Enantioselective Peptide Synthesis by Using the Optically Active Polymer Containing the 1-Benzyl-3-Hydroxy-5-Isobutyl-Hydantoin Structure

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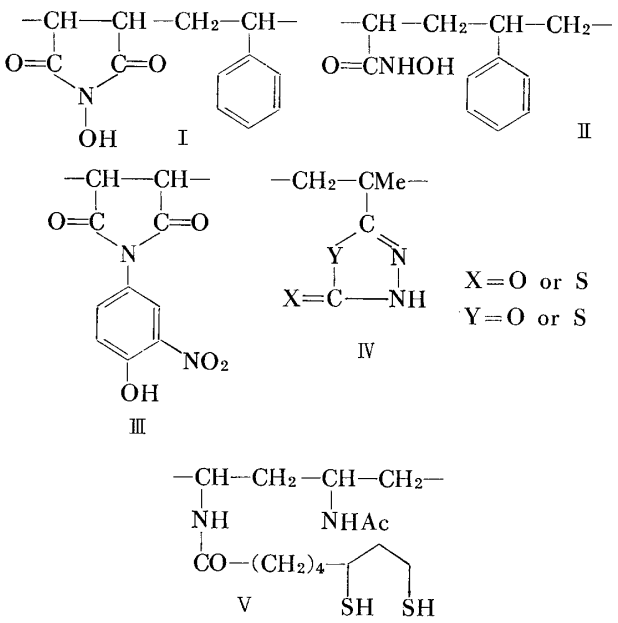
The polymer containing the 1-benzyl-3-hydroxyhydantoin structure was prepared from styrene and 1-chloromethylhydantotin in order to achieve not only the act as acyl activating polymeric ester but the selective reaction using the D, L-amino acid seter. For the enantioselective peptide senthesis, the 1-benzyl-3-hydroxyhydantoin as a model compound and the 1-benzyl-3-hydroxyhydantoin type polymer were allowed to act by two methods-the active ester method and the additive method using N, N'-dicyclohexylcarbodiimide (DCC). Optical yield was appreciated in 45%.

Introduction

In our previous report[1], we have disclosed that optically active 3-hydroxyhydantoins are not only the effective acyl activating reagents for peptide synthesis but also the reagents steering stereoselectivity: As the hydantoin esters prepared from N-blocked amino acids and the 3-hydroxyhydantoins have been treated with racemic amino acid esters, dipeptides with high enantiomeric purity have been allowed to produce during the selective interaction of L- or D-amino acid esters with the hydantoin containing asymmetric center.

On the other hand, it has previously shown in our laboratory that several insoluble polymers (polymeric supports) such as I[2~6], II[6], III[7], IV[8~11] and V[12] are useful in acyl activation because of simplicity in processing and advantage in repeated use.



So we present the synthesis of an optically active 1-benzyl-3-hydroxyhydantoin type polymer P-1 and asymmetric selective deptide synthesis with the aid of this polymer P-1.

Results and Discussion

Synthesis of 1-Benzyl-3-hydroxyhydantoin

Prior to the synthesis of the hydantoin type

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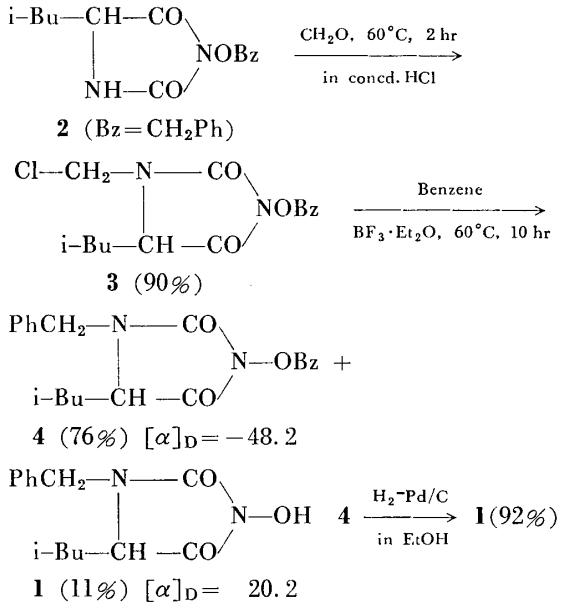
polymer, the introduction of benzyl group at 1-N position of hydantoin ring-1-benzyl-3-hydroxyhydantoin 1 as a model compound-was attempted by the following routes.

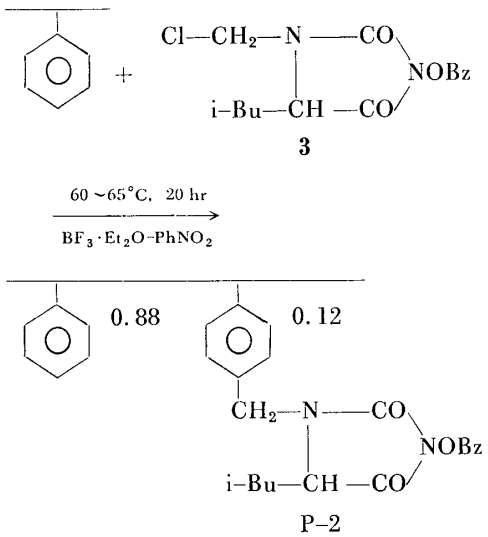


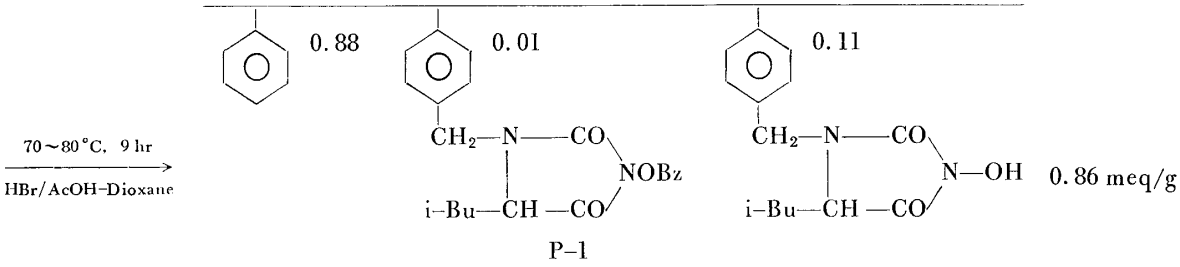
Hydantoin **2**[1] was treated with formalin (ca. 34%) in concd. HCl at 60°C for 2 hr to yield 90% of 1-chloromethylhydantoin **3**. The phenylation of **3** was carried out in benzene solution in the presence of $BF_3 \cdot Et_2O$ at 60°C for 10 hr to give 76% of 1-benzyl-3-benzyloxyhydantoin **4** and 11% of 1-benzyl-3-hydroxyhydantoin **1**. Subsequently, transformation of the compound **4** into the desired N-hydroxy derivative **1** proceeded easily by the usual debenzylation procedure. An adduct was formed between oily hydantoin **1** thus obtained and cyclohexylamine in order to purify by recrystallization (mp 104−5°C).

When **2** was treated with NaH in DMF at 0°C for 30 min followed by stirring the solution with benzyl chloride for 5 hr, benzylation of **2** at 1-N position was also achieved in 98% yield but the optical activity of benzyl derivative obtained was entirely lost.

Synthesis of the Polymer Containing 1-Benzyl-3-hydroxyhydantoin structure

On the basis of the synthesis of the model compound, the preparation of the target polymer P-1 was carried out; 1-chloromethylhydantoin 3 was treated with cross-linked polystyrene (50~60 mesh, 1.5% DVB) in nitrobenzene in the presence of $BF_3 \cdot Et_2O$ (at 60~65°C, for 20 hr), followed by debenzylation of the polymer P-2 by use of hydrogen bromide in the mixed solution of acetic acid and dioxane (at 70~80°C for 9 hr). The introduction of the hydantoin ring into the polystyrene was roughly estimated as about 12 mole-% from the weight gain of the polymer P-2. The content of N-OH moiety in the polymer P-1 was provided as about 11%, based on the amount of cyclohexylacetoamide which was obtained by the reaction of cyclohexylamine with the polymer P-1 acetylated by acetic anhydride. That is, the debenzylation of P-2 with HBr-AcOH was allowed to proceed in about 90 %. The polymer P-1 might also contain undebenzylated 1-benzyl-3-benzyloxyhydantoin group but this group never disturbs the peptide synthesis.



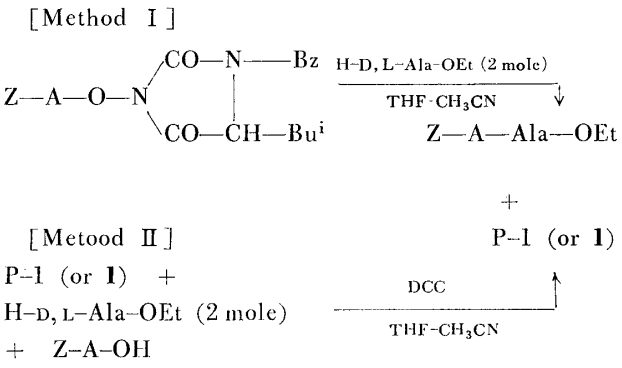


P-1

An alternative route for the synthesis of the polymer P-1 via the reaction of **2** with chloromethylated polystyrene was given up because of above mentioned reason.

Enantioselective Peptide Synthesis

Now, the polymer P-1 obtained and the model compound were employed for the asymmetric selective peptide synthesis, which was examined by means of two methods; one is the reaction via hydantoin ester **5** (method I) and the other is the use of the hydantoin **1** or the polymer P-1 as the additive of DCC method (method II). Esters **5** were prepared from **1** or P-1 and N-bloked amino acids at 0°C for 24 hr in THF in the presence of DCC. The both reactions of dipeptide synthesis were carried out at 0°C for 24 hr. The results are summarized in Table 1.



(A=Gly, L-Ala, Z=$PhCH_2OCO$, Bz=$PhCH_2$, $\vdash C_6H_4-CH_2$)

As for the selectivity of the model compound, the 3-hydroxyhydantoin **1** acted more effective as the additive than as the acyl activating reagent.

It is assumed that the selective reaction proceeds through the higher selective interaction of the D, L-amino component with 3-hydroxyhydantoin **1** than with the hydantoin ester 5. In the active ester method, the lower selectivity would appeared by disturbing of bulky benzyl group close-neighbored to the asymmetric center at 5-C position.

As for the yields and the selectivities of polymer reaction, the method using the polymeric additive was far more superior to the

Table 1. Enantioselective Peptide Synthesis.

Method	Z-Gly-Ala-OEt				Z-L-Ala-Ala-OEt			
	[Model]		[P-1]		[Model]		[P-1]	
	I	II	I	II	I	II	I	II
Y. (%)	75.3	67.6	43.9	91.0	84.6	67.2	41.3	98.2
$[\alpha]_D$[a]	− 7.4	−14.4	− 2.6	−12.2	−28.5	−29.8	−19.9	−21.6
O. Y. (%)[b]	27.3	56.9	9.7	45.2	41.2	46.5	4.5	12.0

a) Dipeptides without recrystallization were used to measure of $[\alpha]_D$ (c=1 in EtOH).

b) Optical yield (O. Y.) was calculated base on the specific rotation of dipeptides. $[\alpha]_D$: Z-Ala-Ala-OEt. L-L; −42.4, L-D; +4.8, Z-Gly-Ala-OEt L; −27.0, D; +27.0.

Table 2. IR spectra of polymers and Model Compounds

	OH	C=O (imide, ester)
1-Benzyl-3-benzyloxy-hydantoin **4**		1780, 1730, 1710
Polymer P-2		1775, 1715, 1705
1-Benzyl-3-hydroxy-hydantoin **1**	3200	1780, 1720, 1700
Polymer P-1	3200	1770, 1710, 1700
1-Benzyl-3-acetoxy-hydantoin		1780, 1760, 1740, 1810
Acetylated Polymer P-1		1770, 1740, 1720, 1810
1-Chloromethyl-3-benzyl-hydantoin **3**		1780, 1740, 1740

polymeric active ester method, and the characteristic of the polymeric reagent was sufficiently observed in simplifying procedures and separating product easier.

Experimental

Preparation of 1-Chloromethyl-3-benzyloxy-5-isobutylhydantoin **3**

Formalin (0.91 ml) [ca. 35%] and 3-benzyloxy-5-isobutylhydantoin (1 g) was suspended in concd. hydrochloric acid (5 ml) and then heated at 60°C for 2 hr. Oily compound was extracted by benzene (60 ml) and washed with water and burine followed by drying over calcium chloride. Removal of benzene gave oily product (1.1 g, 94%) and purification by liquid chromatography (eluted by methylene dichloride) gave pure oily 1-chloromethylhydantoin **3** (0.9 g, 75%).

Preparation of 1-Benzyl-3-benzyloxy-5-isobutylhydantoin **4**

The benzene solution of 1-chloromethylhydantoin **3** (1 g) was heated at 60°C for 10 hr in the presence of trifluoroborone etherate (0.92 ml) [47%] and then washed with water at three times followed by drying over calcium chloride. After evaporation of solvent, the mixture produced was chromatographed over silica-gel. First diphenyl methane (0.05 g, 8.9%) was eluted by methylene chloride. The second component was 1-benzyl-3-benzyloxyhydantoin **4** (0.87 g, 76.4%) and the third was 1-benzyl-3-phenylhydantoin (0.04 g, 3.6 %). Finally 1-benzyl-3-hydroxyhydantoin **1** (0.09 g, 11.1%) effused by chloroform.

Preparation of 1-Benzyl-3-hydroxy-5-isobutylhydantoin **1**

Ethyl alcohol solution of 3-benzyloxyhydantoin **4** (2 g) was treated with hydrogen gas in the presence of 5% paradium carbon (0.1 g) under atmospheric pressure until hydrogen gas was never spent. After evaporation, liquid chromatography eluted by chloroform gave 3-hydroxy derivative.

Direct Benzylation on 1-N Position

3-Benzyloxyhydantoin (1.1 g) dissolved in DMF was added sodium hydride (0.13 g), which was washed with hexane at several times at 0°C between 30 min with stirring and passing through nitrogen gas, and then benzyl chloride (0.58 ml) was treated dropwise to the solution at 0°C followed by additional stirring at 0°C for 5 hr. Solvent was distilled out in vacuo and the residue was dissolved in ethyl acetate. After washing with 2% hydrochloric acid and burine, the solution was dried over sodium sulfate. Removal of solvent yielded 1.52 g (97.7%) of 1-benzyl-3-benzyloxyhydantoin.

Peparation of the Polymer P-2

1-Chloromethylhydantoin **3** (5.59 g) was treated with crosslinked polystyrene at 60°C ~65°C for 20 hr (3.89 g) [50~60 mesh, 1.5% DVB] in nitrobenzene in the presence of $BF_3 \cdot Et_2O$ (5.87 ml). The polymer was filtered and washed with ether and hexane followed by swelling in THF, filtering and washing with hexane. 5.11 g of the polymer P-2 was obtained.

Preparation of the Polymer P-1

The suspension of the polymer P-2 (5.11 g) was heated at 70~80°C for 9 hr in the mixed solution of dioxane and acetic acid saturated by hydrogen bromide. The polymer was filtered and washed with acetic acid, benzene and hexane. Yield 5.04 g. Found N, 2.43.

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