# The Synthesis and Reaction of Monohalogeno-*t*-butyloxycarbonylamino Acids

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Monohalogeno-*t*-butyloxycarbonylamino acids (XBOC-amino acids) were synthesized by the use of the corresponding chloroformates in a basic aqueous solution. Several dipeptides containing XBOC-amino acid were also prepared. The cleavage of the XBOC group was successfully carried out not only under some acidic conditions, but also by heating in methanol or ethanol. In order to demonstrate the usefulness of this group in peptide synthesis, Z–Gly–Lys(Z)–Gly–OEt was synthesized *via* BrBOC–Lys(Z)–Gly–OEt, which had been treated by hot ethanol. Side reaction during the synthesis of XBOC-amino acids will also be described.

The *t*-butyloxycarbonyl (BOC) group is of considerable importance in peptide chemistry, especially in solid-phase synthesis. Since our collaborators reported a method in which the BOC group was introduced by reacting *t*-butyl chloroformate (BOC–Cl) with amino acids in an aqueous alkaline solution,[1] BOC-amino acids have been prepared as a commercial scale. Unfortunately, BOC–Cl is unstable even in inert organic solvents, such as ether, dichloromethane, and tetrahydrofuran, and it can not be stored for a long time at −20°C. Also, the BOC–Cl content in the solution can not be precisely estimated. For these reasons, many investigators have attempted to develop a new protecting group which can be easily synthesized.[2-5] Carpino *et al.* recently reported on the α-halogeno-*t*-butyloxycarbonyl (XBOC) group.[6] They found that α-bromo- and α-chloro-*t*-butyl chloroformate (BrBOC–Cl, ClBOC–Cl) were significantly more stable than BOC–Cl, and that, on treatment with anilines, the corresponding urethans were obtained, while the acylation reaction was generally unsuccessful with amino acid derivatives.

In the present paper, the authors will report on the synthesis, properties and application of BrBOC- and ClBOC-amino acids.[7]

## Results

*Synthesis of XBOC-amino Acids.* α-Bromo- and α-chloro-*t*-butyl alcohol were prepared by Carpino's method, which had been employed for the preparation of α,α-dibromo-*t*-butyl alcohol.[6] These alcohols were converted into the corresponding chloroformates as the usual manner and were purified by distillation. The characterizations of the alcohols and the chloroformates were identical with those previously reported.[6]

The chloroformates were treated with amino acid esters in water–chloroform–tetrahydrofuran and with amino acids in an aqueous alkaline solution.

In order to confirm the structures of the BrBOC- and ClBOC-amino acid benzyl esters thus obtained, the esters were converted into the acids by saponification or hydrogenolysis; the yields were moderate (Eq. (1)).

$$\mathrm{XBOC\text{–}Cl} + \mathrm{C_6H_5CH_2OCO\text{–}\underset{\displaystyle R}{\underset{|}{CH}}\text{–}NH_2} \xrightarrow[\mathrm{H_2O\text{–}CHCl_3\text{–}THF}]{\mathrm{Et_3N}} \mathrm{XBOC\text{–}\underset{\displaystyle R}{\underset{|}{NHCH}}CO_2CH_2C_6H_5} \xrightarrow[\text{or } H_2/Pd]{OH^-} \mathrm{XBOC\text{–}\underset{\displaystyle R}{\underset{|}{NHCH}}COOH} \quad (1)$$

R: amino acid side chain
X: Br, Cl

The results are shown in Tables 1 and 2.

XBOC-amino acids show IR spectra similar to those of BOC-amino acids (Fig. 1).

*Cleavage of the XBOC Group.* A relatively high stability of BrBOC and ClBOC groups is shown in the acidic reagents. Neither of them is completely cleaved when left standing in 10% hydrogen chloride in dioxane or anhydrous trifluoroacetic acid at room temperature for an hour.

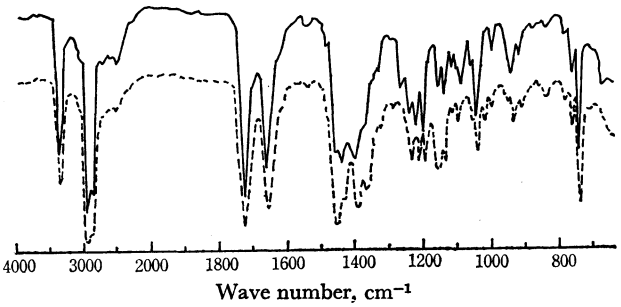



Fig. 1. IR spectra of BrBOC–Trp–OH (——) and BOC–Trp (------) in Nujol.

1) S. Sakakibara, I. Honda, K. Takada, M. Miyoshi, T. Ohnishi, and K. Okumura, This Bulletin, **42**, 809 (1969).
2) G. A. Olah and S. J. Kuhn, *J. Amer. Chem. Soc.*, **82**, 2308 (1960).
3) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).
4) S. Nakanishi, T. C. Myers, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 3099 (1955).
5) E. Schnabel, H. Herzog, P. Hoffman, E. Klauke, and I. Ugi, *Ann. Chem.*, **716**, 175 (1968); *Angew. Chem.*, **80**, 396 (1968).
6) L. A. Carpino, K. N. Parameswaran, R. K. Kirkley, J. W. Spiewak, and E. Schmitz, *J. Org. Chem.*, **35**, 3291 (1970).
7) All amino acid residues are of the L-configuration. The abbreviated designation of amino acids, peptides and their derivatives is in accordance with the proposal of the IUPAC-IUB Commission of Biochemical Nomenclature, which appeared in *Biochemistry*, **5**, 2485 (1966); *ibid.*, **6**, 362 (1967).
8) C. M. Suter and H. D. Zook, *J. Amer. Chem. Soc.*, **66**, 738 (1944).

Table 1. α-Bromo-*t*-butyloxycarbonylamino acids

| Amino acids | Yield (%) | Mp °C | $[\alpha]_D^{20}$ | Analysis (Calcd) C % | H % | N % | Br % |
|---|---|---|---|---|---|---|---|
| Gly | 55 | 103 | — | 33.32 (33.09) | 4.82 (4.75) | 5.43 (5.49) | 31.53 (31.44) |
| Pro | 78 | 117 | −38.0°a) | 40.88 (40.80) | 5.43 (5.48) | 4.77 (4.76) | 27.24 (27.17) |
| Trp | 63 | 110 | +27.0°a) | 49.83 (50.14) | 5.19 (4.99) | 6.85 (7.30) | 20.58 (20.85) |
| Phe·DCHA | 79 | 268 | + 4.6°b) | 59.30 (59.38) | 7.96 (7.82) | 5.27 (5.30) | 14.65 (15.20) |
| Val·DCHA | 47 | 291 | −17.0°b) | 55.54 (55.34) | 8.62 (8.65) | 5.82 (5.86) | 16.50 (16.73) |
| Met·DCHA | 48 | 266 | −26.5°b) | 51.77 (51.85) | 8.10 (8.11) | 5.51 (5.49) | 15.75 (15.68) |
| Ile·DCHA | 41 | 286 | − 6.7°b) | 56.99 (56.20) | 8.83 (8.82) | 5.68 (5.69) | 15.14 (15.26) |
| Ala·DCHA | 60 | 286 | −31.5°b) | 53.34 (53.44) | 8.25 (8.29) | 6.12 (6.23) | 17.74 (17.77) |

a) *c* 1, AcOEt b) *c* 1, AcOH

Table 2. α-Chloro-*t*-butyloxycarbonylamino acids

| Amino acids | Yield (%) | Mp °C | $[\alpha]_D^{20}$a) | Analysis (Calcd) C % | H % | N % | Cl % |
|---|---|---|---|---|---|---|---|
| Gly | 81 | 104.0 | — | 40.40 (40.10) | 5.78 (5.77) | 6.77 (6.68) | 16.55 (16.91) |
| Pro | 86 | 102.0 | −54.9° | 48.22 (47.90) | 6.61 (6.83) | 5.54 (5.58) | 14.24 (14.14) |
| Trp | 76 | 140.2 | − 8.5° | 56.67 (56.55) | 5.78 (5.93) | 8.25 (8.24) | 10.56 (10.43) |
| Ala·DCHA | 72 | 124.0 | −14.3° | 59.36 (59.45) | 9.07 (8.98) | 6.95 (6.93) | 8.90 ( 8.77) |
| Leu·DCHA | 72 | 106.7 | −16.6° | 61.96 (61.78) | 9.73 (9.69) | 6.33 (6.26) | 7.54 ( 7.93) |
| Ile·DCHA | 60 | 120.0 | − 2.0° | 61.94 (61.78) | 9.76 (9.69) | 6.35 (6.26) | 7.41 ( 7.92) |
| Val·DCHA | 63 | 130.0 | − 6.0° | 61.02 (61.02) | 9.50 (9.54) | 6.59 (6.46) | 8.12 ( 8.18) |
| Phe·DCHA | 65 | 248.5 | + 1.5° | 64.59 (64.90) | 8.49 (8.58) | 5.73 (5.82) | 7.39 ( 7.37) |
| *N*,*S*-di-Cys ·DCHA | 60 | 106.4 | −16.1° | 52.27 (52.53) | 7.78 (7.75) | 4.96 (4.90) | 12.24 (12.40) |
| Met·DCHA | 69 | 128.3 | −14.3° | 56.93 (56.81) | 8.87 (8.88) | 6.09 (6.02) | 7.81 ( 7.62) |
| Glu·$(DCHA)_2$ | 68 | 188.0 | − 5.9° | 63.36 (63.33) | 9.65 (9.76) | 6.58 (6.51) | 5.86 ( 5.49) |

a) *c* 1, AcOH

The reduction of the XBOC-group to the BOC group by means of sodium borohydride in water, by means of hydrogenolysis in methanol over a palladium catalyst, or by means of electrolytic reduction does not proceed.

However, the BrBOC group is completely removed under the following conditions: heating in methanol or ethanol; borontrifluoride etherate in trifluoroacetic acid at room temperature for an hour; 4N hydrogen bromide in acetic acid, and sodium in liquid ammonia. The ClBOC group is completely cleaved by borontrifluoride etherate in trifluoroacetic acid, by 4N hydrogen bromide in acetic acid, and by sodium in liquid ammonia.

The cleavage of the BrBOC group by heating in methanol or ethanol is a unique deprotection technique. This reaction, named "self-cleavage" by Carpino, may proceed similarly to the self-cleavage of BrBOC-aniline (Eq. (2)).[6]

The selective cleavage of the BrBOC group may be possible, since other amino-protecting groups such as BOC and the benzyloxycarbonyl (Z) group are stable under heating in methanol or ethanol.

*Peptide Synthesis.* XBOC-amino acids were converted into dipeptides by the mixed anhydride (M.A.) method, which was the better than dicyclohexylcarbodiimide (DCCD) method (Table 3).

The tripeptide sequence, Z–Gly–Val–Gly–OMe, was then synthesized by the M.A. method, couplingZ–Gly–OH with H–Val–Gly–OMe prepared from BrBOC–

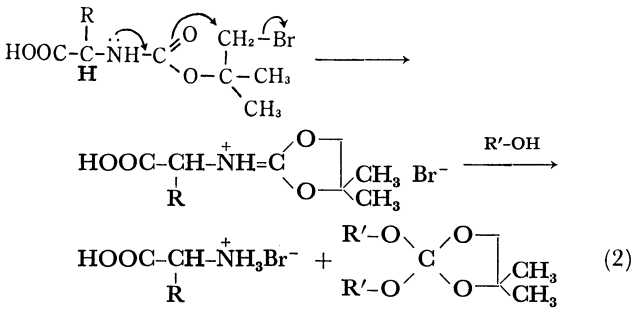
Table 3. Dipeptides containing α-halogeno-*t*-butyloxycarbonylamino acids

| Products | Method | Yield (%) | Mp °C | $[\alpha]_D^{20a)}$ | Analysis (Calcd) C % | H % | N % | Br or Cl % |
|---|---|---|---|---|---|---|---|---|
| BrBOC–Phe–Gly–OEt | DCCD | 29 | 93 | − 9.4° | 50.56 (50.35) | 6.02 (5.87) | 6.40 (6.52) | 18.46 (18.61) |
| BrBOC–Val–Gly–OMe | M.A. | 61 | 100 | −13.6° | 42.26 (42.53) | 6.29 (6.27) | 8.15 (7.63) | 21.56 (21.76) |
| ClBOC–Phe–Gly–OEt | DCCD | 63 | 79 | − 7.7° | 56.04 (56.17) | 6.63 (6.54) | 7.17 (7.27) | 9.52 ( 9.21) |
| ClBOC–Ala–Gly–OEt | DCCD | 59 | 65 | −17.4° | 46.87 (46.67) | 6.88 (6.85) | 9.40 (9.06) | 11.05 (11.45) |
| ClBOC–Val–Gly–OMe | M.A. | 65 | 89 | −13.0° | 48.16 (48.36) | 7.09 (7.18) | 8.96 (8.67) | 10.53 (10.99) |

a) *c* 1, AcOEt

Table 4. Tripeptides obtained from various dipeptides

| Starting compound | Deprotection technique | Yield (%) | Tripeptide Mp °C | Tripeptide $[\alpha]_D^{20}$ (*c* 1, MeOH) |
|---|---|---|---|---|
| BrBOC–Val–Gly–OMe | Reflux in MeOH | 65 | 145—147 | −34.0° |
| ClBOC–Val–Gly–OMe | 4 N HBr–AcOH | 59 | 144—146 | −34.2° |
| Z–Val–Gly–OMe | Hydrogenolysis | 66 | 146—148 | −33.9° |

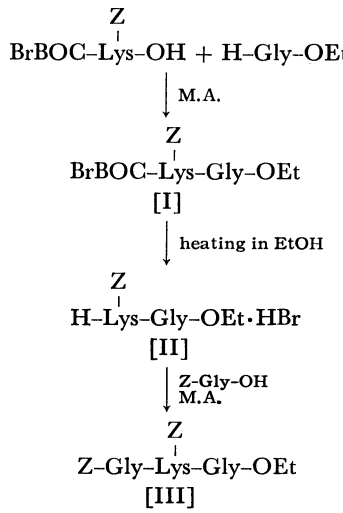



(2)

Val–Gly–OMe and ClBOC–Val–Gly–OMe.

The BrBOC group was removed on heating in methanol, and the ClBOC group was removed by the use of 4N hydrogen bromide in acetic acid. These tripeptides were identical with that obtained from Z–Val–Gly–OMe (Table 4).

The utility of the BrBOC group as an α-amino-protecting group of lysine is demonstrated as follows:




BrBOC–Lys(Z)–OH was coupled with H–Gly–OEt to yield BrBOC–Lys(Z)–Gly–OEt *via* the mixed anhydride in 69%. I was stirred under reflux in ethanol for an hour; dipeptide hydrobromide II was thus obtained in a pure state in a yield of 89%. II was condensed with Z–Gly–OH by the M.A. method to afford Z–Gly–Lys(Z)–Gly–OEt.

The characteristics of the tripeptide are identical with those previously reported.[9]

Thus, the BrBOC group is cleaved selectively by heating in ethanol, so it may be possible to use this group for the protection of amino acids in the synthesis of long, complicated peptides.

*Side Reaction.* In the reaction of the BrBOC–Cl with amino acids or amino acid esters, Carpino did not obtain the urethane derivatives, but the amine hydrobromides and the urea derivatives were isolated. The urea formation in the reaction of *t*-amyl chloroformate with amino acid esters in the presence of triethylamine in an anhydrous organic solvent has been described by Sakakibara and Itoh.[10] We have also found that the urea is largely formed by reacting BOC–Cl or benzyl chloroformate with amino acid esters under the same anhydrous conditions, and that the urea formation decreased when the reaction is carried out in an aqueous solvent. From this point of view, we tried to react the XBOC–Cl with amino acids and amino acid esters under aqueous conditions.

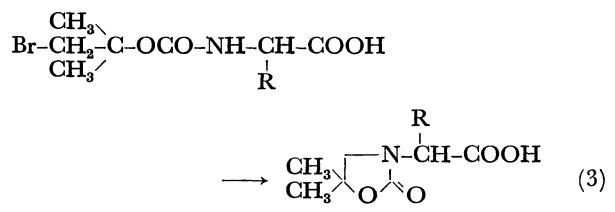
Although the desired XBOC-amino acids and esters were formed quantitatively under those conditions, it was found that the XBOC-amino acids or esters formed in the basic reaction solution were transformed into 2-oxazolidinones to a large extent if the solution was allowed to stand overnight. This phenomenon was also observed when pure BrBOC-amino acid dissolved in a 2N sodium hydroxide solution was stored for 24 hr

9) H. Zahn and H. R. Falkenburg, *Ann. Chem.*, **636**, 117 (1960).
10) S. Sakakibara and M. Itoh, This Bulletin, **40**, 646 (1967).

Table 5. 2-Oxazolidinones derived from α-bromo-*t*-butyloxycarbonylamino acids

| Amino acids | Yield (%) | Mp °C | $[\alpha]_D^{20}$ (*c* 1, AcOEt) | Calcd (%) | | | Found (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N |
| Phe | 42 | 103 | −26.5° | 63.86 | 6.50 | 5.31 | 63.52 | 6.48 | 5.31 |
| Met | 32 | 109 | − 2.0° | 48.57 | 6.92 | 5.66 | 48.83 | 6.88 | 5.59 |
| Leu | 44 | 102 | +10.5° | 57.61 | 8.35 | 6.60 | 57.76 | 8.41 | 6.16 |

(Eq. (3)).



(3)

R: amino acid side chain

ClBOC-amino acids were transformed into 2-oxazolidinones to a smaller extent under the same conditions. This structure is confirmed by IR, elementary analysis, and NMR. The results are shown in Table 5. The NMR spectrum of the 2-oxazolidinone derived from BrBOC-phenylalanine are shown in Fig. 2.

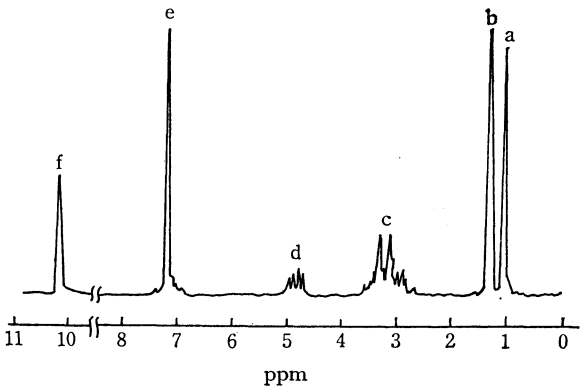



Fig. 2. NMR spectrum of (S)-5,5-dimethyl-3-(α-carboxyphenethyl)-2-oxazolidinone in $CDCl_3$.
a: $CH_3$, b: $CH_3$, c: $CH_2$, d: -CH-, e: ring-CH=, f: OH

## Experimental

*α-Bromo-t-butyl Alcohol.* To a slurry of *N*-bromosuccinimide (178 g) in water (400 m*l*), isobutene gas was bubbled under vigorous stirring at 15—20°C. After 30 min, all of the *N*-bromosuccinimide disappeared; stirring was then continued for an additional 30 min. The mixture was extracted several times with ether, the ether extract was dried over magnesium sulfate, and the solution was evaporated. The remaining oil was distilled to give the alcohol; yield, 105 g (70%); bp 55—56°C/25 mmHg. NMR $\delta$ ($CCl_4$): 1.28 (s, 6H, $CH_3$), 3.28 (s, 1H, OH), 3.42 (s, 2H, $CH_2$).

*α-Chloro-t-butyl Alcohol.* This was obtained from *N*-chlorosuccinimide (100 g), water (380 m*l*), and isobutene as described above except that isobutene was introduced at 60—65°C; yield, 45 g (59%); bp 51—52°C/55 mmHg.

*α-Bromo-t-butyl Chloroformate.* Into a solution of phosgene (65 g, 0.65 mol) and α-bromo-*t*-butyl alcohol (103 g, 0.65 mol) in ether (1000 m*l*), a solution of pyridine (51 g, 0.65 mol) in ether (500 m*l*) was added under stirring at −20——30°C. The mixture was stirred for 2 hr at −20°C and was then allowed to stand overnight at room temperature. The salt was filtered, and the ethereal solution was washed with ice-cold water and with a 3% sodium bicarbonate solution, and dried over magnesium sulfate. The solvent was distilled off, and the remaining oil was distilled to give the chloroformate; yield, 100 g (72%); bp 60—61°C/10 mmHg. IR: $cm^{-1}$ (liq. film) 1770 (C=O); NMR $\delta$ ($CDCl_3$): 1.62 (s, 6H, $CH_3$), 3.63 (s, 2H, $CH_2$).

*α-Chloro-t-butyl Chloroformate.* This was obtained from phosgene (32 g, 0.32 mol), α-chloro-*t*-butyl alcohol (35 g, 0.32 mol), pyridine (25 g, 0.32 mol), and ether (600 m*l*) as described above; yield, 37 g (68%); bp 50—51°C/10 mmHg.

*α-Bromo-t-butyloxycarbonylglycine Benzyl Ester (General Procedure for the Synthesis of BrBOC- and ClBOC-amino Acid Esters).* To a solution of H-Gly-OBzl·TsOH[11] (17 g, 50 mmol) and triethylamine (14 m*l*) in chloroform (200 m*l*) and water (50 m*l*), a solution of α-bromo-*t*-butyl chloroformate (11 g, 50 mmol) in chloroform (100 m*l*) was added at −1—0°C over a 30-min period. After the mixture had been stirred for 1 hr at the same temperature, it was washed successively with N hydrochloric acid, a 4% sodium bicarbonate solution, and water, and then dried over magnesium sulfate in a refrigerator. The solvent was distilled off, and the remaining oil was crystallized by the addition of ethyl acetate and petroleum ether. The crystal (3 g (17%)) was shown to be the urea derivative by IR; mp 105—106°C. From the filtrate, after the removal of the solvent, there was obtained the α-bromo-*t*-butyloxycarbonylglycine benzyl ester, yield of oil, 11 g (61%). IR: $cm^{-1}$ (liq. film) 1755, 1725 (C=O).

*α-Bromo-t-butyloxycarbonylglycine From the Benzyl Ester.*

*a) By Catalytic Hydrogenolysis*: A mixture of the α-bromo-*t*-butyloxycarbonylglycine benzyl ester (8 g) obtained above and a 5% palladium-carbon catalyst (500 mg) in methanol (50 m*l*) was hydrogenated for 2 hr at room temperature. After the removal of the catalyst and the solvent, the white crystals were filtered and recrystallized from ethyl acetate and petroleum ether; yield, 3.0 g (55%); mp 102—103°C.

Found: C, 33.32; H, 4.82; N, 5.45; Br, 30.53%. Calcd for $C_7H_{12}NO_4Br$: C, 33.09; H, 4.75; N, 5.49; Br, 31.44%.

*b) By Alkaline Hydrolysis*: A solution of the α-bromo-*t*-butyloxycarbonylglycine benzyl ester (3 g, 12 mmol) and N sodium hydroxide (12 m*l*) in tetrahydrofuran (50 m*l*) was stirred for 30 min at 0°C. The mixture was then acidified with N hydrochloric acid and was extracted several times with ethyl acetate. The ethyl acetate solution was washed with water and was dried over magnesium sulfate. It was treated as had been described above to give white crystals; yield, 1 g (33%); mp 102—103°C.

Found: C, 33.15; H, 4.95; N, 5.50; Br, 31.03%. Calcd for $C_7H_{12}NO_4Br$: C, 33.09; H, 4.75; N, 5.49; Br, 31.44%.

*α-Bromo-t-butyloxycarbonyl-L-proline (General Procedure for the Synthesis of BrBOC- and ClBOC-amino Acids).* A solution of α-bromo-*t*-butyl chloroformate (10.75 g, 50 mmol) in tetrahydrofuran (20 m*l*) was added slowly to a solution of L-proline (5.75 g, 50 mmol) in a mixture of tetrahydrofuran (30 m*l*)

11) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

and 2N sodium hydroxide (70 ml) at 0—2°C. The mixture was stirred vigorously during the addition of the chloroformate. The stirring was continued for a further hour at 0°C. At the end of this period, the reaction mixture was adjusted to pH 2—3 with N hydrochloric acid, and the product was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate in a refrigerator. After the solvent had been distilled off *in vacuo*, crystals were obtained; those crystals were then recrystallized from ethyl acetate and petroleum ether; yield, 11.5 g (78%). The physical constants of the material are shown in Table 1.

*BrBOC-Val-Gly-OMe (General Procedure for the Synthesis of α-BrBOC- and α-ClBOC-dipeptides).* To a solution of BrBOC-Val-OH (2.5 g, 10 mmol) and triethylamine (1.4 ml) in chloroform (50 ml), ethyl chloroformate (1.2 g, 11 mmol) was added drop by drop at −15——10°C. After 15 min a solution of H-Gly-OMe·HCl[12] (1.38 g, 11 mmol) and triethylamine (1.5 ml) in chloroform (50 ml) was added at −10——5°C. The mixture was stirred for a further hour at 0—10°C and then washed successively with N hydrochloric acid, a 4% sodium bicarbonate solution, and water. After drying over magnesium sulfate in a refrigerator, the solvent was distilled off *in vacuo* and the remaining oil was crystallized by the addition of petroleum ether. It was recrystallized from ethyl acetate and petroleum ether; yield, 2.1 g (65%). The physical constants of the material are shown in Table 3.

*Z-Gly-Val-Gly-OMe.* *a) From BrBOC-Val-Gly-OMe*: BrBOC-Val-Gly-OMe (3.6 g, 10 mmol) was refluxed in methanol for 1 hr. The solvent was distilled off, and the remaining H-Val-Gly-OMe·HBr was used without purification. To a solution of Z-Gly-OH[13] (2.1 g, 10 mmol) and triethylamine (1.5 ml) in chloroform (50 ml), ethyl chloroformate (1.1 g, 10 mmol) was added drop by drop at −15——10°C. After 15 min a solution of the H-Val-Gly-OMe·HBr obtained above and triethylamine (1.4 ml) in chloroform was added at −10——5°C. The mixture was stirred for 1 hr at 0—10°C and then washed successively with 3N hydrochloric acid, a 4% sodium bicarbonate solution, and water. After drying over magnesium sulfate, the solvent was distilled off and the remaining solid was recrystallized from ethyl acetate and petroleum ether; yield, 2.5 g (65%). The value of specific rotation and the melting point are shown in Table 4.

Found: C, 56.63; H, 6.48; N, 10.71%. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08%.

*b) From ClBOC-Val-Gly-OMe*: ClBOC-Val-Gly-OMe (1.6 g, 5 mmol) was dissolved in 4N hydrogen bromide in acetic acid (10 ml) at room temperature. After 1 hr, the solution was evaporated and the remaining oil was triturated with ether. The H-Val-Gly-OMe·HBr thus obtained was coupled with Z-Gly-OH (1.1 g, 5 mmol) as had been described above; yield, 1.1 g (59%). The data of this product are shown in Table 4.

*c) From Z-Val-Gly-OMe*: Z-Val-Gly-OMe[14] (1.6 g, 5 mmol) was hydrogenated over palladium black in methanol in the presence of 2.5 ml of a methanolic solution of 2N hydrogen chloride. The solution was filtered from the catalyst, and the filtrate was evaporated to dryness. The oily residue was coupled with Z-Gly-OH (1.1 g, 5 mmol) as had been described above, yield, 1.2 g (66%). Its properties agreed with those of the products obtained from ClBOC-Val-Gly-OMe or BrBOC-Val-Gly-OMe (see Table 4).

*BrBOC-Lys(Z)-Gly-OEt (I).* BrBOC-Lys(Z)-OH was obtained from BrBOC-Cl (11 g, 50 mmol) and H-Lys(Z)-OH[15] (14 g, 50 mmol) in a manner similar to that described for the preparation of BrBOC-Pro-OH. It was not crystallized and was used without purification; yield of oil, 20 g (87%). The oily BrBOC-Lys(Z)-OH (18.5 g, 40 mmol) thus obtained was coupled with H-Gly-OEt·HCl[12] (5.6 g, 40 mmol) by the mixed anhydride method described for the preparation of BrBOC-Val-Gly-OEt. The resultnig BrBOC-Lys(Z)-Gly-OEt was recrystallized from ethyl acetate and petroleum ether; yield, 16 g (80%); mp 91—93°C, $[\alpha]_D^{25}$ −10.5° (*c* 1, AcOEt).

Found: C, 50.78; H, 5.94; N, 7.75; Br, 14.44%. Calcd for $C_{23}H_{34}N_3O_7Br$: C, 50.83; H, 6.12; N, 7.73; Br, 14.70%.

*H-Lys(Z)-Gly-OEt·HBr (II).* I (5.4 g) was refluxed in EtOH (100 ml) for 1 hr. The solution was then evaporated, and the residue was recrystallized from ethanol and ether; yield, 4.0 g (89%); mp 137—140°C; $[\alpha]_D^{25}$ +13.0° (*c* 1, EtOH).

Found: C, 47.81; H, 6.41; N, 9.30; Br, 17.58%. Calcd for $C_{18}H_{28}N_3O_5Br$: C, 48.11; H, 6.29; N, 9.38; Br, 17.83%.

*Z-Gly-Lys(Z)-Gly-OEt (III).* To a solution of Z-Gly-OH (2.1 g, 10 mmol) and triethylamine (1.4 ml) in chloroform (50 ml), ethyl chloroformate (1.1 g, 10 mmol) was added at −12——10°C. After 15 min, a solution of (II) (4.5 g, 10 mmol) and triethylamine (1.4 ml) in chloroform (30 ml) was added, and the reaction mixture was stirred for 1 hr at 0—10°C. Then, it was washed with N hydrochloric acid, a 4% sodium bicarbonate solution, and water. After drying over magnesium sulfate, the solution was evaporated *in vacuo*, and the remaining oil was crystallized by the addition of petroleum ether. The crystal was recrystallized from ethyl acetate and petroleum ether; yield, 2.8 g (50.5%); mp 156—159°C; $[\alpha]_D^{25}$ −17.2° (*c* 1, AcOH). Lit,[9] mp 155—158°C, $[\alpha]_D^{25}$ −17.0° (*c* 1, AcOH).

Found: C, 60.12; H, 6.66; N, 9.99%. Calcd for $C_{28}H_{36}N_4O_8$: C, 60.36; H, 6.52; N, 10.07%.

*(S)-5,5-dimethyl-3-(α-carboxyphenethyl)-2-oxazolidinone (General Procedure for the Preparation of 2-Oxazolidinone Derivatives).*

*a) From L-Phenylalanine and BrBOC-Cl*: A solution of α-bromo-*t*-butyl chloroformate (11 g, 50 mmol) in tetrahydrofuran (20 ml) was added slowly to a solution of L-phenylalanine (8.2 g, 50 mmol) in a mixture of tetrahydrofuran (30 ml) and 2N sodium hydroxide (80 ml) at 0—2°C under stirring. The stirring was continued for a further 2 hr at 0°C, and then overnight at room temperature. The mixture was acidified with N hydrochloric acid and was extracted with ethyl acetate. The extract was dried over magnesium sulfate. After the solvent had been distilled off, crystals were obtained; they were recrystallized from ether and petroleum ether; yield, 4 g (42%). The data of this product are shown in Table 5.

*b) From BrBOC-L-Phenylalanine*: BrBOC-Phe-OH (3.44 g, 10 mmol) was dissolved in a mixture of N sodium hydroxide (12 ml) and MeOH (50 ml) at room temperature. After 24 hr, the solution was acidified with N hydrochloric acid and extracted with ethyl acetate. The extract was dried and evaporated to dryness. The residue was recrystallized from ether and petroleum ether; yield, 1.6 g (60%). Its properties agreed with those of the product described above.

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