Studies on 2-Aziridinecarboxylic Acid. X.[1] Simple Stereospecific Synthesis of Optically Active Cystine and *threo*-3,3′-Dimethylcystine

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Synopsis. The reaction of (2*S*)-Z-Azy-OBzl, (2*S*, 3*S*)-Z-3-MeAzy-OBzl, and their enantiomers with H_2S gave the optically active cysteine and *threo*-3-methylcysteine derivatives *via* the stereospecific ring-opening reaction of aziridine, and subsequent oxidation and deblocking procedure gave the titled compounds in good yields.

Photaki[2] have reported the preparation of DL-*S*-tritylcysteine from L-serine *via* the β-elimination reaction of its *O*-tosylated derivative. Carter *et al.*[3] and Hoogmartens *et al.*[4] prepared 3-methylcystine *via* addition of thiol to 2-phenyl-4-ethylidene-5(4*H*)-oxazoline. Morell *et al.*[5] have reported that the displacement reaction of the *O*-tosyl-*allo*-threonine derivative with potassium thioacetate gave the *threo*-*S*-acetyl-3-methylcysteine, which was converted into *threo*-3,3′-dimethylcystine by hydrolysis and oxidation procedure. But these methods involved some technical trouble in obtaining the optically pure cystine or 3,3′-dimethylcystine, that is, the Carter-Hoogmartens's procedure requires a complex optical resolution procedure to get the optically pure product, and the Morell's procedure requires *allo*-threonine as a starting material to prepare *threo*-3-methylcysteine. More recently, Wakamiya *et al.*[6] reported the synthesis of *threo*-3,3′-dimethylcystine *via* ring-opening reaction of aziridine with thiobenzoic acid, this reaction still remained the problem concerning to the product, that is, two products of *S*-benzoyl and *O*-thiobenzoyl derivatives were prepared by this reaction procedure, due to the possible equilibrium in thiobenzoic acid, *e.g.* $C_6H_5COSH \rightleftharpoons C_6H_5CSOH$.

In this study, we employed a more simple stereospecific synthesis of optically active cystine and *threo*-3,3′-dimethylcystine. The synthetic route is shown in Scheme 1.

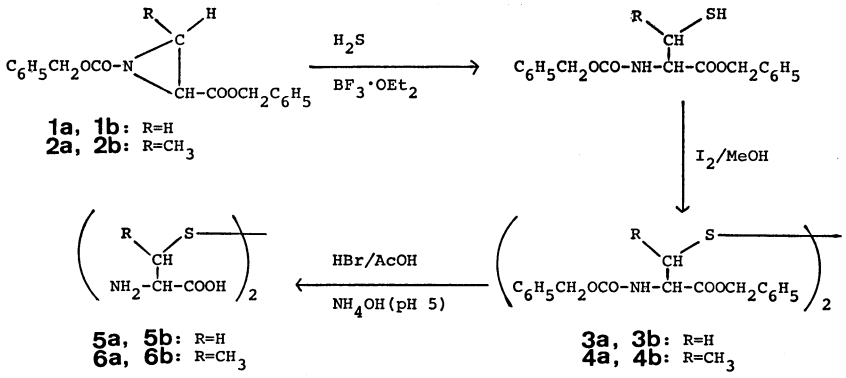
The aziridine derivatives used were benzyl (2*S*)-1-benzyloxycarbonyl-2-aziridinecarboxylate[(2*S*)-Z-Azy-OBzl] (**1a**), benzyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate [(2*S*,3*S*)-Z-3-MeAzy-OBzl] (**2a**), and their enantiomers(**1b** and **2b**), which were prepared by *N*-benzyloxycarbonylation of (2*S*)-H-Azy-OBzl, (2*S*,3*S*)-H-3-MeAzy-OBzl, and their enantiomers with benzyloxycarbonyl chloride as described in our previous paper.[1] The ring-opening reaction of **1a**, **1b**, **2a**, and **2b** were carried out in dichloromethane saturated with H_2S in the presence of boron trifluoride etherate at room temperature for 3 h, and the corresponding cysteine derivatives obtained were oxidized with iodine in methanol solution to give the cystine(**3a**, **3b**) and 3,3′-dimethylcystine(**4a**, **4b**) derivatives. The deblocking procedure of benzyloxycarbonyl and benzyl ester was carried out in acetic acid saturated with HBr for 12 h at room temperature, and the crude cystine(**5a**, **5b**) and 3,3′-dimethylcystine (**6a**, **6b**) were purified by isoelectric point precipitation at pH 5 and recrystallized from hot water or water–ethanol to give the optically pure **5a**, **5b**, **6a**, and **6b**.

The above results show that, compared with conventional methods, synthesis of cysteine and 3-methylcysteine by the stereospecific ring-opening reaction of aziridine with H_2S is very convenient for transforming the serine or threonine into optically pure cystine or *threo*-3,3′-dimethylcystine.

Experimental

Uncorrected melting points are reported. The homogeneity of the products was checked by thin-layer chromatography on silica-gel plates. The optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. The NMR spectra were obtained with Hitachi R 20 B high-resolution NMR spectrometer, the chemical shifts being obtained using TMS as the internal reference.

N,N′-*Bis*(*benzyloxycarbonyl*)-L-*cystine Dibenzyl Ester* (**3a**). Dry H_2S gas was bubbled through a solution of (2*S*-Z-Azy-OBzl (**1a**, 320 mg, 1.03 mmol) in dry CH_2Cl_2 (30 ml) until saturation at room temperature and $BF_3 \cdot OEt_2$ (5 drops) was added. Then H_2S gas was bubbled for additional 15 min. After the reaction mixture was stood at room temperature for 3 h, the solvent was removed *in vacuo*. The residual syrup was dissorved in MeOH (30 ml) at 0 °C and



Scheme 1.

a 0.2 M (1 M=1 mol dm^{-1}) solution of I_2 in MeOH (13 ml) was added dropwise for 45 min with stirring, and additionaly stirred for 45 min at room temperature. And then, 10% sodium thiosulfate was added until the brown color has disappeared. After the reaction mixture was concentrated *in vacuo* to 10 ml, the product was extracted by ethyl acetate and the extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography($CHCl_3$). Crystallization from MeOH-ether-hexane gave **3a** (250 mg, 70%) 85.5—87.0 °C, $[\alpha]_D^{23}$ +38.0° (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$) δ: 3.01 (4H d, CH_2), 5.08, 5.16 (8H 2s, CH_2), 4.62 (2H m, CH), 5.70 (2H bd, NH), 7.31 (20H s, C_6H_5).

Found: C, 62.68; H, 5.31; N, 4.12; S, 9.26%. Calcd for $C_{36}H_{36}N_2O_8S_2$: C, 62.77; H, 5.27; N, 4.07; S, 9.31%.

N,N′-*Bis(benzyloxycarbonyl)*-D-*cystine Dibenzyl Ester* (**3b**). The reaction of (2*R*-Z-Azy-OBzl (**1b**, 320 mg, 1.03 mmol) with H_2S was carried out as described above to give **3b** (285 mg, 80.3%) after recrystallization from MeOH-ether-hexane, mp 86—87 °C, $[\alpha]_D^{23}$ −39.8° (*c* 1.1, $CHCl_3$). NMR ($CDCl_3$) δ: 3.04 (4H d, CH_2), 4.63 (2H m, CH), 5.05, 5.10 (8H 2s, CH_2), 5.79 (2H bd, NH), 7.36 (20H s, C_6H_5).

Found: C, 62.72; H, 5.43; N, 4.22; S, 9.37%. Calcd for $C_{36}H_{36}N_2O_8S_2$: C, 62.77; H, 5.27; N, 4.07; S, 9.31%.

N,N′-*Bis(benzyloxycarbonyl)*-threo-3,3′-*dimethyl*-L-*cystine Dibenzyl Ester* (**4a**). The reaction of (2*S*,3*S*)-Z-3-MeAzy-OBzl (**2a**, 340 mg, 1.05 mmol) with H_2S was carried out as described above to give **4a** (280 mg, 74%) as a syrup, $[\alpha]_D^{23}$ +42.3° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 1.02 (6H d, CH_3), 3.43 (2H dd, CH), 4.60 (2H dd, CH), 5.05, 5.10 (8H 2s, CH_2), 5.80 (2H bd, NH), 7.25 (20H s, C_6H_5).

Found: C, 63.71; H, 5.65; N, 4.10; S, 9.01%. Calcd for $C_{38}H_{40}N_2O_8S_2$: C, 63.68; H, 5.62; N, 3.91; S, 8.94%.

N,N′-*Bis(benzyloxycarbonyl)*-threo-3,3′-*dimethyl*-D-*systine Dibenzyl Ester* (**4b**). The reaction of (2*R*,3*R*)-Z-3-MeAzy-OBzl (**2b**, 340 mg, 1.05 mmol) with H_2S was carried out as described above to give **4b** (295 mg, 78%) as a syrup, $[\alpha]_D^{23}$ −42.5° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 1.23 (6H d, CH_3), 3.44 (2H dd, CH), 4.60 (2H dd, CH), 5.07, 5.11 (8H 2s, CH_2), 5.68 (2H bd, NH), 7.28 (20H s, C_6H_5).

Found: C, 63.75; H, 5.73; N, 4.12; S, 9.11%. Calcd for $C_{38}H_{40}N_2O_8S_2$: C, 63.68; H, 5.62; N, 3.91; S, 8.94%.

L-*Cystine* (**5a**). **3a** (200 mg) was dissolved in acetic acid saturated with HBr (5 ml) at room temperature. After 12 h, the reaction mixture was concentrated *in vacuo*. The residue was triturated with anhydrous ether and was dissolved in small amount of water, and was adjusted to pH 5 with 5 M NH_4OH and ethanol was added. The precipitates were filtered off and recrystallized from hot water to give **5a** (57.8 mg, 78%), mp 204 °C (decomp), $[\alpha]_D^{23}$ −213° (*c* 1.1, 1 M HCl).

Found: C, 30.16; H, 4.92; N, 11.98; S, 26.42%. Calcd for $C_6H_{12}N_2O_4S_2$: C, 29.99; H, 5.03; N, 11.66; S, 26.68%.

D-*Cystine* (**5b**). **3b** (200 mg) was dissolved in acetic acid saturated with HBr (5 ml) at room temperature. After 12 h, the reaction mixture was worked up as described above to give **5b** (55.8 mg, 75.3%), which recrystallized from hot water, mp 206 °C (decomp), $[\alpha]_D^{23}$ +213° (*c* 1.0, 1 M HCl).

Found: C, 30.22; H, 5.12; N, 11.75; S, 26.58%. Calcd for $C_6H_{12}N_2O_4S_2$: C, 29.99; H, 5.03; N, 11.66; S, 26.68%.

L-threo-3,3′-*Dimethylcystine* (**6a**). **4a** (117 mg) was dissolved in acetic acid saturated with HBr (5 ml) at room temperature. After 12 h, the reaction mixture was worked up as described above to give **6a** (55 mg, 83%), was recrystallized from water-ethanol, mp 177.5—178 C (decomp), $[\alpha]_D^{23}$ +412.9° (*c* 0.6, 1 M HCl).

Found: C, 34.63; H, 6.22; N, 10.09; S, 23.32%. Calcd for $C_8H_{16}N_2O_4S_2 \cdot 1/2\,H_2O$: C, 34.64; H, 6.18; N, 10.10; S, 23.12%.

D-threo-3,3′-*Dimethylcystine* (**6b**). **4b** (141 mg) was dissolved in acetic acid saturated with HBr (5 ml) at temperature. After 12 h, the reaction mixture was worked up as described above to give **6b** (40 mg, 75.8%), which was recrystallized from water-ethanol, mp 175 °C (decom), $[\alpha]_D^{23}$ −414° (*c* 1.0, 1 M HCl). [lit,[6] $[\alpha]_D^{19}$ −416° (*c* 0.50, 1 M HCl), lit,[5] $[\alpha]_D^{13}$ −414° (*c* 1.0, 1 M HCl)].

Found: C, 34.65; H, 6.20; N, 10.12; S, 23.25%. Calcd for $C_8H_{16}N_2O_4S_2 \cdot 1/2\,H_2O$: C, 34.64; H, 6.18; N, 10.10; S, 23.12%.

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