

## REFERENCES

1. Kh. S. Mukhammedova, S. T. Akramov, and S. Yu. Yunusov, KhPS [Chemistry of Natural Compounds], 117, 1962.
2. N. S. Vul'fson, V. I. Zaretskii, and V. G. Zaikin, DAN SSSR, 155, 1104, 1964.

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## SOLID-PHASE SYNTHESIS OF A TETRADEPSIPEPTIDE CONTAINING THREE HYDROXY ACIDS

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Continuing our investigations on the solid-phase synthesis of depsipeptides, we have carried out a model synthesis of a tetradepsipeptide (I) containing three hydroxy acids and one amino acid:



C-Terminal unprotected L-phenyllactic acid was added to 8 g of chloromethylated polymer containing 7% of chlorine in absolute alcohol in the presence of triethylamine under the conditions usually used for the solid-phase synthesis of peptides [1]. The amount of L-phenyllactic acid adding (1.16 g) was determined from the amount of triethylamine hydrochloride liberated. The subsequent addition of the O-tert-butyl ether of L-hydroxyisovaleric acid was carried out by the acylation of the hydroxy group of the L-phenyllactic acid in absolute pyridine at  $-10^{\circ}\text{C}$  with a 50% excess of the mixed anhydride obtained by the interaction of the O-tert-butyl ether of L-hydroxyisovaleric acid with benzene-sulfonyl chloride in absolute pyridine [2]. After being allowed to stand for 30 min at  $-10^{\circ}\text{C}$  and for 24 hr at  $20^{\circ}\text{C}$ , the solution was filtered and the reaction resin was washed successively with dioxane, ethanol, ether, and petroleum ether, the washing with each solvent being carried out three times.

The subsequent splitting off of the O-tert-butyl group was effected by treating the polymer with 98%  $\text{CF}_3\text{COOH}$  at  $20^{\circ}\text{C}$  for 1 hr. The addition of the dicyclohexylammonium salt of the O-tert-butyl ether of glycolic acid [3] and of BOC-L-valine [4] was carried out under analogous conditions, but in the case of the O-tert-butyl ether of glycolic acid, the condensation was carried out in methylene chloride.

To complete the growth of the depsipeptide chain, the polymer was washed as described above and was carefully dried in vacuum. Then it was treated with 100%  $\text{CF}_3\text{COOH}$  and with a current of dry HBr for 15 min. After the  $\text{CF}_3\text{COOH}$  had been distilled off in vacuum, the hydrobromide of the tetradepsipeptide (I) that had been formed was extracted by carefully washing the polymer with methanol. The methanolic solution was evaporated to dryness in vacuum. The yield of the depsipeptide hydrobromide  $\text{C}_{21}\text{H}_{30}\text{NO}_8\text{Br}$  (I) was 2.8 g (39%), mp  $62^{\circ}\text{C}$  (from absolute isopropanol),  $[\alpha]_D^{20} -26 \pm 2^{\circ}\text{C}$  (c 2.0; methanol).

The substance gave one spot on chromatography in a thin layer of hydrated silica containing 13% of gypsum in the 1-butanol-acetic acid-water (4:1:1) system,  $R_f$  0.71; and in the 1-butanol-pyridine-acetic acid-water (15:10:3:6) system,  $R_f$  0.79. The spot was revealed with ninhydrin and Bromothymol Blue.

## REFERENCES

1. G. R. Marshall and R. B. Merrifield, Biochemistry, 4, 2394, 1965.
2. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, V. A. Oladkina, and A. A. Shchukina, DAN SSSR, 140, 387, 1961.
3. Cz. Wasielewski, Roczn. Chem., 40, 135, 1966.
4. G. W. Anderson and A. S. McGregor, J. Am. Chem. Soc., 79, 6180, 1957.

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Compounds, AS USSR