

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 H₂S gave the optically active cystine and *threo*-3-methylcystine derivatives *via* the stereospecific ring-opening reaction of aziridine, and subsequent oxidation and deblocking procedure gave the titled compounds in good yields.

Photaki²⁾ have reported the preparation of DL-S-tritylcystine 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-methylcystine, 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-methylcystine. 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.* C₆H₅COSH $\rightleftharpoons$ C₆H₅CSOH.

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

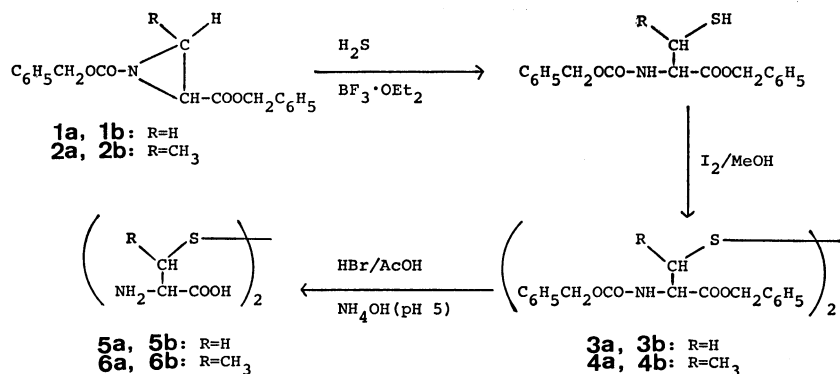
were prepared by *N*-benzyloxycarbonylation of (2*S*)-H-Azy-OBzl, (2*S*,3*S*)-H-3-MeAzy-OBzl, and their enantiomers with benzyloxycarbonyl chloride as described in our previous paper.¹⁾ The ring-opening reaction of **1a**, **1b**, **2a**, and **2b** were carried out in dichloromethane saturated with H₂S in the presence of boron trifluoride etherate at room temperature for 3 h, and the corresponding cystine 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 cystine and 3-methylcystine by the stereospecific ring-opening reaction of aziridine with H₂S 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 Dibenzy Ester (**3a**). Dry H₂S gas was bubbled through a solution of (2*S*)-Z-Azy-OBzl (**1a**, 320 mg, 1.03 mmol) in dry CH₂Cl₂ (30 ml) until saturation at room temperature and BF₃·OEt₂ (5 drops) was added. Then H₂S 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 dissolved in MeOH (30 ml) at 0°C and



Scheme 1.

a 0.2 M (1 M = 1 mol dm⁻³) solution of I₂ in MeOH (13 ml) was added dropwise for 45 min with stirring, and additionally 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 Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography (CHCl₃). Crystallization from MeOH-ether-hexane gave **3a** (250 mg, 70%) 85.5–87.0 °C, $[\alpha]_D^{25} + 38.0^\circ$ (*c* 1.0, CHCl₃). NMR (CDCl₃) δ : 3.01 (4H d, CH₂), 5.08, 5.16 (8H 2s, CH₂), 4.62 (2H m, CH), 5.70 (2H bd, NH), 7.31 (20H s, C₆H₅).

Found: C, 62.68; H, 5.31; N, 4.12; S, 9.26%. Calcd for C₃₆H₃₆N₂O₈S₂: C, 62.77; H, 5.27; N, 4.07; S, 9.31%.

N,N'-Bis(benzyloxycarbonyl)-D-cystine Dibenzy Ester (**3b**). The reaction of (2*R*-Z-Azy-OBzl (**1b**, 320 mg, 1.03 mmol) with H₂S was carried out as described above to give **3b** (285 mg, 80.3%) after recrystallization from MeOH-ether-hexane, mp 86–87 °C, $[\alpha]_D^{25} - 39.8^\circ$ (*c* 1.1, CHCl₃). NMR (CDCl₃) δ : 3.04 (4H d, CH₂), 4.63 (2H m, CH), 5.05, 5.10 (8H 2s, CH₂), 5.79 (2H bd, NH), 7.36 (20H s, C₆H₅).

Found: C, 62.72; H, 5.43; N, 4.22; S, 9.37%. Calcd for C₃₆H₃₆N₂O₈S₂: C, 62.77; H, 5.27; N, 4.07; S, 9.31%.

N,N'-Bis(benzyloxycarbonyl)-threo-3,3'-dimethyl-L-cystine Dibenzy Ester (**4a**). The reaction of (2*S*,3*S*)-Z-3-MeAzy-OBzl (**2a**, 340 mg, 1.05 mmol) with H₂S was carried out as described above to give **4a** (280 mg, 74%) as a syrup, $[\alpha]_D^{25} + 42.3^\circ$ (*c* 1.0, MeOH). NMR (CDCl₃) δ : 1.02 (6H d, CH₃), 3.43 (2H dd, CH), 4.60 (2H dd, CH), 5.05, 5.10 (8H 2s, CH₂), 5.80 (2H bd, NH), 7.25 (20H s, C₆H₅).

Found: C, 63.71; H, 5.65; N, 4.10; S, 9.01%. Calcd for C₃₈H₄₀N₂O₈S₂: C, 63.68; H, 5.62; N, 3.91; S, 8.94%.

N,N'-Bis(benzyloxycarbonyl)-threo-3,3'-dimethyl-D-cystine Dibenzy Ester (**4b**). The reaction of (2*R*,3*R*)-Z-3-MeAzy-OBzl (**2b**, 340 mg, 1.05 mmol) with H₂S was carried out as described above to give **4b** (295 mg, 78%) as a syrup, $[\alpha]_D^{25} - 42.5^\circ$ (*c* 1.0, MeOH). NMR (CDCl₃) δ : 1.23 (6H d, CH₃), 3.44 (2H dd, CH), 4.60 (2H dd, CH), 5.07, 5.11 (8H 2s, CH₂), 5.68 (2H bd, NH), 7.28 (20H s, C₆H₅).

Found: C, 63.75; H, 5.73; N, 4.12; S, 9.11%. Calcd for C₃₈H₄₀N₂O₈S₂: 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 NH₄OH 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), $[\alpha]_D^{25}$

–213° (*c* 1.1, 1 M HCl).

Found: C, 30.16; H, 4.92; N, 11.98; S, 26.42%. Calcd for C₆H₁₂N₂O₄S₂: 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), $[\alpha]_D^{25} + 213^\circ$ (*c* 1.0, 1 M HCl).

Found: C, 30.22; H, 5.12; N, 11.75; S, 26.58%. Calcd for C₆H₁₂N₂O₄S₂: 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), $[\alpha]_D^{25} + 412.9^\circ$ (*c* 0.6, 1 M HCl).

Found: C, 34.63; H, 6.22; N, 10.09; S, 23.32%. Calcd for C₈H₁₆N₂O₄S₂·1/2 H₂O: 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 (decomp), $[\alpha]_D^{25} - 414^\circ$ (*c* 1.0, 1 M HCl). [lit,⁶ $[\alpha]_D^{19} - 416^\circ$ (*c* 0.50, 1 M HCl), lit,⁵ $[\alpha]_D^{19} - 414^\circ$ (*c* 1.0, 1 M HCl)].

Found: C, 34.65; H, 6.20; N, 10.12; S, 23.25%. Calcd for C₈H₁₆N₂O₄S₂·1/2 H₂O: C, 34.64; H, 6.18; N, 10.10; S, 23.12%.

References

- 1) Part IX: K. Nakajima, H. Oda, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **56**, 520 (1983). The abbreviations of the IUPAC-IUB commission (*J. Biol. Chem.*, **247**, 977 (1972)) are used. Z: benzyloxycarbonyl, Bzl: benzyl, "Azyline" is used as the name of 2-aziridinecarboxylic acid, "Azy" being its abbreviation. 3-MeAzy: 3-methyl-2-aziridinecarboxylic acid.
- 2) I. Photaki, *J. Am. Chem. Soc.*, **85**, 1123 (1963).
- 3) H. E. Carter, C. M. Stevens, and L. F. Ney, *J. Biol. Chem.*, **139**, 247 (1941).
- 4) J. Hoogmartens, P. J. Claes, and H. Vanderhaeghe, *J. Org. Chem.*, **39**, 425 (1974).
- 5) J. L. Morell, P. Fleckenstein, and E. Gross, *J. Org. Chem.*, **42**, 355 (1977).
- 6) T. Wakamiya, K. Shinbo, T. Shiba, K. Nakajima, M. Neya, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **55**, 3878 (1982).