Studies on 2-Aziridinecarboxylic Acid. III. Reaction of 1-Acyl-2-aziridinecarboxylic Acid Peptide with Amines

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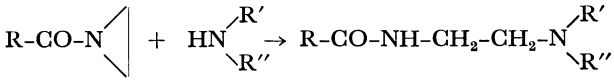
Synopsis. The reaction of Z-Gly-Azy-Gly-OBzl with amines was studied. With primary amines, the 1-acyl group (Z-Gly) of the aziridine peptide mainly migrated to the reactant amine with cleaving of the amide bond between glycine and aziridine, whereas aniline and diethylamine gave diaminopropionic acid derivatives *via* the ring opening reaction.

The present study is a part of an investigation of the reactivity of 1-acylaziridine peptides. It was shown that 1-acylaziridine peptides afford the *O*-esters as a result of the ring opening reaction with carboxylic acids.[1]

In this communication, we wish to give the results of a study of the reactivity of Z-Gly-Azy-Gly-OBzl(**1**)[2] with amines. Ammonia, benzylamine, ethylenediamine, amino acid esters, aniline, and diethylamine were used as the amines.

1-Acylaziridine derivatives generally undergo the ring opening reaction with primary or secondary amine, giving the following ethylenediamine derivatives.[3]



All amines examined, however, caused migration of the 1-acyl group (Z-Gly) from **1** to the reactant amines except aniline and diethylamine. Consequently, the fragment peptides (Z-Gly-NH-R(**2**) and Azy-Gly-OBzl(**3**)) were obtained in quantitative yields (Scheme 1 and Table 1). The results indicate that the reactivity of 1-acylaziridine peptide is independent of both the amount of amine and the reaction temperature. Evidently, the carbonyl carbon of the acyl group on 1-acylaziridine peptide is more positive than that of ordinary amides. The aziridine ring has an electron withdrawing or quasi-aromatic character.[4] A similar property is recognized in a nitrogen-containing heterocyclic ring system as amide component, such as pyrazolides, imidazolides and triazolides. The competitive reaction between migration and the ring opening reaction occurred to give the fragment peptides (**2**, **3**) and diaminopropionic acid derivative (A_2pr; **4**) in aniline. In contrast, only diaminopropionic acid derivative (**5**) was obtained *via* the ring opening reaction in the case of diethylamine. It seems that the reaction is specific for secondary amine.

TABLE 1. REACTION OF **1** WITH AMINES

Exp. No.	Reactant amines	Eq. amt. of amines	Temp °C	Time h	Yield/% 2	3	4 or 5
a	NH_3	excess	−5	1	94.5	92.8	0
b	NH_3	excess	r.t.	1	95.1	92.2	0
c	$PhCH_2NH_2$	20	r.t.	24	77.7	99.5[a]	0
d	$PhCH_2NH_2$	5	r.t.	24	90.4	79.0[a]	0
e	$PhCH_2NH_2$	5	45	24	99.4	41.6[a]	0
f	$(H_2N\text{-}CH_2)_2$	0.5	r.t.	24	77.7	64.6	0
g	$CH_3(NH_2)CO_2Bu^t$	8	r.t.	24	84.8	100	0
h	D-$PhCH(NH_2)CO_2Bu^t$	1.4	r.t.	72	100	100	0
i	$PhNH_2$	20	r.t.	24	14.1	15.0	27.8
j	$PhNH_2$	5	r.t.	72	36.2	28.0	43.7
k	$PhNH_2$	5	45	24	11.5	19.0	51.9
l	$HN(C_2H_5)_2$	20	r.t.	72	0	0	88.5

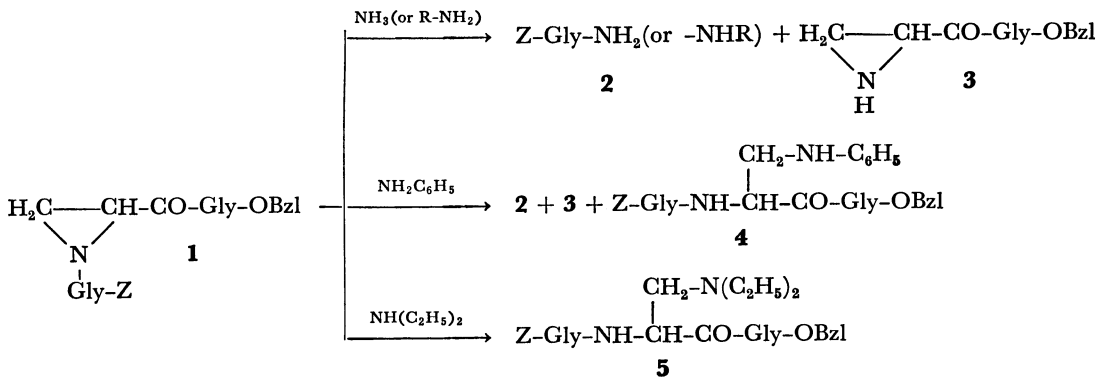
a) Total yield of both products Azy-Gly-OBzl and Ary-Gly-$NHCH_2Ph$.

Experimental

All melting points are uncorrected. NMR spectra were compatible for all products isolated. The purity of products was confirmed by thin layer chromatography on silica gel G.

*Z-Gly-Azy-Gly-OBzl (**1**).* Compound **1** prepared from serine derivative[5] was crystallized from THF–ether; mp 118—119 °C, $[\alpha]_D^{23}$ −52.2° (*c* 1.0, MeOH). NMR (acetone-d_6): δ 2.38 (1H q, J=1.5, 2.9 Hz, aziridine β-proton), 2.52 (1H, q, J=1.5, 5.9 Hz, aziridine β-proton), 3.29 (1H, q, J=2.9, 5.9 Hz, aziridine α-proton), 4.01 (2H t, J=5.0, -NH-C<u>H</u>$_2$-CO-). Found: C, 61.92; H, 5.57; N, 10.07%. Calcd for $C_{22}H_{23}O_6N_3$: C, 62.16; H, 5.45; N, 9.88%.

*Reaction of **1** with Amines. By Ammonia (a)*: Dry ammonia gas was bubbled into a solution of **1** (106 mg, 0.25 mmol) in CH_2Cl_2 (3 ml) at −5 °C until saturation. After being kept at the same temperature for 1 h, the solvent was removed. Dry ether was added to the residual product.



Scheme 1.

Crystals which appeared were collected by filtration, and identified as Z-Gly-NH_2; 52 mg (94.5%), mp 135—136 °C (lit,[6] mp 138—139 °C). From the filtrate, Azy-Gly-OBzl was isolated as crystals from $CHCl_3$–ether–hexane; 54.3 mg (92.8%), mp 118—119 °C, $[\alpha]_D^{23}$ −21.0° (*c* 1.0, $CHCl_3$). Found: C, 61.48; H, 5.97; N, 11.83%. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.52; H, 6.02; N, 11.96%.

By Ammonia (b): Dry ammonia gas was bubbled into a solution of **1** (100 mg, 0.23 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 1 h, the products were isolated as described for (a). Z-Gly-NH_2; 54.3 mg (95.1%). Azy-Gly-OBzl; 56 mg (92.2%).

By Benzylamine (c): Benzylamine (0.56 ml, 5.2 mmol) was added with stirring to a solution of **1** (110 mg, 0.26 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 24 h, ether was added to the reaction mixture. Crystals which appeared were collected by filtration, and identified as Z-Gly-NH-CH_2-C_6H_5; 58 mg (77.7%), mp 118—119 °C (lit,[7] mp 119—120 °C). The filtrate was concentrated *in vacuo*, the residual product being crystallized from MeOH–ether–hexane. The first crop of crystals was Azy-Gly-NH-CH_2-C_6H_5; 53.6 mg (91.6%), mp 140—141 °C, $[\alpha]_D^{23}$ −22.0° (*c* 1.0, MeOH). Found: C, 61.98; H, 6.48; N, 17.87%. Calcd for $C_{12}H_{15}O_2N_3$: C, 61.78; H, 6.48; N, 18.02%. The second crop was Azy-Gly-OBzl; 4.4 mg (7.9%).

By Benzylamine (d): Compound **1** (106 mg, 0.25 mmol) and benzylamine (0.14 ml, 1.25 mmol) were reacted in CH_2Cl_2 (3 ml) at room temperature for 24 h. The products were isolated as described for (c). Z-Gly-NH-CH_2-C_6H_5; 67 mg (90.4%), Azy-Gly-NH-CH_2-C_6H_5 and Azy-Gly-OBzl; 57 mg (79.0%).

By Benzylamine (e): Compound **1** (212 mg, 0.5 mmol) and benzylamine (0.27 ml, 2.5 mmol) were reacted in CH_2Cl_2 (3 ml) at 45 °C for 24 h. The products were isolated as described for (c). Z-Gly-NH-CH_2-C_6H_5; 148.2 mg (99.4 %), Azy-Gly-NH-CH_2-C_6H_5 and Azy-Gly-OBzl; 61 mg (41.6%).

By Ethylenediamine (f): Ethylenediamine (12.4 mg, 0.21 mmol) was added with stirring to a solution of **1** (176 mg, 0.4 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 24 h, crystals which appeared were collected by filtration, and identified as (Z-Gly-NH-CH_2-)$_2$; 71.1 mg (77.7%), mp 206 °C (dec). Found: C, 59.65; H, 5.88; N, 12.47%. Calcd for $C_{22}H_{26}O_6N_4$: C, 59.72; H, 5.92; N, 12.66%. From the filtrate, Azy-Gly-OBzl was obtained; 65.8 mg (64.6%).

By Gly-OBu^t (g): Gly-OBu^t (525 mg, 4 mmol) was added to a solution of **1** (212 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 24 h, the solvent was removed *in vacuo*. The residual oily product was subjected to silica gel column chromatography with ethyl acetate–$CHCl_3$ (1:1 v/v). Z-Gly-Gly-OBu^t; 135 mg (84.8%), oil. Found: C, 59.48; H, 6.98; N, 8.72%. Calcd for $C_{16}H_{22}O_5N_2$: C, 59.61; H, 6.88; N, 8.69%. Azy-Gly-OBzl; 125 mg (100%).

By D-Gly(ph)-OBu^t (h): D-Gly(ph)-OBu^t (72 mg, 0.35 mmol) was added to a solution of **1** (106 mg, 0.25 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 72 h, the products were isolated as described for (g). Z-Gly-D-Gly-(ph)-OBu^t; 99.6 mg (100%), oil, $[\alpha]_D^{23}$ −88.8° (*c* 1.0, $CHCl_3$). Found: C, 66.09; H, 6.96; N, 7.40%. Calcd for $C_{22}H_{26}O_5N_2$: C, 66.39; H, 7.09; N, 7.04%. Azy-Gly-OBzl; 62.5 mg (100%).

By Aniline (i): Aniline (0.88 ml, 10 mmol) was added to a solution of **1** (212 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 24 h, the solvent was removed *in vacuo*. Ether was added to the residue, and crystals which appeared were collected by filtration. The crystals were identified as Z-Gly-NH-C_6H_5; 40.5 mg (14.1%), mp 144.5—146.5 °C (lit,[8] mp 145—146 °C). The filtrate was subjected to silica gel column chromatography with ethyl acetate–$CHCl_3$ (1:1 v/v). Azy-Gly-OBzl; 38.7 mg (15.0%). Z-Gly-A_2pr(NHph)-Gly-OBzl; 71.5 mg (27.8%), mp 80—81.5 °C, $[\alpha]_D^{23}$ +6.5° (*c* 0.25, MeOH). Found: C, 64.75; H, 5.84; N, 10.51%. Calcd for $C_{28}H_{30}O_6N_4$: C, 64.85; H, 5.84; N, 10.80%.

By Aniline (j): Compound **1** (212 mg, 0.5 mmol) and aniline (0.22 ml, 2.5 mmol) were reacted in CH_2Cl_2 (3 ml) at room temperature for 72 h. The products were isolated as described for (i). Z-Gly-NH-C_6H_5; 104 mg (36.2%), Azy-Gly-OBzl; 72.2 mg (28.0%), and Z-Gly-A_2pr(NHph)-Gly-OBzl; 112 mg (43.7%).

By Aniline (k): Compound **1** (212 mg, 0.5 mmol) and aniline (0.22 ml, 2.5 mmol) were reacted in CH_2Cl_2 (3 ml) at 45 °C for 24 h. The products were isolated as described for (i). Z-Gly-NH-C_6H_5; 33 mg (11.5%), Azy-Gly-OBzl; 49 mg (19.0%), and Z-Gly-A_2pr(NHph)-Gly-OBzl; 134 mg (51.9%).

By Diethylamine (l): Diethylamine (1.02 ml, 10 mmol) was added to a solution of **1** (212 mg, 0.5 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 72 h, the solvent was removed *in vacuo*. The residual oily product was subjected to silica gel column chromatography with MeOH–$CHCl_3$ (1:20 v/v). Z-Gly-A_2pr(NEt_2)-Gly-OBzl was obtained as oil; 221 mg (88.5%), $[\alpha]_D^{23}$ −5.1° (*c* 0.4, MeOH). Found: C, 61.67; H, 6.76; N, 10.14%. Calcd for $C_{26}H_{34}O_6N_4 \cdot 1/2H_2O$: C, 61.52; H, 6.95; N, 10.15%.

References

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2) Abbreviations according to IUPAC-IUB commission, *J. Biol. Chem.*, **247**, 977 (1972), are used. Z: benzyloxycarbonyl, Bzl: benzyl ester, OBu^t: *t*-butoxy, Gly(ph): α-phenylglycine, A_2pr: 2,3-diaminopropionic acid. "Azyline" is used as the name of an 2-aziridinecarboxylic acid, "Azy" being its abbreviation.

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