DEPSIPEPTIDES

COMMUNICATION 31. SYNTHESIS OF DEPSIPEPTIDES CONTAINING
α-HYDROXY α-AMINO ACID RESIDUES*

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In [1, 2] we showed that N-acylated α-hydroxy α-amino acids with a free or alkylated hydroxy group react
under definite conditions with amino esters with formation of a peptide link. We obtained di- and tri-peptides
containing an α-hydroxy α-amino acid as the N-end amino acid.

We here report a study of the possibility of the direct aminoacylation of the hydroxy group in derivatives of
α-hydroxy α-amino acids of type (I) for the preparation of depsipeptides of type (III) containing an α-hydroxy
α-amino acid residue as the hydroxy-acid component. The starting compounds (Ia) and (Ib) were prepared by the

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\begin{align*}
&\text{COR} \\
&C_6H_5COHN-CH-\text{OH} \\
&\text{X-CR'} \\
&\text{(I)} \\
&\text{(II)}
\end{align*}
\]

(Ia) : R = OCH_3C_6H_5 \\
(Ib) : R = OCH_3COOC_2H_5 \\
(Ic) : R = NHCH_2COOC_2H_5

(IIa) : X = Cl; R' = CH(CH_3)N(CO)C_6H_4Boc \\
(IIb) : X = Cl; R' = CH(CH_3)N-Boc \\
(IIc) : X = Cl; R' = CH(CH_2)BocNCOCHN-Boc (L-L)

\[
\begin{align*}
&\text{COR} \\
&C_6H_5COHN-CH-O\text{COR'} \\
&\text{(III)} \\
&\text{(IIIa)} : R = OCH_3C_6H_5; \\
&\text{(IIIb)} : R = OCH_3C_6H_5; \\
&\text{(IIIc)} : R = OCH_3COOC_2H_5; \\
&\text{(IIId)} : R = NHCH_2COOC_2H_5; \\
&\text{(IIIf)} : R = OCH_2COOC_2H_5; \\
&\text{(IIIg)} : R = OCH_2C_6H_5; \\
&\text{(IIIh)} : R = OCH_2C_6H_5;
\end{align*}
\]

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previously described method [1, 3]. As regards the dipeptide (Ic), we succeeded in simplifying its synthesis considerably and raising its yield, using the carbodiimide method instead of the method of activated esters [1]. In this case the condensation of N-benzoyl-2-hydroxyglycine [4] with glycine ethyl ester, despite the presence of an extremely active (as will be seen later) α-hydroxy group, goes only at the carboxy group and leads to the formation of the dipeptide (Ic) in 75% yield.

On the basis of data obtained earlier in the study of methods of forming an ester link in depsipeptides [5], we used the acid chloride method in the synthesis of compounds of type (III). By the condensation of N-phthaloylalanyl chloride (IIa) [6] or 1-Boc-L-prolyl chloride (Boc = benzyloxycarbonyl) (IIb) [7] with N-benzoyl-2-hydroxyglycine benzyl ester (Ia) in tetrahydrofuran (THF) in presence of one molecular proportion of pyridine we obtained good yields of the O-(aminoacyl) derivatives (IIIa) and (IIIb). In the same way we synthesized the (ethoxycarbonyl)-methyl ester of N-benzoyl-O-(phthaloylalanyl)-[2-hydroxyglycine] (IIId). We also used the acid chloride method successfully for the preparation of tridepsipeptides with various alternations of hydroxy and amino acid components. By the acylation of the dipeptide (Ic), containing a free α-hydroxy group in the N-end amino acid, with Boc-L-prolyl chloride (IIb) we obtained the tridepsipeptide (IIId); for the preparation of the tridepsipeptides (IIId) and (IIIf) the benzyl (Ia) and (ethoxycarbonyl)methyl (Ib) esters of N-benzoyl-2-hydroxyglycine were acylated with the dipeptide acid chloride (IIc).

Study of the properties of the depsipeptides (IIIa)-(IIIf) showed that they are very labile—their ester link is readily hydrolyzed even in direct titration with 0.01 N NaOH, and the consumption of alkali is strictly one molecular proportion. As a result of the hydrolysis the starting compound (I) and the corresponding acylamino acid or acyl peptide (II) are formed. Thus, after the titration of N-benzoyl-O-(Boc-L-proline)-[2-hydroxyglycine] benzyl ester (IIb) in aqueous alcohol high yields of N-benzoyl-2-hydroxyglycine benzyl ester (Ia) and Boc-L-proline (IIe) were isolated from the solution. The great ease with which depsipeptides of type (III) are split under the conditions of nucleophilic catalysis must evidently be attributed to the electron-acceptor properties of substituents in the immediate vicinity of the ester link (cf. activated esters [8]). This gave us grounds for supposing that the secondary hydroxy group of compounds of type (I) has enhanced activity, analogous to that of the hydroxy group of p-nitrophenol [9]. Hence, unlike the secondary hydroxyl of 2-hydroxyisovaleric acid [5], it could, in our opinion, be esterified by N-substituted amino acids in presence of carbodiimides. It was in fact found that, as a result of the reaction of phthaloylalalalaline (IIId) [6] with N-benzoyl-2-hydroxyglycine benzyl ester (Ia) in presence of dicyclohexylcarbodi-imide, (IIId) was obtained in 65% yield. By the use of the carbodiimide method for the synthesis of compounds of type (III) we were able to use not only Boc-L-proline, but also other Boc-substituted amino acids which usually give low yields in condensation by the acid chloride method as a result of the formation of N-carboxy anhydrides. Thus, we obtained the Boc derivatives (IIIf) and (IIIf). On the other hand, the preparation of (IIId) and (IIIf) by this method was found to be inexpedient, because it was found extremely difficult to purify these amorphous labile substances from dicyclohexylurea.

**EXPERIMENTAL**

**N-Benzoyl-2-hydroxyglycyl-glycine Ethyl Ester (Ic).** A solution of 3.09 g of dicyclohexylcarbodiimide in 12 ml of THF was added to a solution of 2.92 g of N-benzoyl-2-hydroxyglycine and 1.55 g of glycine ethyl ester in 25 ml of THF, and the mixture was left for 15 h at 20°. The precipitate of dicyclohexylurea was filtered off, solvent was driven off in a vacuum at 20°, and the residue was dissolved in 20 ml of ethyl acetate and left at 5° for 12 h. The residue was filtered off, and we obtained 2.4 g of the ester (Ic). The filtrate was washed with 5% NaHCO₃ solution, water, 5% HCl, and again water, dried with MgSO₄ and vacuum-evaporated. The residue was rubbed out with dry ether, and a further 0.75 g of the ester (Ic) was filtered off. Total yield 75% m. p. 127-129° (from ethyl acetate): cf [1].

**N-Benzoyl-O-(phthaloylalanyl)-[2-hydroxyglycine] Benzyl Ester (IIId).** A solution of 0.48 g of phthaloylalanyl chloride (IIa) in 5 ml of THF was added with stirring and cooling to 0° to a solution of 0.56 g of N-benzoyl-2-hydroxyglycine benzyl ester (Ia) in 7 ml of THF, and then a solution of 0.18 g of pyridine in 10 ml of THF was added dropwise with maintenance of the temperature at 0°. The mixture was stirred further for one hour at 0° and then left for 15 h at 20°. The precipitate of pyridine hydrochloride was filtered off, the filtrate was vacuum-evaporated at 20°, the residue was dissolved in ethyl acetate, and the solution was washed with 5% HCl, water, 5% NaHCO₃ and again water and was dried with MgSO₄. Ethyl acetate was vacuum-evaporated, and the residue

*All the compounds described below, except where specially stated otherwise, are racemic.*