Structural Modification of S-Trityl-L-cysteine. Preparation of Some S-(Substituted Trityl)-L-cysteines and Dipeptides of S-Trityl-L-cysteine[†]

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A continued study of structural modification of S-trityl-L-cysteine reveals that for antileukemic activity, steric requirements of the trityl position appear to be more important than consideration of electron localization, hydrocarbon activity, or free radical stability. Activity of certain S-trityl-L-cysteinyl amino acids is observed but is of lesser degree than that of the parent S-trityl-L-cysteine. N-Substituted dipeptides and derivatives of S-trityl-L-cysteine are devoid of activity. Monohydroxymethyl-substituted S-trityl-L-cysteine still retains the original activity whereas the corresponding bis(hydroxymethyl) analog is inactive.

Results from our preliminary structure-activity study¹ of compounds related to the amino acid S-trityl-L-cysteine (I) indicated that the zwitterion form of this molecule may be of importance to its antileukemic property. This is illustrated by the fact that conventional modification of the aliphatic side chain of I (e.g., alkylation, decarboxylation, esterification, etc.) yielded derivatives of inferior activity, whereas substitution on the aromatic ring(s) with mild electron-withdrawing or electron-donating groups often retained or improved the antileukemic activity of the parent compound. These data suggested that either the cysteine portion of I may serve as a carrier for the active transport of the trityl radical or the tritylated amino acid itself may be utilized for in vivo protein synthesis. Since a number of polypeptides possess cross-linked S-S bonds, blockage of the SH group of cysteine by a bulky trityl group could prevent the formation of such a linkage; hence, subsequent protein synthesis may be affected.

(C₆H₅)₃CSCH₂CH(NH₂)COOH

It has been shown that during the process of polypeptide synthesis on ribosomes, some low molecular weight, shortchain peptides can also be directly utilized along with individual amino acids.²⁻⁴ This suggested that synthesis and evaluation of some peptide derivatives of I may be of interest. Furthermore, the additional amino acid unit may modify the aqueous-lipid distribution characteristics, which hopefully would compensate for the aq insolubility of the parent compound.[‡] Some S-(substituted trityl)-L-cysteines were also synthesized wherein the substituted groups are either of a hydrophilic nature or capable of forming watersoluble salts. Compounds related to the ring-hydroxylated derivatives were not considered because of the toxicity exhibited by the phenolic compound 3-[(p-hydroxy- α,α -diphenylbenzyl)thio]-L-alanine.¹

Chemistry. 1. Dipeptides of Trityl-L-cysteine. The general synthesis of Amiard, *et al.*,⁶ was adopted. The Et₂NH salt of *N*,*S*-ditrityl-L-cysteine (II) was prepared from L-cysteine, trityl chloride, and Et₂NH. Treatment of II with the HCl salt of the appropriate ester of amino acids^{1,7} in presence of *N*,*N*'-dicyclohexylcarbodiimide yielded the ester of *N*,*S*-ditrityl-L-cysteinyl derivative of the amino

acid IIIa. The desired dipeptide IIId§ was obtained either by selective detritylation of IIIa to IIIb followed by hydrolysis or by hydrolysis of IIIa to IIIc followed by selective detritylation.

$$(C_{6}H_{5})_{3}CSCH_{2}CHCO_{2}^{-}H_{2}N^{+}(C_{2}H_{5})_{2}$$

$$\stackrel{|}{NHC}(C_{6}H_{5})_{3}$$
II
$$(C_{6}H_{5})_{3}CSCH_{2}CHCONHCHCO_{2}R$$

$$\stackrel{|}{NHY}$$

$$Z$$

IIIa,
$$Y = C(C_6H_5)_5$$
; $R = alky1$
b, $Y = H \cdot HC1$; $R = alky1$
c, $Y = C(C_6H_5)_5$; $R = H$
d, $Y = R = H$

2. S-(Substituted trityl)-L-cysteines. Introduction of CO_2H and CH_2OH groups on the Ph ring(s) was carried out as follows. Oxidation of p-tolydiphenylmethanol (IVa) with KMnO₄ yielded the corresponding carboxylic acid derivative IVb. LAH reduction of this acid afforded (p-hydroxy-methyl)diphenylmethanol (IVc). Condensation of IVb with L-cysteine by the BF₃-AcOH method¹ gave the p-carboxyl derivative of S-trityl-L-cysteine (Va). The corresponding Na salt# (Vb) and Ga salt** (Vc) were also prepared. Treatment of IVc with L-cysteine under similar reaction conditions yielded a mixture of the p-acetoxymethyl derivative of S-trityl-L-cysteine (Vd) and the corresponding p-hydroxymethyl compound Ve. Vd was readily converted to Ve by mild saponification.

The still limited water solubility of Ve prompted the preparation of the corresponding bis(p-hydroxymethyl) analog VIIa from bis(p-tolyl)phenylmethanol (VIa) by an analogous route. Attempted preparation of the bis(p-

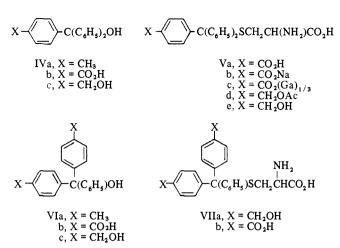
[†]This investigation was supported by Contract No. PH-43-65-94 with Chemotherapy, National Cancer Institute, of the National Institutes of Health, Public Health Service.

[‡]Even the water dilution tolerance of compound I in nonaqueous nontoxic solvent such as propylene glycol⁵ was too low for practical use.

[§] The presence of both polar and nonpolar functions in these dipeptides and their intermediates caused the formation of rather stable emulsions during the process of purification. Even in the presence of a trace of H_2O or EtOH, these compds usually sepd in the form of a gel or gum. Analytically pure products often appeared as amorphous solids with a wide melting range.

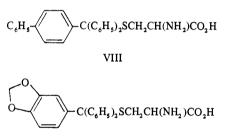
[#]Compd Va was sol in dil NaHCO₃ solution. Its disodium salt did not give a positive ninhydrin test; but the monosodium salt Vb was ninhydrin positive, indicating the existence of the desired zwitterion form of the monosodium salt. The fact that the salt formation was at the aromatic acid portion rather than at the amino acid portion was further substantiated by the fact that pK_a of the monosodium salt was 4.38, which is comparable to that of *p*-toluic acid (pK_a : 4.36).

^{**}Some Ga salts were reported to show selective affinity to malignant tumor cells. See, for example, Edward and Hayes,⁸ Swatzendruber, *et al.*,⁹ and Ando and Hisada.¹⁰



carboxy) analog of S-trityl-L-cysteine (VIIb) by condensation of the intermediate dicarboxylic acid VIb with Lcysteine 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



IX

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) Monohydroxymethylsubstituted 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 energy 12 of 4 position of biphenyl is closer to that of the 2 position rather than 1 position of the naphthalene ring, L-3-{ [(4-biphenylyl)diphenylmethyl]thio}alanine (VIII), as in the case of S-(1-naphthyldiphenylmethyl)-L-cysteine,¹ possesses no activity, whereas S-(2-naphthyldiphenylmethyl)-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

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 $\pm 0.4\%$ 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 Et₂NH 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. (C_a₉H₄₆N₂O₂S) 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 sepd 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 recryst 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 prepd 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 2,2dimethoxypropane, 54 ml of concd HCl, and 100 ml MeOH, 87% yield. Me ester of L-aspartic acid hydrochloride, mp 115-117° (lit.¹⁶ 116-117°), 93% yield.

α-Hydroxy-α,α-diphenyl-p-toluic Acid (IVb). A mixt of 8.3 g (0.03 mole) of p-tolydiphenyl 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 conced *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 prepd in a similar fashion from 8.7 g of bis(p-tolyl)phenylmethanol and 39 g of KMnO₄ in 600 ml of H₂O. The yield of VIb, mp 198-200°, was 84%. Anal. $(C_{21}H_{16}O_5)$ 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

 $[\]dagger$ 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.

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

| | | | | | Yield, % | Antileukemic activity vs. L-1210 | | | |
|--------|--|--|---|-----------------|-------------|--------------------------------------|---|--|---------------------------------------|
| Compd | R ₁ | R ₂ | Molecular formula ^a | Mp, °C | | Dose, mg/kg | Survivors | Wt. diff, <i>T/C</i> | <i>T/C</i> , % |
| | | | (C ₆ H ₅) ₃ CSCH | 2CH(NHR 1)COR 2 | | | | | |
| III-1 | Η | NHCH₂CO₂H | C ₂₄ H ₂₄ N ₂ O ₃ S | 228-230 dec | 67 | 400 300 200 100 50 25 | 7/18 8/10 28/28 28/28 28/28 28/28 6/6 | -3.8 0.4 -1.8 -1.5 -1.2 -0.4 | 80 138 146 130 121 110 |
| III-2 | н | (DL)NHCHCO₂H └ CH₃ | C25H26N2O3S | 140 dec | 60 | 400 200 100 50 25 | 4/12 7/12 12/12 12/12 12/12 12/12 | -0.4 -2.1 -2.9 -1.1 -0.8 -0.7 | - 89 146 125 118 |
| III-3 | Н | (L)NHCHCO ₂ H $\stackrel{ }{CH_2SC(C_6H_5)_3}$ | $C_{44}H_{40}N_2O_3S_2$ | 158 dec | 90 | 50-400 | Nontoxic, inact ^b | -0.7 | 110 |
| III-4 | H · HCl | (L)NHCHCO ₂ CH ₃ CH(CH ₃) ₂ | $\mathrm{C_{28}H_{32}N_2O_3S}\cdot\mathrm{HC1}$ | 125 dec | 50 | 400 200 100 50 | 4/6 6/6 14/14 14/14 | -1.4 -1.8 -0.9 -0.1 | 104 127 120 111 |
| III-5 | H · HC1 | $(L)NHCHCO_2CH_3 \\ \downarrow \\ CH_2CH(CH_3)_2$ | C ₂₉ H ₃₄ N ₂ O ₃ S · HCl | 163-165 | 74 | 400 200 100 | 5/6 6/6 6/6 | -2.7 -2.4 -1.7 | 127 126 108 |
| III-6 | H · HC1 | (L)NHCHCO ₂ C ₂ H ₅ $\stackrel{ }{CH_2SC(C_6H_5)_3}$ | $\mathrm{C_{46}H_{44}N_2O_3S_2}\cdot\mathrm{HCl}$ | 135 dec | 70 | 400 | Nontoxic, inact ^b | -1.7 | 100 |
| III-7 | $C(C_6H_5)_3$ | NHCH ₂ CO ₂ H | $C_{43}H_{38}N_2O_3S$ | 127-129 dec | 85 | 75-400 | Nontoxic, inact ^b | | |
| III-8 | $C(C_6H_5)_3$ | NHCH ₂ CO ₂ C ₂ H ₅ | $C_{45}H_{42}N_2O_3S$ | 112-114 dec | 92 | 50-400 | Nontoxic, inact ^b | | |
| III-9 | $C(C_{\boldsymbol{6}}H_{\boldsymbol{5}})_{\boldsymbol{3}}$ | (DL)NHCHCO ₂ H CH ₃ | $C_{44}H_{40}N_2O_3$ | 130 dec | 95 | 75-300 | Nontoxic, inact ^b | | |
| III-10 | C(C ₆ H ₅) ₃ | $(DL)NHCHCO_2C_2H_5$ $(DL)CH_3$ | $C_{46}H_{44}N_2O_3S$ | 125 dec | 89 | 25-400 | Nontoxic, inact ^b | | |
| III-11 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ H | C ₄₆ H ₄₄ N ₂ O ₃ S | 135 dec | 87 | 200-400 | Nontoxic, inact ^b | | |
| III-12 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ CH ₃ $\stackrel{ }{\leftarrow}$ CH(CH ₃) ₂ | $C_{47}H_{46}N_2O_3S \cdot 0.5H_2O$ | 163-165 | 76 | 40-400 | Nontoxic, inact ^b | | |
| III-13 | $C(C_6H_5)_3$ | (L)NH-CHCO ₂ H \downarrow CH ₂ CH(CH ₃), | $C_{47}H_{46}N_2O_3S$ | 140-142 | 68 | 50-400 | Nontoxic, inact ^b | | |
| III-14 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ CH ₃ CH ₂ CH(CH ₃) ₂ | $C_{48}H_{48}N_2O_3S$ | 161-163 | 78 | 50-400 | Nontoxic, inact ^b | | |
| III-15 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ H CH ₂ CO ₂ H | $C_{45}H_{40}N_2O_5S$ | 145 dec | 87 | 200-400 | Nontoxic, inact ^b | | |
| III-16 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ CH ₃ | C ₄₇ H ₄₄ N ₂ O ₅ S | 140 dec | 91 | 50-400 | Nontoxic, inact ^b | | |
| III-17 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ C ₂ H ₅ $(CH_2)_2CO_2C_2H_5$ | $\mathrm{C}_{\mathfrak{s0}}\mathrm{H}_{\mathfrak{s0}}\mathrm{N}_{2}\mathrm{O}_{\mathfrak{s}}\mathrm{S}$ | 143-144 | 93 | 25-400 | Nontoxic, inact ^b | | |
| III-18 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ C ₂ H ₅ $H_2SC(C_6H_5)_3$ | $\mathrm{C}_{65}\mathrm{H}_{58}\mathrm{N}_{2}\mathrm{O}_{3}\mathrm{S}_{2}$ | 171-173 | 79 | 200-400 | Nontoxic, inact ^b | | |
| III-19 | $C(C_6H_5)_3$ | (L)NHCHCO ₂ H $\stackrel{ }{CH_2(p-C_6H_4OH)}$ | C ₅₀ H ₄₄ N ₂ O ₄ S | 150 dec | 81 | 50-400 | Nontoxic, inact ^b | | |
| III-20 | $C(C_6H_5)_3$ | (L)NHCH- $CO_2C_2H_5$ $CH_2(p-C_6H_4OH)$ | $\mathrm{C}_{\mathfrak{s}\mathfrak{s}}\mathrm{H}_{\mathfrak{4}\mathfrak{s}}\mathrm{N}_{2}\mathrm{O}_{\mathfrak{4}}\mathrm{S}$ | 183-185 | 85 | 50-400 | Nontoxic, inact ^b | | |
| III-21 | $C(C_6H_5)_3$ | N | $C_{46}H_{42}N_2O_3S$ | 148-150 dec | 90 | 50-400 | Nontoxic, inact ^b | | |
| III-22 | $C(C_6H_5)_3$ | (L)ĊO₂H N | $\mathrm{C}_{\mathfrak{s}\mathfrak{z}}\mathrm{H}_{\mathfrak{s}\mathfrak{b}}\mathrm{N}_{2}\mathrm{O}_{\mathfrak{z}}\mathrm{S}$ | 135 dec | 88 | 50-400 | Nontoxic, inact ^b | | |

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

| Table I | Ι. | S-(Substituted | trityl)-L-cysteines |
|---------|----|----------------|---------------------|
|---------|----|----------------|---------------------|

| | | | | Antileukemic activity vs. L-1210 | | | | |
|-------|---|-------------|-------------|----------------------------------|---------------------------------|--------------------|-----------|--|
| Compd | Molecular formula ^a | Mp, °C | Yield, % | 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 | $C_{23}H_{20}(Ga)_{1/3}NO_4S \cdot H_2O$ | 224-225 dec | 90 | 100-400 | Nontoxic and inact ^b | | | |
| Ve | $C_{23}H_{23}NO_3S$ | 145-147 dec | 70 | 600 | 6/6 | -1.7 | 168 | |
| | 23 23 3 | | | 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 | 40 0 | 1/6 | -6.1 | | |
| | 25 21 4 | | | 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.* ($C_{20}H_{18}O_2$) C, H.

Bis(*p***-hydroxymethy1pheny1)***pheny1methanol* (VIc) was prepd in a similar fashion in 82% yield, mp 120–122°. *Anal.* ($C_{21}H_{20}O_3$) 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; pK_a = 4.38. Anal. (C₂₃H₂₁NO₄S) C, H, N. Monosodium salt of Va (Vb) was prepd by addn of an equiv of

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.* ($C_{23}H_{20}NNaO_4S \cdot H_2O$) 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)

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-trifyl-L-cysteines, L-3-{ $[\alpha,\alpha-bis(\alpha-hydroxy-p-tolyl)-benzyl]$ thio}alanine (VIIa), L-3-{[(4-biphenylyl)diphenylmethyl]-

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

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