Zusammenfassung

Beobachtungen bei der Reduktion von Reichsteins Substanz S (I) mittels Zink werden beschrieben. Hierbei können Cortexon (II), 17-Isocortexon (III) und 17-Isoprogesteron (IV) entstehen. Diese Ergebnisse werden diskutiert.

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**98. Hyozo Taniyama, Fumihiko Miyoshi, Yasuo Sano, Soichi Kubota,*¹
Eiichi Sakakibara,*² and Homare Uchida*³ : Synthesis and
Antibacterial Activity of Cystine Derivatives. II.*⁴**

(*Pharmaceutical Faculty, University of Osaka,*¹ Osaka University of Liberal Arts
and Education,*² and National Sanatorium Toneyama Hospital*³*)

For the purpose of preparing chemotherapeutics with specificity to species, anilide and hydrazide derivatives of L-cystine and L-cysteine were prepared and their antibacterial activity was reported in the preceding paper.¹⁾ Interesting results were found in their antibacterial action against tubercle bacilli; the cystine derivatives with amino group substituted with benzyloxycarbonyl group did not show practically any antitubercular action, with the exception of isonicotinoylhydrazide condensate and phenylhydrazide condensate, whereas L-cystine dianilide, by liberating this benzyloxycarbonyl group, showed a tremendous increase in the activity.

From these experimental data, it was presumed that L-cystine dihydrazide derivatives, especially isonicotinoylhydrazide condensate and phenylhydrazide condensate, should show a very strong activity by liberating the group. An attempt was made but in vain to prepare these hydrazide derivatives by the application of du Vigneaud's cystine peptide synthesis.²⁾ In the present series, these compounds were prepared successfully by a new route.³⁾

Further point to be noted was the antitubercular action of L-cystine bis(*p*-alkoxyanilide) derivatives. L-Cystine bis(*p*-methoxyanilide) inhibited the growth of tubercle bacilli in a concentration of 30 γ /cc. and L-cystine bis(*p*-ethoxyanilide) in 3~10 γ /cc. Therefore, it was expected that the *p*-propoxyanilide, *p*-butoxyanilide, *p*-pentyloxyanilide, and *p*-hexyloxyanilide should be stronger in such activity. These compounds were also prepared.

L-Cystine bis(*p*-propoxyanilide) (IX) and L-cystine bis(*p*-butoxyanilide) (X) were prepared by du Vigneaud's method,²⁾ starting with bis(benzyloxycarbonyl)-L-cystine, which was derived to the acid chloride with phosphorus pentachloride, reacted with *p*-propoxyaniline or *p*-butoxyaniline, and the condensation product reduced with sodium in liquid ammonia, with subsequent liberation of the benzyloxycarbonyl group (Chart 1). In the

*¹ Hotarugaike, Toyonaka, Osaka-fu (谷山兵三, 三好文彦, 佐野安雄, 久保田聰一).

*² Tennoji-ku, Osaka (榊原栄一).

*³ Hotarugaike, Toyonaka, Osaka-fu (内田 誉).

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1) Part I: Yakugaku Zasshi, **76**, 1304(1956).

2) H. S. Loring, V. du Vigneaud: J. Biol. Chem., **111**, 385(1935).

3) F. E. King, J. W. Clark-Lewis, R. Wade: J. Chem. Soc., **1957**, 880. Recently, J. C. Sheehan and D. H. Yang also reported the same method for cysteinyl peptide (J. Am. Chem. Soc., **80**, 1158 (1958)).

synthesis of the higher alkoxyanilide derivatives of the series, liberation of the benzyl-oxycarbonyl group could not be successfully effected by this method, and the route shown in Chart 2 was applied.

Chart 1.

Then L-cystine bis(*p*-alkoxyanilide) derivatives of this series with higher alkoxy group and L-cystine dihydrazide derivatives were prepared by a new route,³⁾ starting with L-2,2-dimethyl-3-formyl-4-carboxythiazolidine (I). The condensation of *p*-alkoxyanilines or hydrazides with (I) proceeded by the mixed acid anhydride method using ethyl chloroformate in chloroform or mixture of chloroform and dioxane to form the condensate (II). The condensate (II) was refluxed with 2% hydrochloric acid in methanol for 1~2 hours to remove the formyl group and the solvent was removed by evaporation under a reduced pressure. Treatment of the residue with *N* hydrochloric acid solution caused a cleavage of the thiazolidine ring in (III), giving L-cystine bis(*p*-alkoxyanilide) derivatives and L-cystine dihydrazide derivatives.

Chart 2.

These compounds were optically active, negative to nitroprusside test, and positive to ninhydrin test, and were established to be L-cystyl derivatives.

Antibacterial test *in vitro* of these compounds gave the results listed in Tables I, II, and III, showing inhibitory effect on the growth of tubercle bacilli as was expected, with the exception of phenylhydrazide condensate. For this test against tubercle bacilli, Kirchner medium in which asparagin was substituted with sodium glutamate was used.⁴⁾ The strongest of these compounds was L-cystine bis(isonicotinoylhydrazide) (XXIV) which was inhibitory in a concentration of 0.1 γ/cc., and examinations are being made for biological and biochemical properties of this compound to see if it is a chemotherapeutic with specificity of species or not. It is interesting to note that in mice infected with tubercle bacilli the activity is equal to that of isonicotinoylhydrazide and the toxicity is less weak. Details will be reported later.

In the *p*-alkoxyanilide condensate series, the antitubercular actions increased with

4) H. Taniyama, *et al.*: Yakugaku Zasshi, **74**, 113(1954).

increasing length of alkyl chain and the strongest activity was found in *p*-pentyloxy-anilide condensate (XIX) which showed antitubercular action in the range of 1~0.3 γ /cc.

TABLE I. Antibacterial Activity of L-Cystyl Derivatives against Tubercle Bacilli

R-HN-OC-CHCH ₂ -S-S-CH ₂ CH-CO-NH-R						
		NH ₂	NH ₂			
Compound	Strain	Min. inhibitory concn. ^(a) (γ/cc.)				
R		No.	H ₃₇ Rv	H ₂	Aoyama B	BCG
(IX)		3	3 (1)	1	1
(X)		1	3	1	1
(XIX)		1	1	1	0.3
(XX)		1	3 (1)	1	1
(XXI)		100 (30)	1000 (100)	...	≫1000
(XXII)		(1000)	(1000)	(300)	(300)
(XXIII)		>1000	>1000	(300)	(1000)
-HNOC-	(XXIV)		0.1	0.1	0.1	0.1
-HN-	(XXV)		100 (30)	100	30 (10)	30 (10)
-HNOC-	(XXVI)		300 (100)	300	300	300
Isonicotinoylhydrazide			0.1	0.1	0.1	0.1

^{a)} The values in parentheses are suppressive concentrations. The values marked > are slightly suppressive concentrations and ≫1000 means inactive in 1000 γ /cc. concn.

TABLE II. Antibacterial Activity of Bisbenzyloxycarbonyl-L-cystyl Derivatives against Tubercle Bacilli

		$\text{R}-\text{HN}-\text{OC}-\underset{\text{NH}}{\text{CH}}\text{CH}_2-\text{S}-\text{S}-\text{CH}_2\underset{\text{NHCOOCH}_2-\text{C}_6\text{H}_5}{\text{CH}}-\text{CO}-\text{NH}-\text{R}$				
		$\text{C}_6\text{H}_5-\text{CH}_2\text{OOCNH}$				
Compound	Strain	Min. inhibitory concn. ^{a)} (γ/cc.)				
R		No.	H ₃₇ Rv	H ₂	Aoyama B	BCG
(IV)		>1000	≫1000	≫1000	≫1000
(V)		≫1000	≫1000	≫1000	1000
(VI)		≫1000	(1000)	(1000)	≫1000
(VII)		≫1000	≫1000	≫1000	≫1000
(VIII)		≫1000	≫1000	≫1000	≫1000
-HNOC-	b)		30	10 (3)	30 (10)	30
-HN-	b)		30	100	30	30

^{a)} Same as in Table I.

^{b)} See the reference in Footnote (1).

p-Octyloxyanilide condensate (XXI) showed a tremendous decrease in the activity and the higher members of the series did not show any antitubercular action. In thiazolidine derivatives, antibacterial activity was slightly weaker than that of the corresponding cystyl derivatives, but *p*-hexyloxyanilide condensate (XII) showed the same activity as the corresponding (XX). Thus, the question pending since the previous work was nearly settled.

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TABLE III. Antibacterial Activity of 4-Substituted L-2,2-Dimethyl-3-formylthiazolidines against Tubercle Bacilli

$$\begin{array}{c}
 \text{CH}_2\text{-CH-CO-NH-R} \\
 | \quad | \\
 \text{S} \quad \text{NCHO} \\
 \diagdown \quad \diagup \\
 \text{C} \\
 / \quad \backslash \\
 \text{CH}_3 \quad \text{CH}_3
 \end{array}$$

Compound R	Strain No.	Min. inhibitory concn. ^{a)} (γ/cc.)			
		H ₃₇ Rv	H ₂	Aoyama B	BCG
-OC ₃ H ₁₁	(XI)	10	10	10	>10
-OC ₄ H ₁₃	(XII)	1	1	1	1
-OC ₅ H ₁₇	(XIII)	≫1000	(1000)	10 (1)	(300)
-OC ₆ H ₂₁	(XIV)	≫1000	≫1000	≫1000	≫1000
-OC ₈ H ₂₅	(XV)	1000	1000	(1000)	≫1000
-HNOC-	(XVI)	3	3	3 (1)	10
-HN-	(XVII)	300 (30)	300 (30)	100 (10)	100
-HNOC- -NO ₂	(XVIII)	100	300	300 (100)	...

^{a)} Same as in Table I.

Experimental

Bis(benzyloxycarbonyl)-L-cystine Bis(*p*-propoxyanilide) (IV)—A solution of 4.5 g. of *p*-propoxyaniline in 30 cc. of *N* NaOH was stirred and cooled at 0°. To the solution, 22 cc. of *N* NaOH and bis(benzyloxycarbonyl)-L-cystyl dichloride, obtained by treatment of 5.1 g. of bis(benzyloxycarbonyl)-L-cystine with 6.3 g. of PCl₅ in dehyd. benzene, was added in 5 portions with cooling and stirring. After 30 min., the resulting precipitate was collected and recrystallized from benzene and MeOH to colorless leaflets, m.p. 230~231°; yield, 3.9 g. *Anal.* Calcd. for C₄₀H₄₆O₈N₄S₂: C, 61.99; H, 5.98. Found: C, 61.98; H, 5.91.

Bis(benzyloxycarbonyl)-L-cystine Bis(*p*-butoxyanilide) (V)—This compound was prepared by the method described above for (IV), with 5.0 g. of *p*-butoxyanilide. Colorless needles, m.p. 214~215.5°, as recrystallized from CHCl₃ and MeOH; yield, 4.2 g. *Anal.* Calcd. for C₄₂H₅₀O₈N₄S₂: C, 62.82; H, 6.28. Found: C, 62.30; H, 6.18.

Bis(benzyloxycarbonyl)-L-cystine Bis(*p*-pentyloxyanilide) (VI)—This compound was prepared by the method similar to that for (IV), with 5.4 g. of *p*-pentyloxyanilide. Recrystallization from MeOH gave colorless needles of m.p. 186~187°; yield, 3.2 g. *Anal.* Calcd. for C₄₄H₅₄O₈N₄S₂: C, 63.59; H, 6.55. Found: C, 63.72; H, 6.38.

Bis(benzyloxycarbonyl)-L-cystine Bis(*p*-octyloxyanilide) (VII)—This compound was prepared by the method similar to that for (IV), with 6.6 g. of *p*-octyloxyanilide. Colorless crystals of m.p. 174°, as recrystallized from MeOH; yield, 3.8 g. *Anal.* Calcd. for C₅₀H₆₆O₈N₄S₂: C, 65.62; H, 7.27. Found: C, 65.76; H, 6.97.

Bis(benzyloxycarbonyl)-L-cystine Bis(*p*-dodecyloxyanilide) (VIII)—The compound was prepared as described above for (IV), with 8.3 g. of *p*-dodecyloxyanilide. Colorless crystals of m.p. 166~167°,

as recrystallized from MeOH; yield, 5.1 g. *Anal.* Calcd. for $C_{58}H_{82}O_8N_4S_2$: C, 67.80; H, 8.04. Found: C, 67.15; H, 7.66.

L-Cystine Bis(*p*-propoxyanilide) (IX)—To a suspension of 2.0 g. of (IV) in 20 cc. of liquid NH_3 , metallic Na was added in small pieces under stirring at -60° until the liquid showed permanent blue color. After evaporating liquid NH_3 , the residue was dissolved in minimum volume of H_2O , neutralized with 2*N* HCl, and oxidized by air. The resulting precipitate was collected and recrystallized from MeOH to colorless needles, m.p. 165° ; $[\alpha]_D^{32} + 172.8^\circ$ ($c=1.20$, dioxane); yield, 0.9 g. *Anal.* Calcd. for $C_{24}H_{34}O_4N_4S_2$: C, 56.90; H, 6.76. Found: C, 57.26; H, 6.90.

L-Cystine Bis(*p*-butoxyanilide) (X)—A suspension of 0.8 g. of (V) in liquid NH_3 was reduced with Na as described above for (IX). The resulting product was recrystallized from MeOH to colorless needles, m.p. 140° ; $[\alpha]_D^{20} - 30.0^\circ$ ($c=0.01$, dioxane); yield, 0.4 g. *Anal.* Calcd. for $C_{26}H_{38}O_4N_4S_2$: C, 58.41; H, 7.16. Found: C, 58.12; H, 7.05.

L-2,2-Dimethyl-3-formyl-4-(*p*-pentyloxyphenylcarbamoyl)thiazolidine (XI)—A solution of 1.4 g. of L-2,2-dimethyl-3-formyl-4-carboxythiazolidine (I) and 1.03 cc. of triethylamine in 20 cc. of dehyd. $CHCl_3$ was stirred and cooled at 0° , and 0.66 cc. of ethyl chloroformate was added. After 10 min. of stirring at this temperature, a solution of 1.3 g. of *p*-pentyloxyanilide in 25 cc. of dehyd. $CHCl_3$ was added dropwise, and cooling and stirring were continued for 60 min. The solution was allowed to stand for several hr. at room temperature and washed with H_2O . Evaporation of the solvent under a reduced pressure gave the condensate as a residue which was crystallized from MeOH- H_2O . Recrystallization from ether-petr. ether yielded 2.0 g. of colorless needles, m.p. $108\sim 109^\circ$. *Anal.* Calcd. for $C_{18}H_{26}O_3N_2S$: C, 61.68; H, 7.48. Found: C, 62.65; H, 7.49.

L-2,2-Dimethyl-3-formyl-4-(*p*-hexyloxyphenylcarbamoyl)thiazolidine (XII)—A mixture of 1.9 g. of (I), 1.4 cc. of triethylamine, 0.9 cc. of ethyl chloroformate, and 1.9 g. of *p*-hexyloxyphenylanilide was treated in $CHCl_3$ by the method as described above for (XI). The resulting condensate was recrystallized from petr. ether to colorless leaflets of m.p. $53\sim 54^\circ$; yield, 2.9 g. *Anal.* Calcd. for $C_{19}H_{28}O_3N_2S$: C, 62.62; H, 7.74. Found: C, 62.84; H, 7.69.

L-2,2-Dimethyl-3-formyl-4-(*p*-octyloxyphenylcarbamoyl)thiazolidine (XIII)—A mixture of 1.9 g. of (I), 1.4 cc. of triethylamine, 0.9 cc. of ethyl chloroformate, and 2.2 g. of *p*-octyloxyphenylanilide was treated in $CHCl_3$ by the method similar to that for (XI). The resulting condensate was recrystallized from MeOH- H_2O to colorless leaflets of m.p. 94° ; yield, 2.8 g. *Anal.* Calcd. for $C_{21}H_{32}O_3N_2S$: C, 64.22; H, 8.22. Found: C, 64.13; H, 8.06.

L-2,2-Dimethyl-3-formyl-4-(*p*-decyloxyphenylcarbamoyl)thiazolidine (XIV)—A mixture of 1.6 g. of (I), 1.2 cc. of triethylamine, 0.75 cc. of ethyl chloroformate, and 2.1 g. of *p*-decyloxyphenylanilide was treated in $CHCl_3$ by the method similar to that for (XI). Colorless leaflets of m.p. 94° , as recrystallized from MeOH- H_2O ; yield, 2.3 g. *Anal.* Calcd. for $C_{23}H_{36}O_3N_2S$: C, 65.69; H, 8.63. Found: C, 65.36; H, 8.43.

L-2,2-Dimethyl-3-formyl-4-(*p*-dodecyloxyphenylcarbamoyl)thiazolidine (XV)—As described above for (XI), 1.4 g. of (I), 1.0 cc. of triethylamine, 0.66 cc. of ethyl chloroformate, and 2.1 g. of *p*-dodecyloxyanilide were treated in $CHCl_3$. Colorless leaflets of m.p. 98° , as recrystallized from petr. benzene; yield, 2.1 g. *Anal.* Calcd. for $C_{25}H_{40}O_3N_2S$: C, 66.93; H, 8.99; N, 6.25. Found: C, 67.03; H, 8.94; N, 6.28.

L-2,2-Dimethyl-3-formyl-4-isonicotinohydrazidocarbonylthiazolidine (XVI)—As described above for (XI), 1.9 g. of (I), 1.4 cc. of triethylamine, 0.9 cc. of ethyl chloroformate, and 1.4 g. of isonicotinoylhydrazide were treated in $CHCl_3$ -dioxane. Colorless plates of m.p. $220\sim 220.5^\circ$ (decomp.), as recrystallized from MeOH; yield, 2.2 g. *Anal.* Calcd. for $C_{18}H_{16}O_3N_4S$: C, 50.61; H, 5.23. Found: C, 50.46; H, 5.19.

L-2,2-Dimethyl-3-formyl-4-phenylhydrazinocarbonylthiazolidine (XVII)—As described above for (XI), 1.0 g. of (I), 0.75 cc. of triethylamine, 0.47 cc. of ethyl chloroformate, and 0.57 g. of phenylhydrazine were treated in $CHCl_3$. Colorless needles of m.p. 155° , as recrystallized from MeOH; yield, 1.2 g. *Anal.* Calcd. for $C_{13}H_{17}O_2N_3S$: C, 55.85; H, 6.14. Found: C, 55.29; H, 6.02.

L-2,2-Dimethyl-3-formyl-4-(*p*-nitrobenzohydrazidocarbonyl)thiazolidine (XVIII)—As described above for (XI), 1.9 g. of (I), 1.4 g. of triethylamine, 0.9 cc. of ethyl chloroformate, and 1.8 g. of *p*-nitrobenzoylhydrazide were treated in $CHCl_3$. Colorless needles of m.p. $181\sim 182^\circ$, as recrystallized from benzene-MeOH; yield, 2.1 g. *Anal.* Calcd. for $C_{14}H_{16}O_5N_4S$: C, 47.73; H, 4.58. Found: C, 47.61; H, 4.80.

L-Cystine Bis(*p*-pentyloxyanilide) (XIX)—A solution of 2.0 g. of (XI) in 2% MeOH-HCl was refluxed for 1 hr. The solvent was evaporated under a reduced pressure and the residue was dissolved in 30 cc. of *N* HCl. After standing, neutralization of the solution with *N* NaOH and aeration gave a crystalline precipitate which was collected and recrystallized from MeOH to colorless needles, m.p. $156\sim 158^\circ$; $[\alpha]_D^{32} - 23.5^\circ$ ($c=0.66$, dioxane); yield, 1.3 g. *Anal.* Calcd. for $C_{28}H_{42}O_4N_4S_2$: C, 59.75; H, 7.52. Found: C, 59.97; H, 7.48.

L-Cystine Bis(*p*-hexyloxyanilide) (XX)—After deformylation of 2.5 g. of (XII) with methanolic HCl, it was treated with *N* HCl and *N* NaOH by the method similar to that for (XIX). Colorless plates of m.p. 160°; $[\alpha]_D^{20} - 33.8^\circ$ ($c=0.089$, dioxane), as recrystallized from MeOH; yield, 1.7 g. *Anal.* Calcd. for $C_{30}H_{46}O_4N_4S_2$: C, 60.98; H, 7.81. Found: C, 60.68; H, 7.75.

L-Cystine Bis(*p*-octyloxyanilide) (XXI)—2.3 g. of (XIII) was treated as for (XX). Colorless plates of m.p. 159°; $[\alpha]_D^{20} - 11.6^\circ$ ($c=0.086$, dioxane), as recrystallized from petr. benzene-benzene; yield, 1.7 g. *Anal.* Calcd. for $C_{34}H_{54}O_4N_4S_2$: C, 63.12; H, 8.41; N, 8.69. Found: C, 63.42; H, 8.44; N, 8.68.

L-Cystine Bis(*p*-decyloxyanilide) (XXII)—1.4 g. of (XIV) was treated as for (XX). Recrystallization from petr. benzene-benzene yielded 0.7 g. of colorless plates, m.p. 153°; $[\alpha]_D^{20} - 13.0^\circ$ ($c=0.10$, pyridine). *Anal.* Calcd. for $C_{38}H_{62}O_4N_4S_2$: C, 64.91; H, 8.89. Found: C, 65.13; H, 8.88.

L-Cystine Bis(*p*-dodecyloxyanilide) (XXIII)—1.7 g. of (XV) was treated as for (XX). Recrystallization from benzene yielded 1.1 g. of colorless plate, m.p. 146°; $[\alpha]_D^{20} - 11.3^\circ$ ($c=0.11$, pyridine). *Anal.* Calcd. for $C_{42}H_{70}O_4N_4S_2$: C, 66.44; H, 9.29. Found: C, 66.07; H, 9.14.

L-Cystine Bis(isonicotinoylhydrazide) (XXIV)—A solution of 2.0 g. of (XVI) in 2% MeOH-HCl was refluxed for 2 hr. Evaporation of the solvent under a reduced pressure gave a crystalline residue which was dissolved in 30 cc. *N* HCl. After standing for a while, the solvent was evaporated under a reduced pressure and was recrystallized from MeOH, yielding 1.4 g. of colorless prisms, m.p. 225~226°(decomp.); $[\alpha]_D^{19} + 21.0^\circ$ ($c=1.0$, H_2O). *Anal.* Calcd. for $C_{18}H_{22}O_4N_8S_2 \cdot 4HCl$: C, 34.62; H, 4.20; N, 17.95. Found: C, 34.25; H, 4.42; N, 17.79.

L-Cystine Bis(phenylhydrazide) (XXV)—One g. of (XVII) was deformylated with methanolic HCl and treated with *N* HCl and *N* NaOH by the method similar to that for (XXIV). Recrystallization from MeOH yielded 0.8 g. of colorless leaflets, m.p. 224°(decomp.); $[\alpha]_D^{19} + 9.5^\circ$ ($c=1.0$, H_2O). *Anal.* Calcd. for $C_{18}H_{24}O_2N_6S_2 \cdot 2HCl$: C, 43.82; H, 5.31. Found: C, 43.69; H, 5.59.

L-Cystine Bis(*p*-nitrobenzoylhydrazide) (XXVI)—One g. of (XVIII) was treated as for (XXV). Recrystallization from MeOH yielded 0.6 g. of colorless needles, m.p. 217°(decomp.); $[\alpha]_D^{32} - 48.4^\circ$ ($c=0.972$, H_2O). *Anal.* Calcd. for $C_{20}H_{22}O_8N_6S_2 \cdot 2HCl \cdot 2H_2O$: C, 35.56; H, 4.18. Found: C, 35.38; H, 4.34.

Antibacterial Tests with *Mycobacterium tuberculosis*—The *in vitro* tests were carried out by the method reported by Taniyama, *et al.*⁴⁾

Summary

L-Cystine dihydrazide and L-cystine bis(*p*-alkoxyanilide) derivatives listed in Tables I, II, and III were prepared and submitted to antibacterial tests with *Mycobacterium tuberculosis*. Two methods were used for the synthesis of these compounds. The one was du Vigneaud's method and the other was a new route to cysteinyl peptides. In the antibacterial test *in vitro*, the strongest activity among these compounds was found in L-cystine bis(isonicotinoylhydrazide) which was inhibitory in a concentration of 0.1 γ /cc. L-Cystine bis(*p*-pentyloxyanilide) showed antibacterial action in the range of 1~0.3 γ /cc.

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