Chemical Studies on Tuberactinomycin. XIV.[1] Novel Synthesis of DL-Capreomycidine[2]

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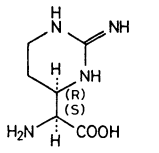
Cyclic guanidino amino acid, capreomycidine, is a component of antituberculous peptides, capreomycin and tuberactinomycin N and O. Its epimer was also found in protease inhibitors, chymostatin and elastatinal. A new synthetic approach to DL-capreomycidine *via* β-hydroxyornithine was studied for the purpose of total synthesis of capreomycidine and epicapreomycidine of natural forms or its hydroxy derivative, tuberactidine.

Antituberculous peptide, capreomycin, contains a unique cyclic guanidino amino acid capreomycidine (**1**) as a component.[3] A second case of its natural occurrence was revealed in the recent studies on similar antibiotics, tuberactinomycins, also as a constituent amino acid of two congeners N and O.[4] After the chemical structure of capreomycidine had been determined by Herr,[3] its stereochemistry was assumed by Bycroft *et al.*[5,6] to be (*S*)-α-[(4*R*)-2-iminohexahydro-4-pyrimidyl]glycine (L-capreomycidine) (**1**) and confirmed by X-ray analysis of tuberactinomycin O.[4a] A diastereoisomer of L-capreomycidine, (*S*)-α-[(4*S*)-2-iminohexahydro-4-pyrimidyl]glycine (L-epicapreomycidine) (**2**) was recently found as a component amino acid in protease inhibitors such as chymostatin[7] and elastatinal.[8] Occurrence of two diastereoisomers of one amino acid in nature is not so rare, particularly in the field of peptide antibiotics, but capreomycidine can be regarded as an example for consideration of amino acid biosynthesis from the view point of stereochemistry.



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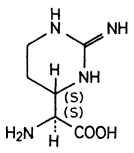

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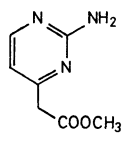

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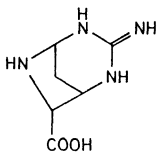

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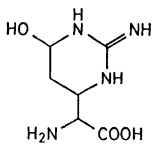

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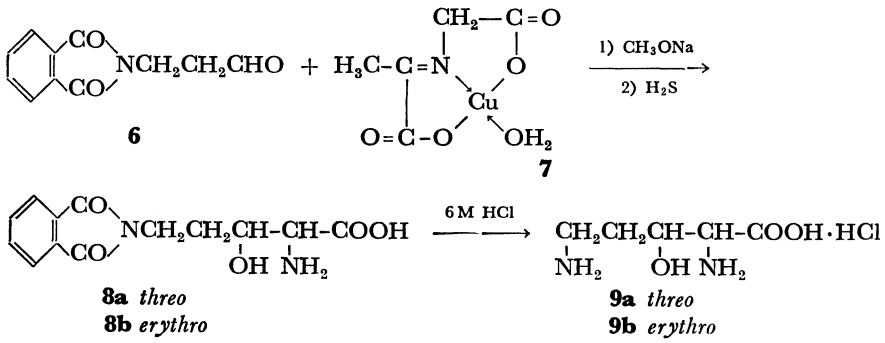
Concerning the synthesis of capreomycidine, Bycroft *et al.* presented a synthetic approach to DL-compound in 1971.[9] Their method is based on oximation of methyl (2-amino-4-pyrimidyl)acetate (**3**) followed by hydrogenation. However, according to their scheme, synthesis of an optically active form of this amino acid would require much effort particularly in the procedure of optical resolution. In fact they have not yet succeeded in preparing L-capreomycidine. As regards their failure in the synthesis of viomycidine (**4**) from 6-hydroxy analog of **3**, the approach seems unpromising for the synthesis of tuberactidine (**5**) which is another cyclic guanidino amino acid in tuberactinomycin group. The situation prompted us to search for a more favorable synthetic route to secure a common intermediate from which both optically active capreomycidine and tuberactidine could be obtained. This may offer a requisite tool for the synthesis of biologically important peptides containing cyclic guanidino amino acid.

In this connection, we describe a new synthetic method of DL-capreomycidine through β-hydroxyornithine for the preparation of optically active isomer. β-Hydroxyornithine was prepared in a previous synthesis of γ-hydroxy-β-lysine through rather tedious steps *via* 5-phthalimino-2-pentenoic acid.[10] We have improved the approach by a completely different method based on aldol condensation of 3-phthalimidopropionaldehyde (**6**)[11] with [*N*-(1-carboxylatoethylidene)glycinato]aquacopper(II) (**7**)[12] introduced by Ichikawa *et al.*[13] (Scheme 1).

After removal of copper(II) ion from the condensate, N^{δ}-phthaloyl-β-hydroxyornithine (**8**) was obtained as a mixture of *threo* (**8a**) and *erythro* (**8b**) forms in the ratio 89 : 11.[14] Each isomer was separated by fractional crystallization from water. Such a remarkable stereoselectivity was favorable for our purpose of preparing

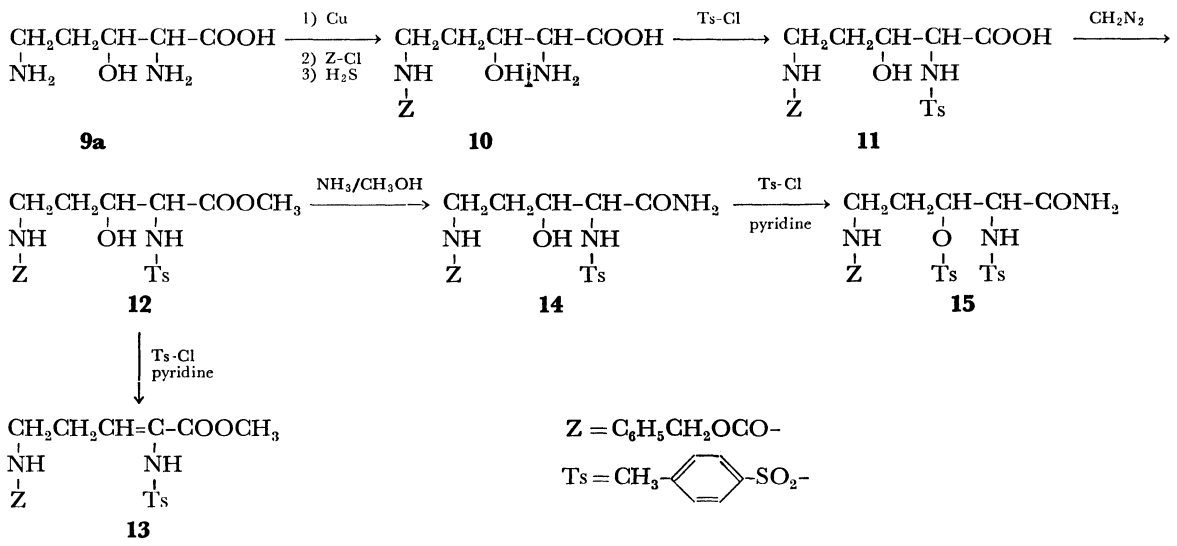


6 **7**

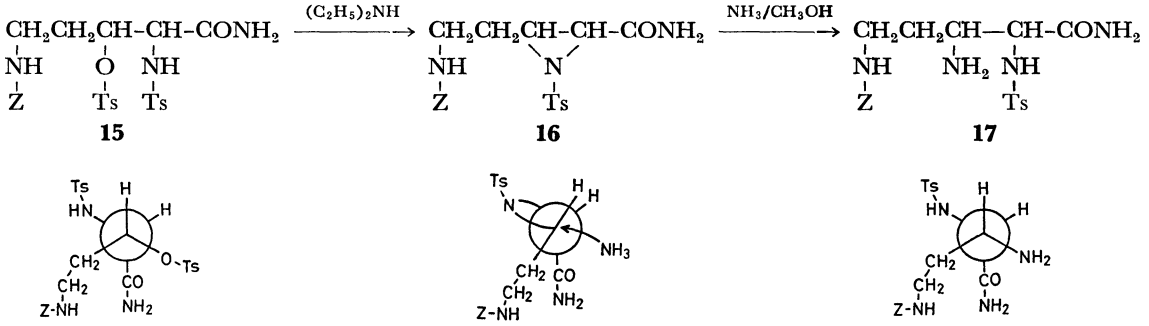
8a *threo*
8b *erythro*

9a *threo*
9b *erythro*

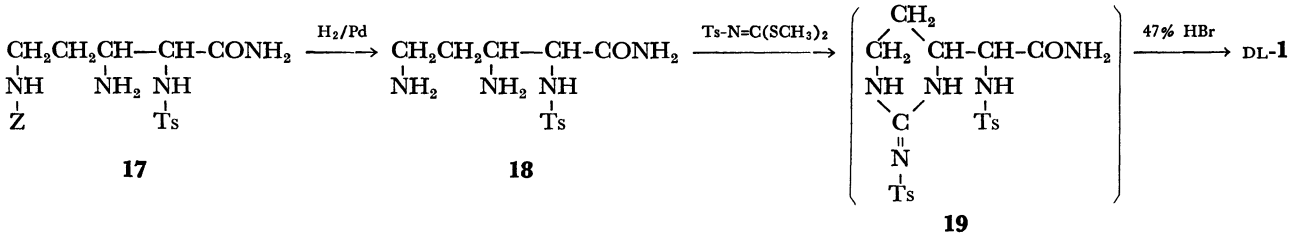
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

capreomycidine of natural *threo* form, if the β-hydroxyl group could be converted into amino group without inversion of its configuration.

Removal of phthaloyl group from **8a** gave *threo*-β-hydroxyornithine (**9a**) which was anew benzyloxycarbonylated selectively at δ-amino group *via* copper(II) complex. Such an exchange of the protecting group was required for smooth deprotection in later synthetic step. N^{δ}-Benzyloxycarbonyl derivative **10** thus obtained was then tosylated at α-amino group to afford N^{δ}-benzyloxycarbonyl-N^{α}-tosyl-β-hydroxyornithine (**11**). (Scheme 2).

For conversion of β-hydroxyl into β-amino group, *O*-tosylation had been first carried out. However, *O*-tosylate of β-hydroxy acid is liable to turn to α,β-unsaturated compound by treatment with base when carboxyl group is free or esterified, whereas its acid amide often gives the desired *O*-tosylate.[15] In fact, methyl ester **12** readily gave α,β-unsaturated compound **13** even during the course of *O*-tosylation of **12** in pyridine. Thus, we converted methyl ester **12** into amide **14** with ammonia in methanol prior to *O*-tosylation. Amide **14** thus obtained afforded the desired *O*-tosyl derivative **15** in a satisfactory yield. *O*-Tosylate **15** was treated with diethylamine in tetrahydrofuran to yield aziridine compound **16**,[15] which was then converted into β-aminoornithine derivative **17** with ammonia in methanol (Scheme 3). In order to confirm the position and configuration of the newly introduced amino group, **17** was reversely deaminated with sodium nitrite to give hydroxy compound identified with the starting material **14** on thin-layer chromatography, affording *threo*-β-hydroxyornithine (**9a**) on hydrolysis. The fact that *threo* configuration was maintained in **17** was elucidated by the double inversion throughout the course of reaction (Scheme 3). Triamino deriva-

tive **17** thus established was debenzyloxycarbonylated by catalytic hydrogenation and then guanidinated with *N*-(*p*-tolylsulfonyl)bis(methylthio)methanimine[16] to afford a cyclic guanidino compound **19**, which, without isolation, was hydrolyzed with hydrobromic acid to give the final product (**1**). (Scheme 4). It was identical with that of natural L-capreomycidine on thin-layer chromatogram and amino acid analysis. IR and NMR spectra of the synthetic flavianate were also superposable with those of a natural specimen.

The novel synthesis of DL-capreomycidine, being entirely different from the former method,[9] is promising in view of preparation of an optically active guanidino amino acid particularly L-capreomycidine, L-epicapreomycidine or L-tuberactidine.[17]

Experimental

N$^{\delta}$-Phthaloyl-β-hydroxyornithine (8). Phthalimide (147 g, 1.00 mol) was suspended in 300 ml of absolute ethanol in which sodium metal (0.45 g) had been dissolved. Acrylaldehyde (56.1 g, 1.00 mol) in 50 ml of absolute ethanol was added dropwise to the suspension at room temperature for 50 min with stirring under nitrogen atmosphere. [*N*-(1-carboxylatoethylidene)glycinato]aquacopper(II) dihydrate (**7**)[13] (162 g, 0.621 mol) and 350 ml of absolute methanol were immediately added to the viscous pale yellow solution obtained. To the suspension was added sodium methoxide (54.0 g, 1.00 mol) in 150 ml of absolute methanol for 50 min. After being stirred at 30 °C overnight under nitrogen atmosphere, the reaction mixture was neutralized with 9 ml of acetic acid, and diluted with 1 litre of water. Greenish viscous precipitate was filtered off, and the filtrate was kept for further treatment (filtrate A).

The precipitate was dissolved in 1 M hydrochloric acid and the insoluble material was filtered off. Hydrogen sulfide was bubbled through the filtrate for 1 h. Cupric sulfide was filtered off and washed with 1 M hydrochloric acid. Filtrate and washings were combined, aerated, concentrated *in vacuo*, and neutralized with pyridine. Addition of ethanol gave precipitate of crude *threo* N$^{\delta}$-phthaloyl compound **8a** (77.6 g). This was recrystallized from water to give pure **8a**: yield 48.2 g (28%), mp 214.5 °C (dec).

Found: C, 52.65; H, 5.59; N, 9.46%. Calcd for $C_{13}H_{14}N_2O_5 \cdot H_2O$: C, 52.70; H, 5.44; N, 9.46%.

Filtrate A was treated as above to recover **8a** (2.28 g, 1.3%). Pure *erythro* compound (**8b**) was obtained from the mother liquor: yield 0.71 g (0.4%), mp 245 °C (dec).

Found: C, 55.49; H, 5.12; N, 10.03%. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07%.

threo-*β-Hydroxyornithine Hydrochloride (9a).* N$^{\delta}$-Phthaloyl-*threo*-β-hydroxyornithine (**8a**) (5.40 g, 18.2 mmol) was dissolved in 130 ml of 6 M hydrochloric acid and heated under reflux for 12 h. Phthalic acid was filtered off and the filtrate was extracted with ethyl acetate. Aqueous layer was concentrated *in vacuo*. Concentration after addition of a small amount of water was repeated several times to remove excess hydrochloric acid. Oily product was dissolved in a small amount of water, neutralized with pyridine, and then precipitated by addition of ethanol. Crystallization from water and ethanol gave **9a**: yield 3.20 g (87%), mp 189—190 °C (dec).

Found: C, 29.54; H, 7.56; N, 13.97; Cl, 17.47%. Calcd for $C_5H_{13}N_2O_3Cl \cdot H_2O$: C, 29.63; H, 7.46; N, 13.83; Cl, 17.50%.

erythro-*β-Hydroxyornithine Hydrochloride (9b).* N$^{\delta}$-Phthaloyl-*erythro*-β-hydroxyornithine (**8b**) (1.00 g, 3.60 mmol) was hydrolyzed with 60 ml of 6 M hydrochloric acid and treated as above: yield 580 mg (87%), mp 225 °C (dec).

Found: C, 32.26; H, 7.18; N, 15.30; Cl, 19.29%. Calcd for $C_5H_{13}N_2O_3Cl$: C, 32.53; H, 7.10; N, 15.17; Cl, 19.20%.

N$^{\delta}$-*Benzyloxycarbonyl*-threo-*β-hydroxyornithine (10).* Basic copper carbonate (23.9 g, 100 mmol) was added portionwise under boiling to a solution of *threo*-β-hydroxyornithine hydrochloride (**9a**) (10.1 g, 50.0 mmol) in 250 ml water. After additional 15 min boiling, excess copper carbonate was filtered off and washed with hot water. The combined filtrate and washings were subjected to acylation with benzyloxycarbonyl chloride (14.5 g, 85.0 mmol) and sodium hydrogencarbonate in the usual way. The reaction product precipitated was filtered, suspended in 200 ml of water, and 6 M hydrochloric acid was added to the suspension until precipitate dissolved. Hydrogen sulfide was passed through the solution, and the resulting cupric sulfide was filtered off. Neutralization of the solution with sodium hydrogencarbonate gave crystals (12.4 g) which were recrystallized from water: yield 10.3 g (71%), mp 212—213 °C (dec).

Found: C, 53.55; H, 6.58; N, 9.61%. Calcd for $C_{13}H_{18}N_2O_5 \cdot 1/2H_2O$: C, 53.60; H, 6.57; N, 9.62%.

N$^{\alpha}$-*Benzyloxycarbonyl*-N$^{\alpha}$-p-*tolylsulfonyl*-threo-*β-hydroxyornithine (11).* Triethylamine (3.00 g, 29.7 mmol) and *p*-toluenesulfonyl chloride (2.80 g, 14.7 mmol) were added portionwise during a period of 30 min to a suspension of N$^{\delta}$-benzyloxycarbonyl-*threo*-β-hydroxyornithine (**10**) (2.77 g, 9.52 mmol) in 24 ml of aqueous tetrahydrofuran (H_2O–THF= 2 : 1). The reaction mixture was stirred at room temperature for 1.5 h, concentrated to approximately 8 ml *in vacuo*, and extracted several times with ether. The aqueous layer was acidified with 2 M hydrochloric acid to produce an oily material which was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The oily residue was triturated with ether to crystallize. It was recrystallized from ethanol, ether, and hexane: yield 3.75 g (90%), mp 169.5—170 °C.

Found: C, 54.69; H, 5.59; N, 6.41; S, 7.20%. Calcd for $C_{20}H_{24}N_2O_7S$: C, 55.03; H, 5.54; N, 6.42; S, 7.32%.

N$^{\delta}$-*Benzyloxycarbonyl*-N$^{\delta}$-p-*tolylsulfonyl*-threo-*β-hydroxyornithine Methyl Ester (12).* Compound **11** (5.62 g, 12.9 mmol) was dissolved in a mixture of 15 ml each of anhydrous dioxane and anhydrous tetrahydrofuran. Diazomethane in ether was added to the solution under ice cooling until its yellow color remained. Excess diazomethane was decomposed with acetic acid with stirring for 30 min. The reaction mixture was concentrated *in vacuo* to give an oily residue, which was crystallized by addition of a small amount of ether.

It was recrystallized from ethyl acetate and hexane: yield 5.37 g (93%), mp 127—128 °C.

Found: C, 55.81; H, 5.83; N, 6.20; S, 7.19%. Calcd for $C_{21}H_{26}N_2O_7S$: C, 55.99; H, 5.82; N, 6.22; S, 7.12%.

N$^{\delta}$-*Benzyloxycarbonyl*-N$^{\delta}$-p-*tolylsulfonyl*-α,β-*dehydroornithine Methyl Ester (13).* To a solution of methyl ester **12** (1.02 g, 2.27 mmol) in 3 ml of anhydrous pyridine was added dropwise a solution of *p*-toluenesulfonyl chloride (864 mg, 4.53 mmol) in anhydrous pyridine with stirring under ice cooling. Stirring was continued under cooling for 30 min and then at room temperature overnight. The reaction mixture was concentrated *in vacuo*, dissolved in 20 ml of water, and extracted three times with 10 ml of ethyl acetate. The extract was washed with water, 1 M hydrochloric acid, saturated sodium chloride solution and dried over anhydrous sodium sulfate. The oily residue obtained after vacuum concentration was purified on silica gel column using benzene–ethyl acetate (3 : 1) as a solvent. Pure unsaturated compound

was obtained from the eluate: yield 0.70 g (71%), mp 85—86 °C, after recrystallization from ethyl acetate and hexane.

Found: C, 58.33; H, 5.60; N, 6.58; S, 7.36%. Calcd for $C_{21}H_{24}N_2O_6S$: C, 58.32; H, 5.59; N, 6.48; S, 7.41%.

*N^{δ}-Benzyloxycarbonyl-N^{δ}-p-tolylsulfonyl-*threo*-β-hydroxyornithine Amide (**14**).* Methyl ester **12** (4.50 g, 10.0 mmol) was dissolved in 80 ml of methanol. The solution was saturated with ammonia in a pressure bottle and kept at room temperature for 2 days. Concentration *in vacuo* gave an oily residue, which was crystallized by trituration with hexane. It was recrystallized from ethyl acetate and hexane: yield 4.17 g (96%), mp 134.5 °C.

Found: C, 54.94; H, 5.83; N, 9.48; S, 7.44%. Calcd for $C_{20}H_{25}N_3O_6S$: C, 55.16; H, 5.79; N, 9.65; S, 7.36%.

*N^{δ}-Benzyloxycarbonyl-N^{α},O-bis(*p*-tolylsulfonyl)-*threo*-β-hydroxyornithine Amide (**15**).* *p*-Toluenesulfonyl chloride (9.33 g, 48.9 mmol) in 20 ml of pyridine was added dropwise to a solution of amide **14** (3.55 g, 8.15 mmol) in 15 ml of pyridine for 4 h under stirring and cooling in ice–salt bath. After additional 4 h stirring in a chilled bath, the reaction mixture was poured on crushed ice in 35 ml of concentrated hydrochloric acid. Aqueous solution was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The oily residue obtained was purified by silica gel column chromatography: Silica gel 50 g; column 2.3 × 30 cm; each 10 g fraction. The following solvents were used successively, benzene (100 ml), benzene–ethyl acetate (4 : 1 = 250 ml, 3 : 1 = 400 ml, 2 : 1 = 350 ml), ethyl acetate (850 ml). Fractions 16 to 35 gave α,β-unsaturated amide as an oily substance (340 mg, 10%). Desired *O*-tosylate was obtained as crystals from fractions 36—84 (2.35 g, 49%), the starting material **14** being recovered from fractions 101—145 (1.15 g, 32%). *O*-Tosylate was recrystallized from chloroform and ether for elemental analysis, mp 146—147 °C.

Found: C, 55.03; H, 5.32; N, 7.10; S, 10.82%. Calcd for $C_{27}H_{31}N_3O_8S_2$: C, 54.99; H, 5.30; N, 7.13; S, 10.88%.

*5-Benzyloxycarbonylamino-*cis*-2,3-(*p*-tolylsulfonylepimino)pentanamide (**16**).* Diethylamine (114 mg, 1.55 mmol) was added at 35—37 °C to a solution of ditosyl amide **15** (457 mg, 0.774 mmol) in 5 ml of anhydrous tetrahydrofuran. The reaction mixture was stirred for 3 h at the temperature and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with water, 1 M hydrochloric acid, and again water to neutral. Organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crystalline residue was recrystallized from chloroform and ether: yield 289 mg (89%), mp 136—137 °C.

Found: C, 57.16; H, 5.62; N, 10.08; S, 7.71%. Calcd for $C_{20}H_{23}N_3O_5S$: C, 57.54; H, 5.55; N, 10.07; S, 7.68%.

*threo-3-Amino-5-benzyloxycarbonylamino-2-(*p*-tolylsulfonylamino)-pentanamide (**17**).* Gaseous ammonia was bubbled into a solution of aziridine compound **16** (1.02 g, 2.44 mmol) in 200 ml of methanol until saturation. It was kept in a pressure bottle at room temperature for 4 days, and concentrated *in vacuo*. Evaporation was repeated twice after dissolution of the residue in methanol. Finally, residual oil was dissolved in 15 ml of 0.2 M hydrochloric acid and extracted with ethyl acetate. The aqueous layer was concentrated *in vacuo* and the oily residue was crystallized by trituration with ether: yield 1.01 g (87%). It was recrystallized from methanol and ether, mp 115—117 °C.

Found: C, 49.26; H, 5.86; N, 11.58; S, 6.52; Cl, 7.25%. Calcd for $C_{20}H_{26}N_4O_5S \cdot HCl \cdot H_2O$: C, 49.12; H, 5.98; N, 11.46; S, 6.56; Cl, 7.25%.

*threo-3,5-Diamino-2-(*p*-tolylsulfonylamino)pentanamide (**18**).* 3-Amino compound **17** (1.01 g, 2.14 mmol) obtained above was dissolved in 20 ml of methanol containing 0.18 ml (2.16 mmol) of concentrated hydrochloric acid and hydrogenated in the presence of palladium black. After the completion of reduction had been checked on TLC, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The crystalline residue was recrystallized from methanol and ether: yield 0.73 g (91%), mp 189—191 °C.

Found: C, 37.00; H, 5.93; N, 14.62; S, 8.31; Cl, 18.11%. Calcd for $C_{12}H_{20}N_4O_3S \cdot 2HCl \cdot H_2O$: C, 36.83; H, 6.18; N, 14.32; S, 8.19; Cl, 18.12%.

*DL-Capreomycidine (**1**) Diflavianate.* 3,5-Diamino compound **18** (200 mg, 0.511 mmol), *N*-(*p*-tolylsulfonyl)bis(methylthio)methanimine[16] (141 mg, 0.511 mmol) and 0.51 ml of 1 M sodium hydroxide were dissolved in 95% ethanol. The solution was heated under reflux for 3 h. After addition of 0.51 ml of 1 M sodium hydroxide, heating was continued for 6 h. The reaction mixture was concentrated *in vacuo* to yield a residue which was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The oily residue was immediately hydrolyzed with 47% hydrobromic acid in the presence of 2 ml of anisole under reflux for 24 h. The hydrolyzate was extracted with benzene several times, diluted with water, and extracted with ethyl acetate. The aqueous layer was concentrated *in vacuo* and ethanol was added to the residue. After removal of insoluble material by filtration, the filtrate was concentrated again. The residue was dissolved in 2 ml of water containing excess flavianic acid, 2 ml of ethanol being added. It was allowed to stand to yield yellow needles: Yield 90 mg (21%). For elemental analysis, it was recrystallized from water, mp 217—219 °C (dec).

Found: C, 36.42; H, 3.55; N, 13.34; S, 7.49%. Calcd for $C_{26}H_{24}N_8O_{18}S_2 \cdot 3H_2O$: C, 36.54; H, 3.54; N, 13.11; S, 7.50%.

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