(C_6H_5)_3CSCH_2CH(NHR_1)COR_2$									
III-1	H	NHCH ₂ CO ₂ H	C ₂₄ H ₂₄ N ₂ O ₃ S	228–230 dec	67	400	7/18	–3.8	80
						300	8/10	0.4	138
						200	28/28	–1.8	146
						100	28/28	–1.5	130
						50	28/28	–1.2	121
						25	6/6	–0.4	110
III-2	H	(DL)NHCHCO ₂ H CH ₃	C ₂₅ H ₂₆ N ₂ O ₃ S	140 dec	60	400	4/12	–2.1	–
						200	7/12	–2.9	89
						100	12/12	–1.1	146
						50	12/12	–0.8	125
						25	12/12	–0.7	118
III-3	H	(L)NHCHCO ₂ H CH ₂ SC(C ₆ H ₅) ₃	C ₄₄ H ₄₀ N ₂ O ₃ S ₂	158 dec	90	50–400	Nontoxic, inact ^b		
III-4	H · HCl	(L)NHCHCO ₂ CH ₃ CH(CH ₃) ₂	C ₂₈ H ₃₂ N ₂ O ₃ S · HCl	125 dec	50	400	4/6	–1.4	104
						200	6/6	–1.8	127
						100	14/14	–0.9	120
						50	14/14	–0.1	111
III-5	H · HCl	(L)NHCHCO ₂ CH ₃ CH ₂ CH(CH ₃) ₂	C ₂₉ H ₃₄ N ₂ O ₃ S · HCl	163–165	74	400	5/6	–2.7	127
						200	6/6	–2.4	126
						100	6/6	–1.7	108
III-6	H · HCl	(L)NHCHCO ₂ C ₂ H ₅ CH ₂ SC(C ₆ H ₅) ₃	C ₄₆ H ₄₄ N ₂ O ₃ S ₂ · HCl	135 dec	70	400	Nontoxic, inact ^b		
III-7	C(C ₆ H ₅) ₃	NHCH ₂ CO ₂ H	C ₄₃ H ₃₈ N ₂ O ₃ S	127–129 dec	85	75–400	Nontoxic, inact ^b		
III-8	C(C ₆ H ₅) ₃	NHCH ₂ CO ₂ C ₂ H ₅	C ₄₅ H ₄₂ N ₂ O ₃ S	112–114 dec	92	50–400	Nontoxic, inact ^b		
III-9	C(C ₆ H ₅) ₃	(DL)NHCHCO ₂ H CH ₃	C ₄₄ H ₄₀ N ₂ O ₃	130 dec	95	75–300	Nontoxic, inact ^b		
III-10	C(C ₆ H ₅) ₃	(DL)NHCHCO ₂ C ₂ H ₅ CH ₃	C ₄₆ H ₄₄ N ₂ O ₃ S	125 dec	89	25–400	Nontoxic, inact ^b		
III-11	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ H CH(CH ₃) ₂	C ₄₆ H ₄₄ N ₂ O ₃ S	135 dec	87	200–400	Nontoxic, inact ^b		
III-12	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ CH ₃ CH(CH ₃) ₂	C ₄₇ H ₄₆ N ₂ O ₃ S · 0.5H ₂ O	163–165	76	40–400	Nontoxic, inact ^b		
III-13	C(C ₆ H ₅) ₃	(L)NH–CHCO ₂ H CH ₂ CH(CH ₃) ₂	C ₄₇ H ₄₆ N ₂ O ₃ S	140–142	68	50–400	Nontoxic, inact ^b		
III-14	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ CH ₃ CH ₂ CH(CH ₃) ₂	C ₄₈ H ₄₈ N ₂ O ₃ S	161–163	78	50–400	Nontoxic, inact ^b		
III-15	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ H CH ₂ CO ₂ H	C ₄₅ H ₄₀ N ₂ O ₅ S	145 dec	87	200–400	Nontoxic, inact ^b		
III-16	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ CH ₃ CH ₂ CO ₂ CH ₃	C ₄₇ H ₄₄ N ₂ O ₅ S	140 dec	91	50–400	Nontoxic, inact ^b		
III-17	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ C ₂ H ₅ (CH ₂) ₂ CO ₂ C ₂ H ₅	C ₅₀ H ₅₀ N ₂ O ₅ S	143–144	93	25–400	Nontoxic, inact ^b		
III-18	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ C ₂ H ₅ CH ₂ SC(C ₆ H ₅) ₃	C ₆₅ H ₅₈ N ₂ O ₃ S ₂	171–173	79	200–400	Nontoxic, inact ^b		
III-19	C(C ₆ H ₅) ₃	(L)NHCHCO ₂ H CH ₂ (<i>p</i> -C ₆ H ₄ OH)	C ₅₀ H ₄₄ N ₂ O ₄ S	150 dec	81	50–400	Nontoxic, inact ^b		
III-20	C(C ₆ H ₅) ₃	(L)NHCH–CO ₂ C ₂ H ₅ CH ₂ (<i>p</i> -C ₆ H ₄ OH)	C ₅₈ H ₄₈ N ₂ O ₄ S	183–185	85	50–400	Nontoxic, inact ^b		
III-21	C(C ₆ H ₅) ₃	 (L)CO ₂ H	C ₄₆ H ₄₂ N ₂ O ₃ S	148–150 dec	90	50–400	Nontoxic, inact ^b		
III-22	C(C ₆ H ₅) ₃	 (L)CO ₂ CH ₂ C ₆ H ₅	C ₅₃ H ₄₈ N ₂ O ₃ S	135 dec	88	50–400	Nontoxic, inact ^b		

^aAll compds analyzed correctly for C, H, N. ^bAll animals survived, T/C below 124.

Table II. *S*-(Substituted trityl)-L-cysteines

Compd	Molecular formula ^a	Mp, °C	Yield, %	Antileukemic activity vs. L-1210			
				Dose, mg/kg	Survivors	Wt. diff, T - C	T/C, %
Va	C ₂₃ H ₂₁ NO ₄ S	175-177 dec	76	25-400	Nontoxic and inact ^b		
Vb	C ₂₃ H ₂₀ NNaO ₄ S · H ₂ O	195-197 dec	95	25-400	Nontoxic and inact ^b		
Vc	C ₂₃ H ₂₀ (Ga) _{1/3} NO ₄ S · H ₂ O	224-225 dec	90	100-400	Nontoxic and inact ^b		
Ve	C ₂₃ H ₂₃ NO ₃ S	145-147 dec	70	600	6/6	-1.7	168
				400	18/18	-2.5	162
				265	12/12	-1.0	148
				175	6/6	-1.3	146
				85	6/6	-0.8	127
VIIa	C ₂₄ H ₂₅ NO ₄ S	143-145 dec	69	25-400	Nontoxic and inact ^b		
VIII	C ₂₈ H ₂₅ NO ₂ S	177-178 dec	35	25-400	Nontoxic and inact ^b		
IX	C ₂₃ H ₂₁ NO ₄ S	187-189 dec	95	400	1/6	-6.1	
				200	6/6	-6.8	
				100	6/6	-2.0	164
				50	6/6	-1.1	120

^aAll compds analyzed correctly for C, H, N. ^bAll survived. T/C below 124.

decompd with H₂O. The product was isolated by Et₂O extn in the usual manner and recrystd (EtOH-hexane) to give 14.8 g (85% yield) of IVc, mp 115-117°. *Anal.* (C₂₀H₁₈O₂) C, H.

Bis(*p*-hydroxymethylphenyl)phenylmethanol (VIc) was prepd in a similar fashion in 82% yield, mp 120-122°. *Anal.* (C₂₁H₂₀O₃) C, H.

L- α -[(2-Amino-2-carboxyethyl)thio]- α,α -diphenyl-*p*-toluic acid (Va) was prepd from 6.3 g (0.04 mole) of anhyd L-cysteine hydrochloride, 13 g (0.043 mole) of IVb, 60 ml of AcOH, and 11 ml of BF₃-Et₂O by a reported general procedure.¹ The yield was 12.5 g, mp 175-177° dec. The compd gave a positive ninhydrin test; p*K*_a = 4.38. *Anal.* (C₂₃H₂₁NO₄S) C, H, N.

Monosodium salt of Va (Vb) was prepd by addn of an equiv of aq NaHCO₃ to an MeOH soln of Va. The mixt was evapd to dryness *in vacuo*, and the residue was triturated successively with EtOH, Et₂O, and hexane, mp 195-197° dec. The product was very sol in H₂O. It gave a positive ninhydrin test. *Anal.* (C₂₃H₂₀NNaO₄S · H₂O) C, H, N.

Ga Salt of Va (Vc). To a soln of 0.36 g of KHCO₃ in 50 ml of H₂O was added 1.5 g of Va followed by dropwise addn of a soln of 0.26 g of Ga₂(SO₄)₃ in 20 ml of H₂O, with stirring. The resulting white colloidal ppt was purified by centrifugation, decantation, and washing (H₂O, Me₂CO, and Et₂O, successively) to give 1.6 g of Vc, mp 224-225° dec. The product gave a positive ninhydrin test after long standing. It was quite insol in boiling H₂O (less than 1 g/l). *Anal.* (C₂₃H₂₀Ga_{1/3}NO₄S · H₂O) C, H, N.

L-3-[[*p*-(Hydroxymethyl)- α,α -diphenylbenzyl]thio]alanine (Ve) was prepd from 6.5 g of IVc, 3.5 g of anhyd L-cysteine hydrochloride, 25 ml of AcOH, and 5.4 ml of BF₃-Et₂O by a reported general procedure.¹ The product was contaminated with the *p*-acetoxymethylphenyl compd Vd, mp 148-150°, which was converted to Ve by hydrolysis in 1 *N* KOH in MeOH at 40-50° for 10 min followed by acidification with 50% AcOH. The product was purified by recrystn from MeOH-H₂O, mp 145-147° dec. It gave a positive ninhydrin test. Solubility in hot H₂O was 0.1 g per 100 ml. *Anal.* (C₂₃H₂₃NO₃S) C, H, N.

Substituted *S*-trityl-L-cysteines, L-3-[[α,α -bis(α -hydroxy-*p*-tolyl)benzyl]thio]alanine (VIIa), L-3-[[4-biphenyl]diphenylmethyl]-

thio]alanine (VIII), and L-3[[α,α -diphenylpiperonyl]thio]alanine (IX), were prepd by same general procedures.

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