Studies on 2-Aziridinecarboxylic Acid. VI.[1] Synthesis of β-Alkoxy-α-Amino Acids *via* Ring-opening Reaction of Aziridine

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Synopsis. The reaction of aziridine derivatives having a urethane-type protecting group with several alcohols in the presence of boron trifluoride etherate afford the corresponding optically pure *O*-alkylserine and *O*-alkylthreonine derivatives *via* a ring-opening reaction of aziridine in good yield.

In 1976, we reported that *N*-aminoacyl 2-aziridinecarboxylic acid derivatives, *e.g.*, Z-Gly-(2*S*)-Azy-Gly-OBzl, were coverted into the corresponding *O*-alkylserine peptide by the reaction of several alcohols in the presence of boron trifluoride etherate.[2] The yields, however, were usually very poor.

In this communication, we describe the results of aziridine derivatives having a urethane-type protecting group, benzyl (2*S*)-1-benzyloxycarbonyl-2-aziridinecarboxylate[(2*S*)-Z-Azy-OBzl(**1**)] and methyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate [(2*S*,3*S*)-Z-3-MeAzy-OMe(**2**)], with several alcohols. **1** and **2** were synthesized according to our previous report.[3,4]

(2*S*)-Z-Azy-OBzl(**1**) and (2*S*,3*S*)-Z-3-MeAzy-OMe (**2**) were very stable in alcoholic solution at a room temperature, even under heating and no ring-opening reaction of the aziridine residue with alcohols was observed. However, if a catalytic amount of boron trifluoride etherate was added to the alcoholic solution of the aziridine derivatives, the reaction occurred easily to give the corresponding *O*-alkylserine(**3**—**9**) and -threonine(**10**—**16**) derivatives in good yield as shown in Scheme 1 and Table 1.

The synthesized *O*-alkylserine and threonine derivatives were easily transformed into the corresponding L-*O*-alkyl serine(**17**, **18**, **19**) and L-*O*-alkylthreonine (**20**, **21**, **22**, **23**) by catalytic hydrogenolysis or the combination of catalytic hydrogenolysis and hydrolysis as shown in Scheme 1, giving the titled compounds.

This study showed that the ring-opening reaction of aziridine derivatives having the urethane-type protecting groups is an effective method for synthesizing optically active β-alkoxy-α-amino acids.

Experimental

The melting points given are uncorrected. Optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. The NMR spectra were obtained with a Hitachi R-20 B high resolution spectrometer using TMS as the internal reference.

(2S)-Z-Azy-OBzl (1). To a solution of (2*S*)-H-Azy-OBzl[3] (1.2 g, 6.7 mmol) and Et_3N (0.76 ml, 5.4 mmol) in $CHCl_3$ was added benzyloxycarbonyl chloride (0.86 ml, 5.4 mmol) at 0 °C with stirring. After being stirred overnight, it was washed with 10% citric acid, 1 M (1 M=1 mol dm^{-3}) $NaHCO_3$, and water, then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography and 1.61 g (96% from Z–Cl[1]) of **1** was obtained, $[\alpha]_D^{23}$ −18.1° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 2.37 (1H q, *J*=1.5, 5 Hz), 3.08 (1H q, *J*=3.0, 5.0 Hz), 5.05, 5.07 (4H 2s), 2.54 (1H q, *J*=1.5, 3.0 Hz), 7.26 (10H s).

Found: C, 69.15; H, 5.53; N, 4.42%. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

(2S,3S)-Z-3-MeAzy-OMe (2). To a solution of (2*S*,3*S*)-H-3-MeAzy-OMe[4] (11.3 g, 78 mmol) and Et_3N (10.9 ml, 78 mmol) in $CHCl_3$ (200 ml) was added 2-benzyloxycarbonyloximino-2-phenylacetonitrile (Z–ON) (19.7 g, 70 mmol) at room temperature with stirring. After the reaction mixture was worked up as described above, 14.8 g (85% from Z–ON) of **2** was isolated as syrup, $[\alpha]_D^{23}$ −66.2° (*c* 1.1, MeOH). NMR ($CDCl_3$) δ: 1.25 (3H d, *J*=6.0 Hz), 2.75 (1H m), 3.20 (1H d, *J*=6.5 Hz), 3.35 (3H s), 5.10 (2H s), 7.28 (5H s).

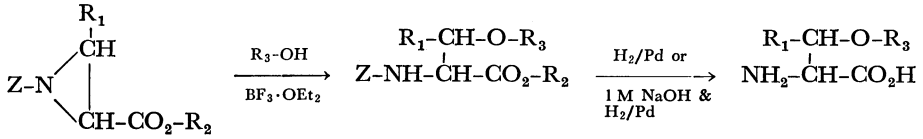
Found: C, 62.34; H, 6.15; N, 5.48%. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62%.

L-*Z-Ser(OMe)-OBzl (3).* *General Method* via *Ring-opening Reaction of Azy*: **1** (0.3 g, 0.96 mmol) was dissolved in $CHCl_3$ (3 ml) and MeOH (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperature. The reaction mixture was left standing for 12 h, then washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography with elution by $CHCl_3$. The effluent was concentrated *in vacuo* and 0.21 g (64%) of **3** was obtained. NMR ($CDCl_3$) δ: 3.26 (3H s), 3.69 (2H m, β-proton), 4.52 (1H, α-proton), 5.74 (1H bd).

Found: C, 66.39; H, 6.21; N, 4.16%. Calcd for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08%.

L-*Z-Thr(OBu^t)-OMe (13).* Via *Ring-opening Reaction of 3-MeAzy*: **2** (0.2 g, 0.8 mmol) was dissolved in $CHCl_3$ (2 ml) and *t*-BuOH (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperature. The reaction mixture was left standing overnight at room temperature and was worked up as described above. 243 mg (94%) of **13** was obtained. NMR ($CDCl_3$) δ: 1.10 (9H s), 1.19 (3H d), 4.15 (1H m, β-proton), 4.25 (1H q, α-proton), 5.50 (1H b).

Found: C, 63.25; H, 7.94; N, 4.21%. Calcd for $C_{17}H_{25}O_5N$: C, 63.14; H, 7.79; N, 4.33%.



1: R_1=H, R_2=Bzl
2: R_1=Me, R_2=Me

3—9: R_1=H, R_2=Bzl
10—16: R_1=Me, R_2=Me

17—19: R_1=H
20—23: R_1=Me

Scheme 1.

Table 1. Properties and yields of *O*-alkyl-L-serine, L-threonine, and their derivatives

No.	Product[c] R_1	R_2	R_3	Yield/%	$[\alpha]_D^{24}$/°(MeOH)	Mp θ_m/°C
3	H	Bzl	Me	64	−19.1 (*c* 1.4)	syrup
4	H	Bzl	Pr^i	95	−19.5 (*c* 1.1)	syrup
5	H	Brl	Bu^s	73	−17.4 (*c* 0.9)	syrup
6	H	Bzl	Bu^t	58	−20.0 (*c* 1.1)	syrup
7	H	Bzl	Hex[c]	57	−20.1 (*c* 1.1)	57—58
8	H	Bzl	Bzl	100	−9.8 (*c* 1.1)	86—87
9	H	Bzl	Ph	27	−8.6 (*c* 1.1)	syrup
10	Me	Me	Me	98	−6.4 (*c* 1.1)	syrup
11	Me	Me	Pr^i	98	−10.7 (*c* 1.4)	syrup
12	Me	Me	Bu^s	92	−14.1 (*c* 1.2)	syrup
13	Me	Me	Bu^t	94	−3.1 (*c* 1.1)	syrup
14	Me	Me	Hex[c]	92	−9.1 (*c* 1.1)	syrup
15	Me	Me	Bzl	98	−6.9 (*c* 1.1)	72.5—73.0
16	Me	Me	Ph	57	+24.2 (*c* 1.1)	syrup
17	H	H	Pr^i	87	−11.8 (*c* 1.0)[a]	221 (d.)
18	H	H	Bu^t	100	−14.8 (*c* 1.0)[a]	209 (d.)
19	H	H	Hex[c]	82	−10.0 (*c* 1.0)[a]	193 (d.)
20	Me	H	Pr^i	86	−29.8 (*c* 1.1)[b]	212 (d.)
21	Me	H	Bu^s	75	−28.8 (*c* 1.0)[b]	198 (d.)
22	Me	H	Bu^t	82	−37.8 (*c* 1.0)[a]	207 (d.)
23	Me	H	Hex[c]	83	−35.5 (*c* 0.8)[a]	201 (d·)

a) Solvent: H_2O, b) solvent: 1 M HCl, c) Me: methyl, Bzl: benzyl, Pr^i: isopropyl, Bu^s: *s*-butyl, Bu^t: *t*-butyl, Ph: phenyl, Hex[c]: cyclohexyl.

Via t-*Butylation with Isobutylene of* L-*Z-Thr-OMe*: To a solution of L-Z-Thr-OMe (2.67 g, 10 mmol) and isobutylene (15 ml) in CH_2Cl_2 (15 ml) was added conc. H_2SO_4 (1 ml). The reaction mixture was left standing at room temperature for 3 d, and then washed with 1 M $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography. 2.42 g (75%) of **13** was obtained, $[\alpha]_D^{24}$ +4.7° (*c* 2.0, DMF).

L-*Z-Ser(OBzl)-OH.* Via *Ring-opening Reaction of Azy*: **1** (0.2 g, 0.64 mmol) was dissolved in $CHCl_3$ (2 ml) and benzyl alcohol (5 ml), then $BF_3 \cdot OEt_2$ (3 drops) was added at room temperarure. The reaction mixture was left standing overnight and then worked up as described above. The obtained **8** (100% yield) was dissolved in MeOH (3 ml) and 2 M NaOH (5 ml) was added with stirring at room temperature for 2 h, then the solution was concentrated *in vacuo*. The residue was dissolved in water and adjusted to pH 2 with 3 M HCl, and the product was extracted with ethyl acetate. The solution was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from CCl_4, 211 mg (100%), mp 99.5—100 °C, $[\alpha]_D^{24}$ +9.4° (*c* 1.3, MeOH). [mp 99—100 °C, $[\alpha]_D^{24}$ +9.5° (*c* 1.1, MeOH), prepared from Z–Cl and L-H-Ser(OBzl)-OH].

Found: 65.38; H, 5.85; N, 4.32%. Calcd for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.81; N, 4.25%.

*O-Isopropyl-*L-*serine (18)*: H_2 gas was bubbled through a solution of **4** (218 mg, 0.59 mmol) in MeOH (10 ml) containing Pd black (100 mg) for 2 h. The catalyst removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from water–acetone, and 75.5 mg (87%) of **18** was obtained.

O-*Isopropyl-*L-*threonine (20)*. **11** (224 mg, 0.72 mmol) was hydrolyzed with 1 M NaOH (2.5 ml) in MeOH (3 ml) at room temperature for 1 h. After L-Z-Thr(OPr^i) had been isolated by the usual procedure, the benzyloxycarbonyl group was removed by the catalytic hydrogenation described above. The product was crystallized from water-acetone, and 100 mg (85.7%) of **20** was obtained.

References

1) Part V. K. Okawa, K. Nakajima, T. Tanaka, and M. Neya, *Bull. Chem. Soc. Jpn.*, **55**, 174 (1982). Abbreviations of the IUPAC-IUB commission, *J. Biol. Chem.*, **247**, 977 (1972), are used. Z: benzyloxycarbonyl, OBzl: benzyl ester, OMe: methyl ester, Z–Cl: benzyloxycarbonyl chloride, Z–ON: 2-benzyloxycarbonyloximino-2-phenylacetonitrile. "Azyline" is used as the name of 2-aziridinecarboxylic acid, "Azy" being its abbreviation. 3-MeAzy: (2*S*,3*S*)-3-methyl-2-aziridinecarboxylic acid.

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4) K. Okawa and K. Nakajima, *Biopolymers*, **20**, 1811 (1891).