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THE STRUCTURE AND TOTAL SYNTHESIS OF SPORIDESMOLIDE II

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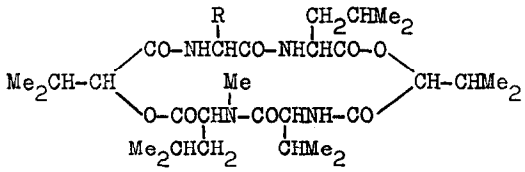
IN 1960 D.W.Russell et al. (1) found that a strain of Sporidesmium bakeri, besides sporidesmolide I, produces another substance, which was given the name sporidesmolide II. The cyclohexadepsipeptide structure (I) postulated by Russell (1,2) for sporidesmolide I we later confirmed by total synthesis of this compound (3-5). As for sporidesmolide II, which until recently could be isolated only contaminated with sporidesmolide I, it was known to have properties similar to those of the latter (2). By studying the hydrolyzates of various sporidesmolide fractions with the aid of paper chromatography, Russell concluded that sporidesmolide II has the structure of the cyclohexadepsipeptide (II), differing from sporidesmolide I in containing a D-isoleucine instead of D-valine residue (1,2). However it was not known whether this residue was D-allo-isoleucine or D-isoleucine, because

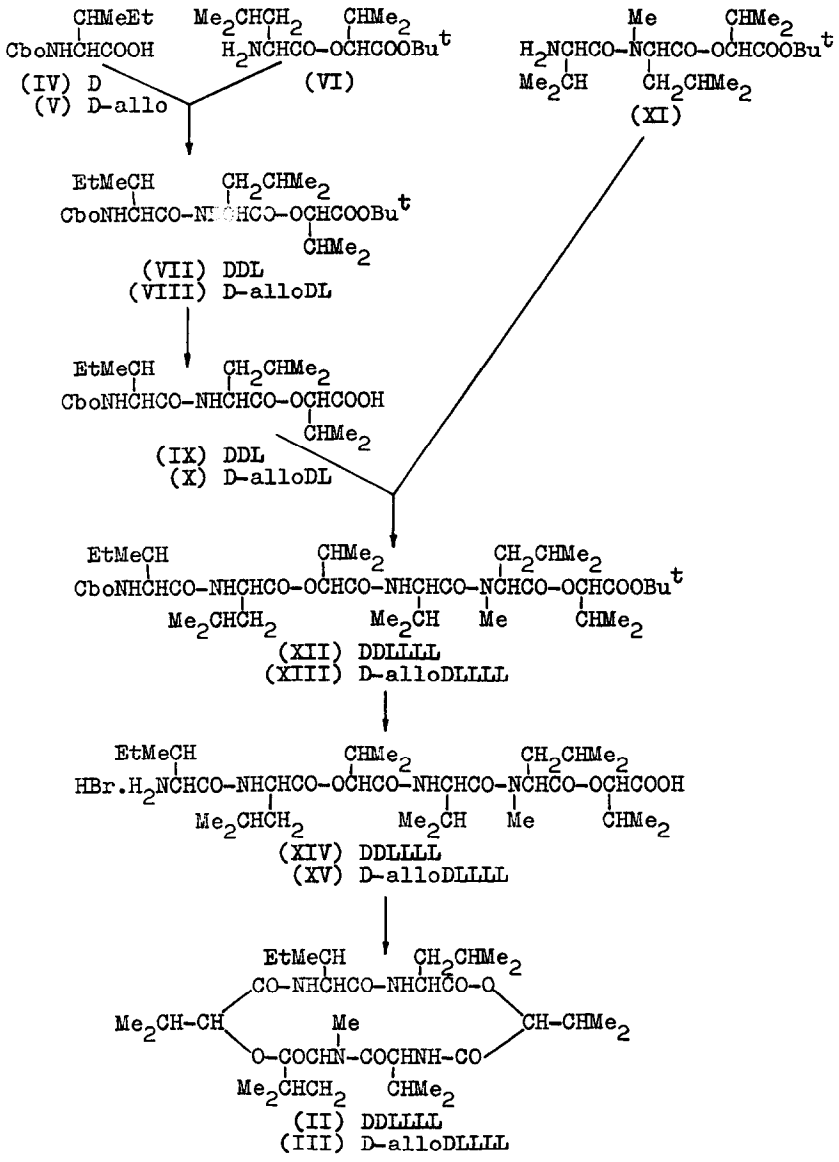
these two amino acids are not separated by paper chromatography under the conditions employed by Russell. Sporidesmolide II might therefore possess the structure (III) containing a D-allo-isoleucine residue.



(I) DDLLLL; R=$CHMe_2$
(II) DDLLLL; R=CHMeEt
(III) D-alloDLLLL; R=CHMeEt

With the objective of elucidating the structure of sporidesmolide II, we synthesized the cyclodepsipeptides (II) and (III) by a route analogous to that of the earlier described synthesis of sporidesmolide I (5) (see Scheme 1). Condensation of carbobenzoxy-D-isoleucine (IV) or carbobenzoxy-D-allo-isoleucine (V) with tert.-butyl D-leucyl-L-α-hydroxyisovalerate (VI) (5) by the mixed anhydride method (ClCOOEt in tetrahydrofuran) afforded the protected tridepsipeptides (VII) and (VIII), which were transformed into the respective acids (IX) and (X) by trifluoroacetic acid. Condensation of (IX) and (X) with tert.-butyl L-valyl-N-methyl-L-leucyl-L-α-hydroxyisovalerate (XI) (5) by the acid chloride method (PCl_5, Et_3N in tetrahydrofuran) yielded the corresponding hexadepsipeptides (XII) and (XIII) which were converted to the hydrobromides (XIV) and (XV) by hydrogen bromide in glacial acetic acid. The cyclodepsipeptides (II) and (III) were then obtained from the hydro-

Scheme 1


(IV) D
(V) D-allo
(VI)
(XI)
(VII) DDL
(VIII) D-alloDL
(IX) DDL
(X) D-alloDL
(XII) DDLLLL
(XIII) D-alloDLLLL
(XIV) DDLLLL
(XV) D-alloDLLLL
(II) DDLLLL
(III) D-alloDLLLL

bromides by ring closure, using the acid chloride method ($SOCl_2$, Et_3N in benzene). The constants and analytic data of the compounds are presented in Table 1.

Table 1

Comp.	M.p	$[\alpha]_D^{20}$	Analysis							
			Found %				Calculated %			
			C	H	N	Br	C	H	N	Br
II	236-238°	-201° (c 0.7, $CHCl_3$)	62.8	9.4	8.5		62.6	9.3	8.6	
III	228-230°	-195° (c 0.6, $CHCl_3$)	62.7	9.3	8.5		62.6	9.3	8.6	
VII	92-93°	+24° (c 1.0, C_6H_6)	65.2	8.7	5.4		65.1	8.7	5.2	
VIII	66-67°	+22° (c 0.8, C_6H_6)	65.3	8.5	5.3		65.1	8.7	5.2	
IX	amorph.	+46° (c 0.9, C_6H_6)	62.5	7.8	5.8		62.7	8.0	5.9	
X	amorph.	+45° (c 1.0, C_6H_6)	62.6	7.8	5.9		62.7	8.0	5.9	
XII	89-92°	-17° (c 1.5, C_6H_6)	64.1	9.0	6.5		64.2	8.9	6.5	
XIII	78-81°	-21° (c 0.7, C_6H_6)	63.9	8.9	6.6		64.2	8.9	6.5	
XIV	amorph.	-49° (c 1.0, EtOH)				10.8				10.6
XV	amorph.	-48° (c 1.0, EtOH)				10.7				10.6

Our compounds did not differ chromatographically (thin layer chromatography on Al_2O_3) and in their IR spectra from the sample of the natural sporidesmolide II kindly sent to us from New Zealand by Dr. A.Taylor. Both synthetic compounds and

the natural product exhibited very close specific rotations and melting points and showed no mixed melting point depression. It was thus impossible on this basis to give preference to any one of the structures (II) and (III) for sporidesmolide II.

Having received from us samples of the synthetic preparations Dr. Taylor in a private communication indicated that he intended to attack this problem by X-ray and mass spectrometric methods. We in turn having at our disposal Dr. Taylor's natural product compared its complete acid hydrolysis together with that of the synthetic compounds (II) and (III) (heating with conc. HCl-AcOH (1:1) mixture at 120° for 24 hrs.). On the one hand the resultant hydrolyzates were subjected to analysis on a modified Moore and Stein type of automatic amino acid analyzer (6), and on the other hand the mixture of isolated amino acids was converted to their N-acetylated butyl esters (n-BuOH + HCl then Ac_2O), followed by gas liquid chromatography (150°, diatomaceous brick (120-150 mesh) impregnated with 3% of carrier weight of polyethyleneglycol (Carbowax 1540)). The results of the analyses, in complete agreement with each other, showed that it was D-allo-isoleucine which was the constituent of sporidesmolide II so that the latter has the structure of the cyclodepsipeptide (III).

It should be pointed out that slight epimerization of isoleucine occured during hydrolysis of compounds (II) and (III). The somewhat too high content of valine found by us for the natural specimen of sporidesmolide II is apparently due to the presence of a certain amount of sporidesmolide I in the sample.

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