hyperbaric oxygen (MANAX et al.[4]) or perfusion techniques (HUMPHRIES et al.[5]; HITCHCOCK et al.[6]; DUNEA et al.[7]). The low temperature appears to be the important factor[8].

Zusammenfassung. Es gelingt die normale Nierenfunktion des 20 h bei 4°C tiefgekühlten Organs durch Perfusion mit Novocain und Reomacrodex von 40°C wieder herzustellen.

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STUDIORUM PROGRESSUS

The Structure-Antimicrobial Relation for Valinomycin Depsipeptides

We have recently shown by total synthesis that valinomycin[1], discovered in 1955 by BROCKMANN[2], is a cyclododecadepsipeptide (I) comprising 3 fragments of which each contains a D-valine, L-lactic acid (L.Lac), L-valine and D-α-hydroxyisovaleric acid (D.HyV) residue. Having available a general method for the synthesis of such cyclic depsipeptides[1,3–5] we were able to undertake the preparation of various valinomycin analogues in order to expand our investigations into the structure-activity relation of cyclodepsipeptides and also, in cooperation with B. C. PRESSMAN (USA), to attempt to shed some light on the mode of their action.

We synthesized a number of linear and cyclic analogues of valinomycin differing in the chain length or ring size and in the nature, configuration and position of the amino and hydroxy acid residues (II–XXXV in Table I). The antimicrobial activity of the compounds was investigated by the serial dilution technique on Gram-positive and Gram-negative bacteria and on yeasts (glucose-peptone medium), on acid fast bacteria (Soton's medium) and on phytopathogenic fungi (Chapek-Dox medium). All the compounds investigated were dissolved in DMF or Me_2CO, and successively diluted with water until a 2% aqueous DMF (Me_2CO) solution was reached. The results of tests of the valinomycin analogues are given in Tables II and III[6]. Moreover Table III presents for comparative purposes data on the synthetic enniatins A and B (XXXVI and XXXVIII), their analogues (XXXIX to XLI), sporidesmolide I (XLII) and serratamolide (XLIII), all of which had previously not been tested with respect to the aforementioned fungi.

Contrary to valinomycin (I), its linear tetra-, octa-, dodeca- and hexadecadepsipeptide analogues (II–V) are completely inactive. Regarding the activity of the cyclic analogues, this depends upon a number of factors which will be discussed in the following: (1) Similar to the enniatin cyclodepsipeptides[6], the size of the ring is here also of essential importance. All the cyclotetra- and cyclooctadepsipeptides (VI–XV) we investigated were found to be completely inactive, whereas many cyclododecadepsipeptides (XVI–XXIII) displayed considerable activity, which disappears again on passing over to the cyclohexadecadepsipeptide (XXXV). A marked difference between the valinomycin and the enniatin series is that optimum activity in the former is observed with the 36-membered ring, whereas in the latter it occurs with the 18-membered ring. (2) The structure of the radicals and the configurations of the amino acid residues in the valinomycin molecule can undergo considerable changes (true, on a limited section of the chain) without considerable loss in activity. Thus if a D-valine residue in valinomycin is substituted by a D-alanine (XXI), D-leucine (XX) or D-allo-isoleucine (XIX) residue or an L-valine residue is substituted by an L-allo-isoleucine (XVIII) residue, the activity and spectrum of the compound in general change little. Even inversion of the configuration of one of the valine residues (D to L or L to D; compounds XVI and XVII) leads only to partial and not total inactivation. Considerable retention of activity is observed also when, in one of the valinomycin fragments, the D- and L-valine residues are simultaneously replaced by D- and L-leucine (XXII) or D- and L-alanine (XXIII). However, when all the 6 amino acid residues of the valinomycin analogues are either only D- or L-valine (XXX and XXXI), or 3 D-valine residues are replaced by D-allo-isoleucine (XXXII), the compounds

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Table I

	Compound[7]	M.p. °C (solvent for cryst.)	$[\alpha]_D^{20}$
I	cyclo-(D.Val→L.Lac→L.Val→D.HyV)$_3$ [1]		
II	H-D.Val-L.Lac-L.Val-D.HyV-OH[3]		
III	H-(D.Val-L.Lac-L.Val-D.HyV)$_2$-OH[3]		
IV	H-(D.Val-L.Lac-L.Val-D.HyV)$_3$-OH	amorph.	+ 24° (c 1, EtOH)
V	H-(D.Val-L.Lac-L.Val-D.HyV)$_4$-OH	amorph.	− 12° (c 1. EtOH)
VI	cyclo-D.Val→D.HyV→D.Val→D.HyV [4]		
VII	cyclo-L.Val→L.HyV→L.Val→L.HyV [4]		
VIII	cyclo-D.Val→L.Lac→L.Val→L.HyV	252 (ethanol)	−51 ° (c 2, $CHCl_3$)
IX	cyclo-D.Val→L.Lac→L.Val→L.Lac	246 (ethanol)	− 73° (c 1, $CHCl_3$)
X	cyclo-(D.Val→L.Lac→L.Val→D.HyV)$_2$ [4]		
XI	cyclo-(D.Val→D.HyV→D.Val→D.HyV)$_2$ [4]		
XII	cyclo-(L.Val→L.HyV→L.Val→L.HyV)$_2$ [4]		
XIII	cyclo-(L.Val→L.Lac→L.Val→D.HyV)$_2$	232 (ethanol)	− 37° (c 1, $CHCl_3$)
XIV	cyclo-(D.Val→L.HyV→L.Val→D.HyV)$_2$	241 (pet. ether)	0° (c 2, $CHCl_3$)
XV	cyclo-D.Val→L.Lac→L.Val→L.Lac→L.Val→D.HyV→D.Val→D.HyV	222 (benzene-ether)	+ 2° (c 2, $CHCl_3$)
XVI	cyclo-L.Val→L.Lac→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	219 (dipropyl ether)	+24° (c 1, C_6H_6)
XVII	cyclo-D.Val→L.Lac→D.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	96; 187[8] (pet. ether)	+ 29° (c 0.6, EtOH)
XVIII	cyclo-D.Val→L.Lac→L.aIle→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	176 (pet. ether)	+ 33° (c 1, C_6H_6)
XIX	cyclo-D.aIle→L.Lac→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	164 (ethanol)	+25° (c 1, EtOH)
XX	cyclo-D.Leu→L.Lac→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	167 (pet. ether)	+ 40° (c 1, C_6H_6)
XXI	cyclo-D.Ala→L.Lac→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	173 (pet. ether)	+ 36° (c 1, C_6H_6)
XXII	cyclo-D.Leu→L.Lac→L.Leu→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	165 (pet. ether)	+ 45° (c 1, C_6H_6)
XXIII	cyclo-D.Ala→L.Lac→L.Ala→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	amorph.	+ 34° (c 1, C_6H_6)
XXIV	cyclo-(D.Val→L.HyV→L.Val→D.HyV)$_3$	274 (dipropyl ether)	0° (c 2, $CHCl_3$)
XXV	cyclo-(D.Val→L.Lac→L.Val→L.Lac)$_3$	222 (dibutyl ether)	− 23° (c 1, $CHCl_3$)
XXVI	cyclo-D.Val→L.HyV→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	210 (ethanol)	+ 25° (c 1, C_6H_6)
XXVII	cyclo-(D.Val→L.Lac→L.Val→L.HyV)$_3$	223 (heptane)	− 35° (c 1, $CHCl_3$)
XXVIII	cyclo-D.Val→L.Lac→L.Val→L.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	180 (hexane)	+ 2° (c 1, C_6H_6)
XXIX	cyclo-(D.Val→D.Lac→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)$_2$	122; 155[8] (hexane)	+ 44° (c 1, C_6H_6)
XXX	cyclo-(D.Val→L.Lac→D.Val→D.HyV)$_3$	amorph.	+ 60° (c 0.5, C_6H_6)
XXXI	cyclo-(L.Val→L.Lac→L.Val→D.HyV)$_3$	130 (dipropyl ether)	− 36° (c 1, EtOH)
XXXII	cyclo-D.aIle→L.Lac→L.Val→D.HyV)$_3$	70; 173[8] (ethanol)	+ 28° (c 1, C_6H_6)

Table I (continued)

	Compound[7]	M.p. °C (solvent for cryst.)	$[\alpha]_D^{20}$
XXXIII	$\overline{\text{–(D.Val→L.Lac→L.Val→D.Lac)}_3\text{–}}$	210 (dipropyl ether)	0° (c 2, $CHCl_3$)
XXXIV	$\overline{\text{–D.Val→L.Ala→L.Val→D.HyV(D.Val→L.Lac→L.Val→D.HyV)}_2\text{–}}$	192 (pet. ether)	+ 40° (c 1, EtOH)
XXXV	$\overline{\text{–(D.Val→L.Lac→L.Val→D.HyV)}_4\text{–}}$	236 (ethanol)	– 23° (c 1, $CHCl_3$)
XXXVI	$\overline{\text{–(L.N–MeaIle→D.HyV)}_3\text{–}}$ [9,10]		
XXXVII	$\overline{\text{–(L.N–MeVal→D.HyV(L.N–MeaIle→D.HyV)}_2\text{–}}$ [10]	117 (aq. methanol)	– 94° (c 1, $CHCl_3$)
XXXVIII	$\overline{\text{–(L.N–MeVal→ D.HyV)}_3\text{–}}$ [11]		
XXXIX	$\overline{\text{–(L.N–MeVal→ D.HyV)}_4\text{–}}$ [11]		
XL	$\overline{\text{–(L.N–MeLeu→D.HyV)}_3\text{–}}$ [12]		
XLI	$\overline{\text{–(L.N–MeVal→ D.HyV)}_2\text{–}}$ [13]		
XLII	$\overline{\text{–D.Val→D.Leu→L.HyV→L.Val→L.N-MeLeu→L.HyV–}}$ [14]		
XLIII	$\overline{\text{–L.Ser→D–}\beta\text{ · HyDec→L.Ser→D–}\beta\text{ · HyDec–}}$ [15]		
XLIV	$\overline{\text{–OCH}_2\text{CONH(CH}_2)_{11}\text{CO–}}$ [16]		
XLV	$\overline{\text{–O(CH}_2)_2\text{CONH (CH}_2)_5\text{CO–}}$ [16]		
XLVI	$\overline{\text{–O(CH}_2)_2\text{CONH (CH}_2)_4\text{CO–}}$ [16]		

Table II

Compound	Minimal growth inhibiting concentration (γ/ml)								
	Staph. aureus 209 P	*Staph. aureus* UV-3	*Sarcina lutea*	*B. mycoides*	*B. subtilis*	*E. coli*	*Mycob. phlei*	*Cand. albicans*	*Sacch. cereviseae*
I	> 50	0.8	1.5	> 50	> 50	> 50	0.3	0.8	0.8
II–XIII	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
XIV, XV	> 50	50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
XVI	> 50	8	20	> 50	> 50	> 50	1.5	8	8
XVII	> 50	6	20	> 50	> 50	> 50	1	8	8
XVIII	> 50	0.6	1.5	> 50	> 50	> 50	0.4	0.8	0.8
XIX	> 50	0.8	1.5	> 50	> 50	> 50	0.3	0.8	0.8
XX	> 50	0.7	1.5	> 50	> 50	> 50	0.3	0.8	0.8
XXI	> 50	0.7	1.5	> 50	> 50	> 50	0.4	0.8	0.8
XXII	> 50	8	22	> 50	> 50	> 50	1	8	9
XXIII	> 50	8	16	> 50	> 50	> 50	1.3	8	8
XXIV–XXXIII	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
XXXIV	4.5	1	2	> 50	> 50	> 50	0.4	4.5	4
XXXV	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50
XLIII	10	4.5	4.5	10	10	> 100	4.5	> 100	> 100

[7] The synthesis of compounds not described by us earlier will be published elsewhere.

[8] The first figure is the softening temperature with ensuing resolidification; the second figure is the melting point.

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Table III

Compound[17]	Minimal growth inhibiting concentration (γ/ml)											
	Alternaria mali	*Botrytis allii*	*Botrytis cinerea*	*Botrytis fabae*	*Cercospora beticola*	*Fusicladium pirinum*	*Helmintosporium sativum*	*Helmintosporium turcicum*	*Nigrospora orysae*	*Sclerotinia libertiana*	*Sclerotium bataticola*	*Rhizoctonia aderholdii*
I	1.5	1	0.7	0.8	0.8	1.5	1.5	1.5	1.5	0.8	1.5	1
VIII–X	> 50	> 25	> 25	> 50	> 50	> 25	> 25	> 25	> 25	> 50	> 25	> 25
XVI, XVII	–	–	9	9	–	9	–	–	–	9	–	9
XVIII, XX	–	–	0.7	0.7	–	0.7	–	–	–	0.7	–	0.7
XIX	–	0.7	–	0.7	–	0.7	–	–	–	0.7	–	0.7
XXIII	–	–	0.7	0.7	–	–	–	–	–	1	–	–
XXVI, XXVIII	> 50	–	> 50	–	> 50	–	> 50	–	–	–	–	–
XXXI	–	–	> 50	–	> 50	–	–	> 50	–	–	–	–
XXXIV	2	2	2	2	2	3	2	2	–	2	2	2
XXXV	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	–	> 50	> 50	> 50
XXXVI	4.5	12	4.5	10	6	9	9	5	4.5	5	6	9
XXXVIII	> 25	9	10	12	10	9	> 25	> 25	8	10	7.5	9
XXXIX, XLI	> 25	> 25	> 50	> 25	> 50	> 25	> 25	> 25	> 25	> 25	> 25	> 25
XL	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25	> 25
XLII	–	–	> 50	–	> 50	–	–	–	–	> 50	–	> 50
XLIII	> 25	> 25	> 25	> 25	9	9	9	> 25	> 25	9	> 25	9

Table IV. Potassium ion transport induction properties of cyclodepsipeptides[21,22]

Compound	I	XVI	XXIX	XXXI	X	XXXVI	XXXVII	XXXVIII	XXXIX	XL	XLI	XLII
Relative induction activity	100	13	2.2	0.00	0.00	0.61	0.46	1.3	0.23	0.15	0.00	0.01

are practically inactive. (3) Quite the opposite is observed in the hydroxy acid residues of valinomycin, a change in the radical structure or in the configuration of which is ordinarily accompanied by practically complete loss of antimicrobial activity. Thus the substitution in valinomycin of even one L-lactic acid residue by L-α-hydroxyisovaleric acid (XXVI), not to mention all 3 L-lactic acid residues (XXIV), causes the complete loss of activity of the compound. Also the valinomycin analogues are deprived of activity in which not only all three but even a single D-α-hydroxyisovaleric acid residue is replaced by an L-α-hydroxyisovaleric acid (XXVII and XXVIII) or an L-lactic acid residue by a D-lactic acid residue (XXIX). (4) It is of particular interest that the substitution of an ester group by an amide group in valinomycin does not lead to any appreciable change in the antimicrobial properties of the molecule. Thus, it was found that substitution of one of the L-lactic acid residues by L-alanine (XXXIV) changes little the activity of the compound.

From a comparison of the data on the antimicrobial activity of the valinomycin and enniatin cyclodepsipeptides and of serratamolide, one may infer that the size of the ring, while it must be confined within certain limits, can nevertheless vary considerably[18]; under certain conditions an ester group may be substituted by an amide group, and sometimes[19] a methyl amide group by an amide group; it is also noteworthy that the amino acid residues can undergo structural and configurational changes to a greater extent than the hydroxy acid residues.

The antibiotic activity of the depsipeptides we have studied is apparently a result of their interaction with the lipoproteids of the cell membranes which is manifested in their capacity for inducing active transport of some monovalent ions in mitochondria.

Recently, PRESSMAN has shown that valinomycin brings about a very strong active transport of K^+, but not of Na^+ ions in animal mitochondria[20]. Further, in a cooperated study by PRESSMAN and us of a number of synthetic valinomycin and enniatin analogues, the conclusion was drawn that a parallelism exists between the antimicrobial activity of the depsipeptide antibiotics and their ion transport induction properties. Among the valinomycin analogues this parallelism is not only qualitative (active K^+, but no Na^+ transport), but, to a first approximation, also quantitative (Tables II and III with Table IV).

[17] The compounds given in the Table do not inhibit growth of *Denterophoma tracheiphila*, *Fusarium culmorum*, *Fusarium oxysporum* and *Verticillium dahliae*.

[18] According to preliminary data the 16-membered cyclodidepsipeptide (XLIV) possesses weak antimicrobial properties, but its analogues (XLV) and (XLVI) do not.

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Thus, the antimicrobial activity and the ion transport induction capacity of compound (XVI) are both approximately 1:10 that of valinomycin (I), and both properties are either completely or almost completely absent from compounds (X), (XXIX) and (XXXI). A similar picture is to be seen in the enniatin analogues: compounds (XXXVI to XXXVIII) differing comparatively little in antimicrobial properties have also closely related ion transport induction properties; compound (XXXIX) with narrow antimicrobial spectrum shows also diminished ion transport induction activity, and in compounds (XL) and (XLI) both these properties are either only very weakly manifested or are completely absent[23]. Finally, as has been shown earlier, all cyclohexadepsipeptides of the sporidesmolide series lack antimicrobial activity[6], and the results of the tests carried out on sporidesmolide I (XLII) by PRESSMAN have shown that it is practically devoid of the ability to induce ion transport.

Apparently the depsipeptide antibiotics are inducers of K^+ ion transport as the result of interaction with a specialized mitochondrial receptor site controlling this transport. In agreement with PRESSMAN, we believe that this interaction can hardly be due merely to the surface active properties of the molecules, but it is still difficult to make any conjecture as to the structural features of these compounds which determine their ability to interact with the receptor, not to mention the nature of this interaction.

Zusammenfassung. Auf Grund eines grossen Vergleichsmaterials wurden die Strukturelemente, die für die antimikrobielle Aktivität der Cyclodepsipeptide nötig sind, ermittelt. Insbesondere wurden Ringgrösse, Ersatz der Ester- oder N-Methylamid-Gruppe durch eine Amidgruppe, strukturelle und konfigurative Änderung der Aminosäure- und Hydroxysäurereste studiert.

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[23] Naturally the valinomycin depsipeptides, differing considerably in structure from the enniatin depsipeptides differ also in the antimicrobial spectrum and especially in the degree (but not selectivity) of their ion transport induction in mitochondria. Valinomycin differs from the enniatins also in toxicity. Thus, according to K. A. SEDOV, the toxicity of valinomycin on peroral administration (LD_{50} 2.5 mg/kg, mice) is practically the same as its toxicity on subcutaneous or interperitoneal administration[24], whereas like most cyclopeptides enniatin B is little toxic on peroral administration (it gives no toxic effects even in doses of 1 g/kg body weight).

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ADDENDUM: A. KREBS und H. SCHALTEGGER, Exper. *21*, 128 (1965).

In unseren *Untersuchungen über den Wirkungsmechanismus von Chrysarobin und Dithranol bei Psoriasis* wurde ausgeführt, dass wir unter Cytostase nicht nur ausschliesslich Chemotherapie maligner Tumoren verstehen, sondern allgemein Hemmung der Zellteilung durch *verschiedene Mechanismen*. So können z.B. an der epidermalen Regeneration auch neuronale Steuerelemente beteiligt sein. Wir können daher nur sagen, dass Dithranol in einen Regelkreis eingreift, welcher möglicherweise bei Psoriasis so gestört ist, dass dadurch z.B. die Zellteilungsrate sehr stark erhöht wird. Der im zweiten Absatz der «Schlussfolgerungen» angeführte Passus «spezifisch zellteilungshemmend» könnte zur einseitigen Auffassung führen, dass nur eine direkte Zellteilungshemmung durch Dithranol in Betracht käme. Im übrigen wird das Bakterienwachstum durch Dithranol nicht gehemmt[1].

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