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TOTAL SYNTHESIS OF ANGOLIDE

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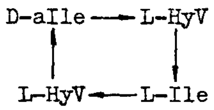
RECENTLY Russell et al. (1) isolated from the metabolic products of a Pithomyces fungus species a new cyclodepsipeptide to which he gave the name angolide. The acid hydrolysis of this compound yields L-α-hydroxyisovaleric acid and an equimolar mixture of L-isoleucine and D-allo-isoleucine (1). Its hydrazinolysis leads to a mixture of 2 hydrazides of which, apart from hydroxyisovaleric acid, one contains isoleucine and the other allo-isoleucine, thus showing that the angolide molecule consists of regularly alternating hydroxy and amino acid residues (2). However, the size of the angolide ring was still to be elucidated. Since in the case of cyclic depsipeptides the ordinary methods of molecular weight determination often give very low values (3,4), Russell asked us to determine the molecular weight of angolide thermoelectrically. The results obtained by M.Yu.Feigina (M.W. = 413, 422 in CF_3COOH) showed that angolide is a cyclotetradepsipeptide and that consequently its structure is that of Formula I. These data were further confirmed in our institute mass spectrometrically by N.S.Wulfson, V.A. Puchkov and V.N.Bochkarev (M.W. = 426), which moreover, on the basis of the depsipeptide fragmentation rules we had formulated earlier (5), substantiated Russell's conclusion that the hydroxy and amino acid residues of this metabolite alternate regularly. Indeed, the fragmentation of angolide takes place according to the CO_2 type, characteristic of cyclotetradepsipeptides of regular structure, in which CO_2 is first evolved and then the amino and hydroxy acid residues are eliminated*.



(I)

In the present paper we report on the total synthesis of angolide which we have carried out to verify Russell's formulation of the angolide structure, according to a scheme similar to that used by us earlier for the synthesis of cyclotetradepsipeptides (3) (Scheme 1). Condensation of benzyloxycarbonyl-D-allo-isoleucine (II) and of benzyloxycarbonyl-L-isoleucine (IV) with tert.-butyl L-α-hydroxyisovalerate (III) by the mixed anhydride method ($PhSO_2Cl$ in pyridine) gave compounds (V) and (VI), respectively. The former was converted to the acid (VII)

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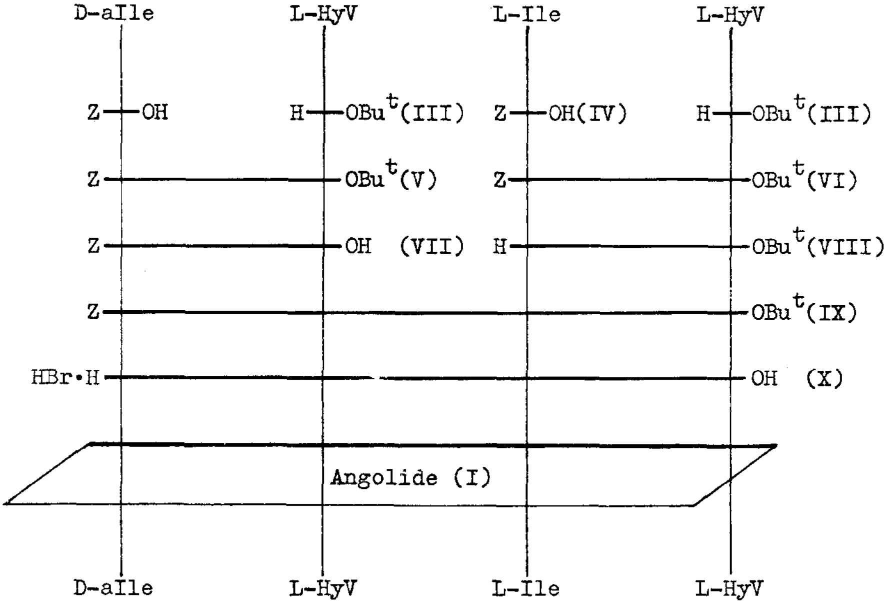
*In a private communication Russell informed us that J.S.Shannon had independently carried out a mass spectrometric study of angolide.

Scheme 1



with the aid of CF_3COOH and the latter was hydrogenolyzed over Pd black to yield the amino ester (VIII). The fragments (VII) and (VIII) were then condensed by the acid chloride method (1. PCl_5 in ether; 2. Et_3N in THF, -20°) to form the protected tetradepsipeptide (IX). Both protective groups were simultaneously removed by HBr in AcOH and the resultant linear tetradepsipeptide hydrobromide (X) was cyclized by the acid chloride method (1. $SOCl_2$; 2. Et_3N in benzene) affording the cyclotetradepsipeptide (I) in 28% yield (after recrystallization from alcohol); m.p. 260°, $[\alpha]_D^{22}$ -83°($CHCl_3$). The product showed identical properties (m.p., mixed m.p., specific rotation, chromatographic behavior, IR spectrum) with those of the naturally occurring angolide. Compounds (V), (VI) and (IX) were purified chromatographically on alumina (gradient elution with benzene-ethyl acetate solvent); compound (VIII), by vacuum distillation. The analyses of the intermediates (V) - (X) are in good agreement with the calculated values.

The synthesis of angolide thus proves its structure. It is noteworthy that angolide is the first naturally occurring cyclotetradepsipeptide built up of α-hydroxy and α-amino acid residues

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