SYNTHESIS OF ORNITHINE-CONTAINING DEPSIPEPTIDES

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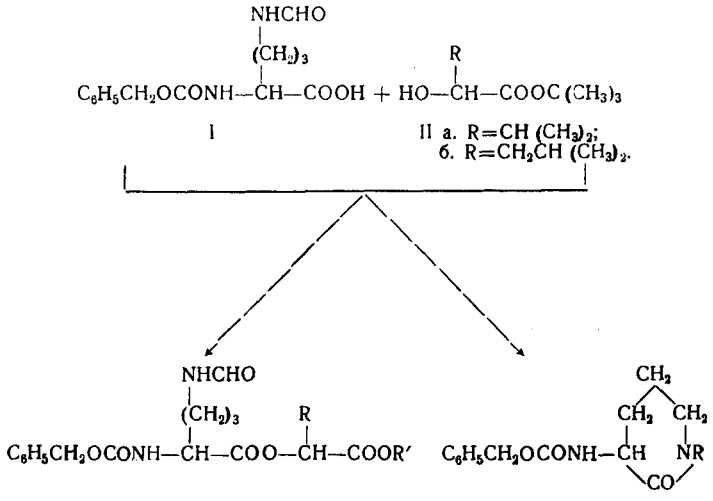
At the present time, methods for the synthesis of depsipeptides have been well studied, and carbonyldiimidazole and benzenesulfonyl chloride are being used most successfully to create an ester bond between an amino acid and a hydroxy acid [1]. However, during the synthesis of ornithine-containing depsipeptides that were required to prepare the depsipeptide analogs of gramicidin S, we came up against difficulties due to features of the chemical behavior of N^{α}, N^{ω}-diacyl derivatives of diamino acids.

It is known that N^{α}, N^{ω}-diacyl derivatives of α, γ-diaminobutyric acid, of ornithine, and of lysine, the carboxy groups of which are activated by the reagents usually used in peptide chemistry, readily cyclize into five- and seven-membered N-acyllactams [2-4]. The ease of ring closure to form a lactam depends both on the activating reagent and on the nature of the acyl groups. In particular, it has been established that a tosyl group in the N^{ω} position particularly favors the cyclization of N^{α}, N^{ω}-diacyl derivatives of diamino acids [3]. Intramolecular aminolysis is practically completely suppressed in the presence of a nucleophilic component (esters of amino acids, phenols, or N-hydroxysuccinimide), and the corresponding dipeptides or activated esters of N^{α}, N^{ω}-diacyl diamino acids are usually formed in high yield.

To obtain a compound of type (III), we studied the condensation of N^{α}-benzyloxycarbonyl-N^{δ}-formylornithine (I) with the hydroxy esters (IIa) and (IIb). A marked difference in the behavior of the diacylamino acid (I) according to the method used for forming the ester bond was observed. Thus, when carbonyldiimidazole was used, instead of the esters of protected aminoacyloxy acids (IIIa) and (IIIb), two neutral compounds were isolated which were identified after separation on a column of Al_2O_3, by means of their IR and mass spectra and elementary analysis, as the lactams (IVa) and (IVb).



III. a. R=CH(CH3)2, R'=C(CH3)3;
b. R=CH2CH(CH3)2; R'=C(CH3)3;
c. R=CH(CH3)2, R'=H;
d. R=CH2CH(CH3)2, R'=H.

IV a. R=CHO;
b. R=H.

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Lactam (IVa), unlike compounds of this type with a benzyloxycarbonyl or a tosyl group in position 1, proved to be unstable, and in aqueous organic solutions or on standing in the air it gradually hydrolyzed to the deformylated compound (IVb); this apparently explains the presence of the latter in the reaction products.

Under the action of one equivalent of hydrogen chloride in methanol, the lactam (IVa) was partially converted into the lactam (IVb), and when an excess of hydrogen chloride was added the benzyloxycarbonyl group was split off stimulataneously with the formyl group. In the latter case, in addition to 3-aminopiperidinone, small amounts of ornithine and of ornithine methyl ester were also detected.

The lactams (IVa) and (IVb) were also isolated when the di(acylamino) acid (I) was treated with dicyclohexylcarbodiimide. The reaction with benzenesulfonyl chloride took place completely differently. When this reagent was used for the condensation of N^{α}-benzyloxycarbonyl-N^{δ}-formylornithine with tert-butyl esters of hydroxy acids under standard conditions (0 to −5°C) [5], no formation of a lactam was observed, but the yield of the aminoacyloxy esters (IIIa) and (IIIb) did not exceed 5-8%. Lowering the temperature to −15 to −20°C and a strict observance of these temperature conditions enabled the yield of compounds (IIIa) and (IIIb) to be raised to 80%.

EXPERIMENTAL

N^{α}-Benzyloxycarbonyl-N^{δ}-formyl-L-ornithyl-L-α-hydroxyisovaleric Acid (IIIc). With stirring, to a solution of 0.48 g of N^{α}-benzyloxycarbonyl-N^{δ}-formyl-L-ornithine in 2 ml of pyridine cooled to −15 to −20°C were added 0.21 ml of benzenesulfonyl chloride and, after 15 min, a solution of 0.27 g of tert-butyl L-α-hydroxyisovalerate in 2 ml of pyridine cooled to −20°C; the mixture was stirred at 0°C for 2 h and was left overnight at 18-20°C. Then it was poured onto ice and was extracted with ethyl acetate. The ethyl acetate solution was washed with 1 N HCl at 0°C, with water, with 8% $NaHCO_3$, and with water again. Then it was dried and evaporated. This gave 0.57 g (81%) of compound (IIIa) in the form of a chromatographically homogeneous oil.

The depsipeptide ester (IIIa) (0.57 g) was dissolved in 3 ml of CF_3COOH, and after 30 min the solution was evaporated. The residue was crystallized from absolute ether, and 0.41 g (82%) of the acid (IIIc) was filtered off [mp 133-134°C (from ethanol), $[\alpha]_D^{20}$ −19.5° (c 1.5; ethanol)].

Found %: C 57.65; H 6.76; N 7.07. Mol. wt. 387 (titration with 0.01 N NaOH). $C_{19}H_{26}N_2O_7$. Calculated %: C 57.86; H 6.64; N 7.10. Mol. wt. 394.

N^{α}-Benzyloxycarbonyl-N^{δ}-formyl-L-ornithyl-L-α-hydroxyisocaproic Acid (IIId). Under the conditions of the preceding experiment, compound (IIIb) was obtained with a yield of 79%, and it was converted into the acid (IIId) with a yield of 87% [mp 127-128°C (from ethanol), $[\alpha]_D^{20}$ −25.8° (c 1.5; ethanol)].

Found %: C 58.85; H 6.83; N 6.88. Mol. wt. 406 (titration with 0.01 N NaOH). $C_{20}H_{28}N_2O_7$. Calculated %: C 58.81; H 6.91; N 6.83. Mol. wt. 408.

3-Benzyloxycarbonylamino-1-formylpiperidin-2-one (IVa) and 3-Benzyloxycarbonylaminopiperidin-2-one (IVb). A solution of 0.8 g of N^{α}-benzyloxycarbonyl-N^{δ}-formyl-L-ornithine in 10 ml of dry tetrahydrofuran (freshly distilled over $LiAlH_4$) was treated with 1.2 g of carbonyldiimidazole, the mixture was kept for 15 min, and 0.47 g of the ester (IIa) in 5 ml of tetrahydrofuran was added. The solution was left at 20°C for 20 h or was heated at 60°C for 1 h and was evaporated. The residue was dissolved in 30 ml of ethyl acetate; this solution was washed with 1 N HCl, with water, with 8% $NaHCO_3$, and with water again, and was dried and evaporated. The oily residue was crystallized from methanol. This gave 0.2 g (27%) of compound (IVa) with mp 97-98°C, $[\alpha]_D^{20}$ −0.8° (c 1; dimethylformamide).

Found %: C 60.86; H 5.94; N 10.34. Mol. wt. 276 (mass-spectrometrically). $C_{14}H_{16}N_2O_4$. Calculated %: C 60.84; H 5.84; N 10.14. Mol. wt. 276.

IR spectrum, ν_{max}, cm^{-1}: 1680 (urethane), 1720 (lactam carbonyl), 3320 (stretching vibrations of a NH group).

After the separation of compound (IVa), the methanolic solution was evaporated, and the residue was triturated with petroleum ether, after which 0.32 g of an amorphous powder was filtered off and chromatography was performed on a column of Al_2O_3 (activity grade II) in the hexane−ethyl acetate system (gradient elution). This gave 0.1 g (13%) of compound (IVa) (total yield 40%) and 0.15 g (22%) of (IVb) with mp 174-176°C (from ethyl acetate), see [6]. Mol. wt. 248 (mass-spectrometrically).

SUMMARY

The reaction of N^{α}-benzyloxycarbonyl-N^{δ}-formyl-L-ornithine with α-hydroxy esters has been studied and conditions have been found under which aminoacylation takes place in high yield.

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