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THE STRUCTURE AND TOTAL SYNTHESIS OF VALINOMYCIN

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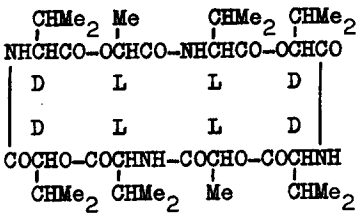
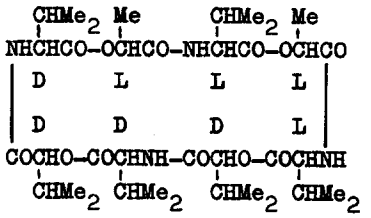
IT was recently shown (1,2) that formulas (I) and (II) proposed by Brockmann (3) for valinomycin do not reflect the structure of this antibiotic.



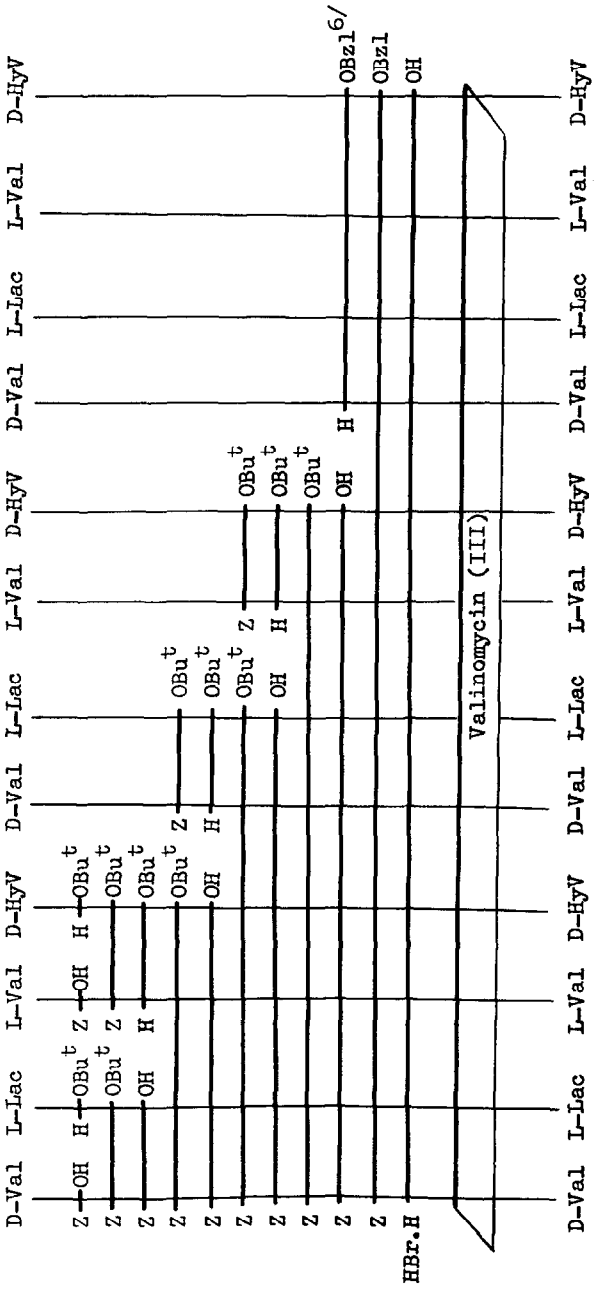
(I)

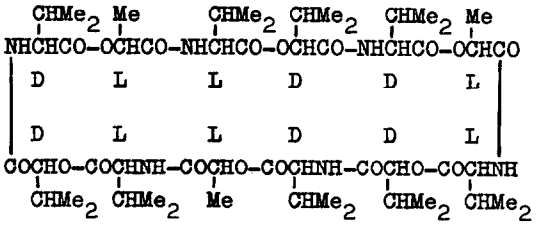


(II)

Soon after, Brockmann et al. (4) determining the molecular weight of valinomycin by a sedimentation method found it to be 1149±50; we in turn obtained a value of 1070±30 by the thermoelectric method on a specimen kindly given to us by Dr. Taber. It thus appeared that valinomycin is a cyclododecadepsipeptide (M.W. 1111.3) to which could be ascribed at least 4 different formulas. Of these one, namely Formula (III) appeared to us to be the most likely on the basis of Brockmann's data on the hydrolysis of valinomycin (3).

Scheme 1
Synthesis of Valinomycin





(III)

On the basis of earlier developed methods for the synthesis of depsipeptides (1,5,6) we prepared the compound corresponding to Formula (III) according to Scheme 1.

In this synthesis the ester bond was formed by the mixed anhydride (benzenesulfochloride) or acid chloride ($SOCl_2$ + 1 mole pyridine) methods. The amide bond was in all cases formed by the acid chloride method ($SOCl_2$, Et_3N or pyridine). The tert.-butyl protective group was removed by means of trifluoroacetic acid and the benzyl or carbobenzoxy groups, by hydrogenolysis in the presence of palladium on carbon or palladium black. All the protected linear depsipeptides were purified by chromatography on alumina (activity II) in the system benzene - ethyl acetate, gradually raising the ethyl acetate concentration from 1 to 15%. The individuality of the compounds was verified by thin layer chromatography on alumina in the systems benzene - ethyl acetate (8:2), benzene - ethyl acetate - ethanol (9:1:0,2) and chloroform - ethyl acetate (8:2).

Cyclization of the resultant linear dodecadepsipeptide was achieved by the acid chloride method ($SOCl_2$, Et_3N in

benzene at 20°). The mixture obtained was separated on alumina. Elution with benzene - ethyl acetate (4:1) afforded the crystalline cyclododecadepsipeptide (III), isolated in 10% yield. This substance had a m.p. 187° (from diisobutyl ether), $[\alpha]_D^{20}$ +32,8° (c 1,25 in benzene), M.W. 1085±30 (thermoelectric method in ethyl acetate); it showed no mixed melting point depression with a sample of the natural antibiotic. The synthetic and natural specimens exhibited identical i.r. spectra and the same biological activities against Candida albicans (0,75 γ/ml) and M. phlei (4 γ/ml).

The identity of the synthetic cyclododecadepsipeptide with valinomycin unambiguously shows that the latter has the structure (III).

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