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THE SYNTHESIS, BY TWINNING, OF A CYCLODEPSIPEPTIDE RELATED TO SERRATAMOLIDE

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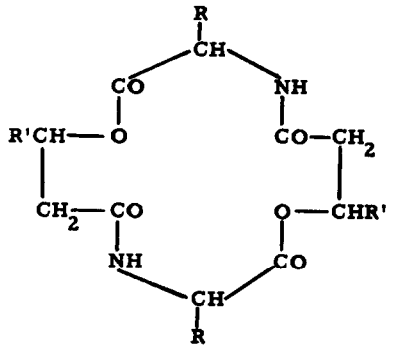
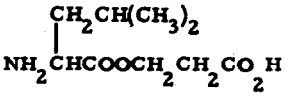
The molecular structure of the antibiotic serratamolide has been established[1] as (I) by degradation. Moreover, the synthesis of this cyclodepsipeptide and a number of related compounds has been achieved by Shemyakin and co-workers.[2] They utilised a procedure involving formation of the appropriate bis-β-hydroxyacyl-2,5-diketopiperazine followed by hydroxyl-amide interaction and rearrangement into the cyclodepsipeptide. Protecting groups were removed at intermediate stages to ensure that the reaction took the appropriate course.

We have found that the synthesis of a typical member (II) of this





(III)

(I): R = CH_2OH, R' = $(CH_2)_6CH_3$

(II): R = $CH_2CH(CH_3)_2$, R' = H

series may be achieved more conveniently and in good yield by treatment of the linear ester O-L-leucyl-β-hydroxypropionic acid (III) with thionyl chloride in benzene under conditions of high dilution. The product, m.p. 220-224°, had M.W. 370, determined by mass spectrometry; analytical data confirmed the molecular formula $C_{18}H_{30}N_2O_6$. The infrared spectrum showed both amide-I (6.0μ) and amide-II (6.45μ) bands in addition to a strong ester peak (5.7μ). The mass spectrum showed that fragmentation was largely in accord with the "CO_2" pattern observed in the case of related compounds.[3] The major peaks are given in Table I together with their intensities relative to the peak at m/e 86.

TABLE I

m/e	86	55	158	44	30	27	140	43	41
Relative intensity	100	91	33	30	26	24	24	21	18

There are a number of cases in which linear peptides have undergone twinning reactions to give the corresponding cyclic compounds.[4,5] It has been suggested[5] that in these reactions, an association of two molecules involving intermolecular hydrogen bonding between carbonyl and imide groups precedes the cyclisation process. Such an effect cannot apply in the case that we have described but it is possible to represent an intermediate in which intermolecular hydrogen bonding occurs between amine and carbonyl functions. With the aid of models it may be shown that two trans planar amide groups can be readily included in the fourteen-membered ring of the cyclodepsipeptide (II) and that the conformation of the ring favours the formation of a transannular hydrogen bond between the two trans amide functions. No intramolecular cyclisation of the linear ester (III), with formation of a seven-membered ring was observed. This was attributed to the fact that such a structure could not include a trans planar amide function.

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