SYNTHESIS OF "MESO ANALOGS" OF VALINOMYCIN AND DIASTEREOISOMERS OF THE COMPOUND CYCLO(D-VALYL-L-α-HYDROXYISOVALERYL-L-VALYL-D-α-HYDROXYISOVALERYL)$_3$

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At the present time a large amount of information is available according to which the action of antibiotics with a cyclodepsipeptide structure such as, for example, valinomycin and the enniatins, on the cells of living organisms is connected with an increase in the flows of potassium ions through biological (mitochondrial, etc.) membranes [1]. This effect is also observed with synthetic double-layer membranes [2]. It has been shown [3] that the antibiotic activity of these cyclodepsipeptides is closely connected with their capacity for forming in solutions complexes with the corresponding cations, the effectiveness and ionic selectivity of complex formation depending to a considerable extent on the conformation of the depsipeptide under the given conditions. It has been established that the capacity of cyclodepsipeptides for selectively increasing the K^+ permeability of model membranes is a necessary but not sufficient condition for their exhibition of antibiotic activity. Thus, many membrane-active analogs of valinomycin not differing from the natural antibiotic in respect of ionic selectivity are incapable of suppressing the growth of microorganisms. Among them, particular attention is attracted by the so-called "meso analogs" of valinomycin (compounds IXa-d, see Table 11) which, thanks to the high symmetry of their molecules, are particularly convenient subjects for conformational investigations. The study of the conformational states of the cyclodepsipeptides under various conditions permits a deeper investigation of the nature of their interaction with the ions which they transport through membranes and the behavior of these compounds in the membranes. For this purpose we have synthesized the above-mentioned meso analogs of valinomycin and analogs of compound (XIa) in the molecule of which one or more amino acid or hydroxy acid residues has been replaced by the corresponding residue with the opposite configuration (compounds XIe-l, see Table 11). The synthesis of compound XIa was effected in accordance with Scheme 1, and that of compounds XIb-m in accordance with Scheme 2. To create the ester linkages we employed the mixed-anhydride method using benzenesulfonyl chloride, and the amide linkages, including those leading to cyclization, were created by the acid chloride and dicyclohexylcarbodiimide methods in the presence of N-hydroxysuccinimide. The benzyloxycarbonyl and tert-butyl groups were used to protect amino and carboxy groups, respectively.

EXPERIMENTAL

The cyclodepsipeptides in the pure form were isolated by chromatography on columns of neutral alumina (activity grade III) by gradient elution with mixtures of benzene and ethyl acetate, the process being monitored on a Pye gas-liquid chromatograph with an argon ionization detector. The individualities of the compounds were checked by thin-layer chromatography on alumina or silica gel. The yields and characteristics of all the intermediate and final compounds are given in Tables 1-11. The elementary analysis of these compounds corresponded to the calculated figures.

1. tert-Butyl Esters of N-Benzyloxycarbonylaminoacyloxy Acids (compounds Ia-h, Table 1). With stirring (0°C, 10 min), 0.02 mole of benzenesulfonyl chloride and, after 15 min, 0.02 mole of the tert-butyl

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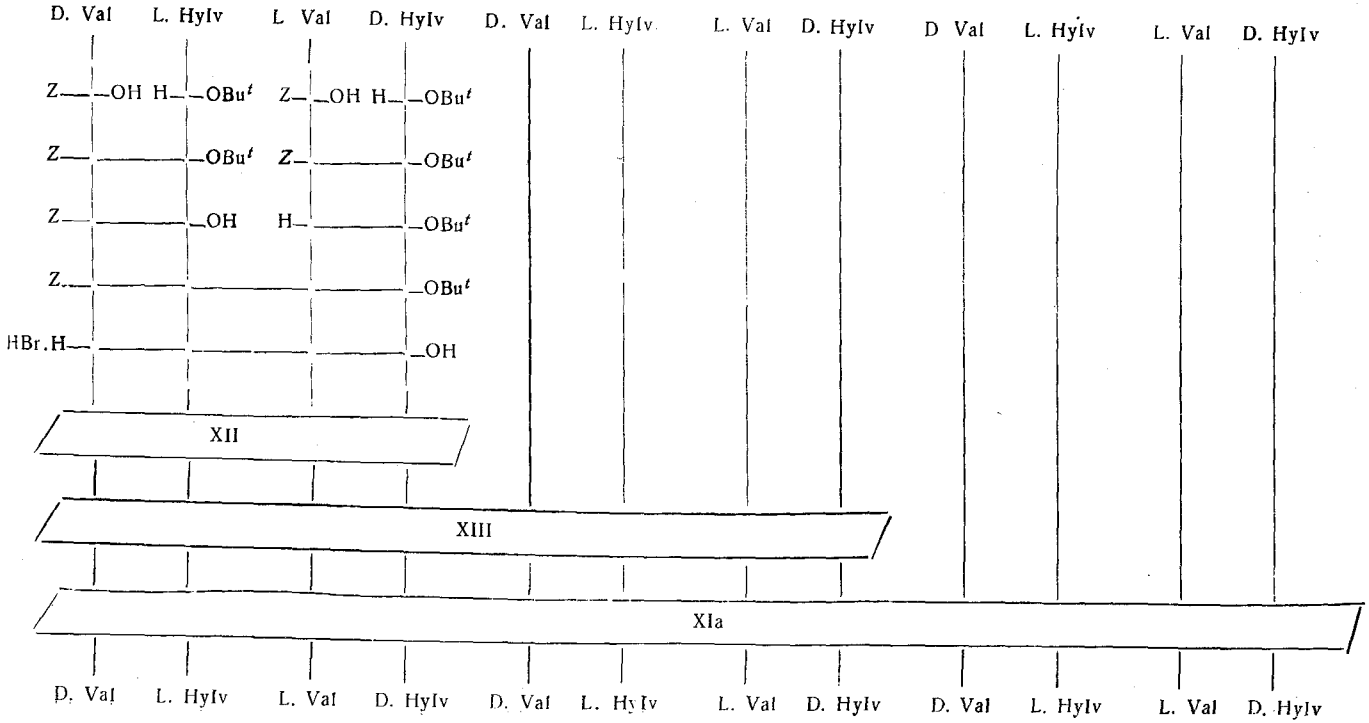
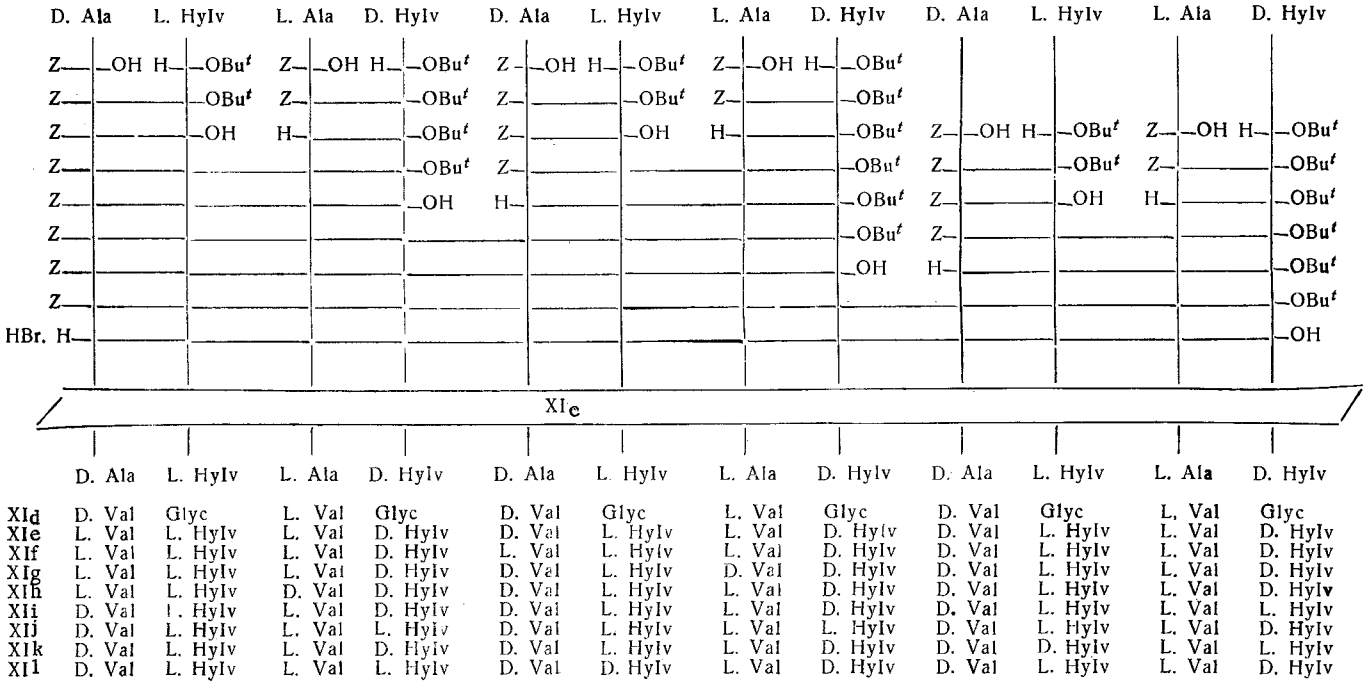
Scheme 1


D. Val
L. Hyiv
L Val
D. Hyiv
D. Val
L. Hyiv
L. Val
D. Hyiv
D Val
L. Hyiv
L. Val
D. Hyiv
Z—OH H—OBu^t
Z—OBu^t
Z—OH
Z—OBu^t
HBr.H—OH
Z—OH H—OBu^t
Z—OBu^t
H—OBu^t
XII
XIII
XIa
D. Val
L. Hyiv
L. Val
D. Hyiv
D. Val
L. Hyiv
L. Val
D. Hyiv
D. Val
L. Hyiv
L. Val
D. Hyiv

Scheme 2



XId	D. Val	Glyc	L. Val	Glyc	D. Val	Glyc	L. Val	Glyc	D. Val	Glyc	L, Val	Glyc
XIe	L. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv
XIf	L. Val	L. Hylv	L. Val	D. Hylv	L. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv
XIg	L. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	D. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv
XIh	L. Val	L. Hylv	D. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv
XIi	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	L. Hylv
XIj	D. Val	L. Hylv	L. Val	L. Hylv	D. Val	L. Hylv	L. Val	L. Hylv	D. Val	L. Hylv	L. Val	D. Hylv
XIk	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv	D. Val	D. Hylv	L. Val	L. Hylv
XIl	D. Val	L. Hylv	L. Val	L. Hylv	D. Val	D. Hylv	L. Val	D. Hylv	D. Val	L. Hylv	L. Val	D. Hylv

TABLE 1. tert-Butyl Esters of N-Benzyloxycarbonylaminoacyloxy Acids

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
Ia	Z-D. Val-L. HyIv-OBu^t [4]	88	−8 (*c* 1;benzene)
Ib	Z-L. Val-D. HyIv-OBu^t [5]	90	+8,4 (*c* 2;ethanol)
Ic	Z-L. Val-L. HyIv-OBu^t [6]	77	−17 (*c* 2;ethanol)
Id	Z-D. Val-D. HyIv-OBu^t [6]	78	+24 (*c* 0,1;benzene)
Ie	Z-D. Ala-L. HyIv-OBu^t	85	−7 (*c* 0,2;benzene)
If	Z-L. Ala-D. HyIv-OBu^t [4]	78	+8 (*c* 0,2 ethanol)
Ig	Z-D. Val-Glyc-OBu^t	84	+37 (*c* 0,1;benzene)
Ih	Z-L. Val-Glyc-OBu^t	82	−34 (*c* 0,1;benzene)

TABLE 2. N-Benzyloxycarbonylaminoacyloxy Acids

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
IIa	Z-D. Val-L. HyIv-OH [4]	77	+3 (*c* 1; benzene)
IIb	Z-L. Val-L. HyIv-OH [6]	79	+20 (*c* 1; ethanol)
IIc	Z-D. Val-D. HyIv-OH [6]	76	+37 (*c* 1; ethanol)
IId	Z-D. Ala-L. HyIv-OH	75	+5,2 (*c* 0,1; ethanol)
IIe	Z-D. Val-Glyc-OH*	82	+40 (*c* 0,1; benzene)

*mp 78-80°C (benzene−hexane).

TABLE 3. tert-Butyl Esters of Aminoacyloxy Acids

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
IIIa	H-L. Val-D. HyIv-OBu^t [4, 5]	75	+40 (*c* 0,5; benzene)
IIIb	H-L. Ala-D. HyIv-OBu^t [4]	72	+43 (*c* 0,3; ethanol)
IIIc	H-L. Val-Glyc-OBu^t	71	+33 (*c* 0,1;benzene)
IIId	H-D. Val-D. HyIv-OBu^t [6]	73	+20 (*c* 1; ethanol)
IIIe	H-L. Val-L. HyIv-OBu^t [6]	76	−16 (*c* 0,12; benzene)

ester of the corresponding hydroxy acid in 15 ml of anhydrous pyridine were added to a solution of 0.02 mole of a N-benzyloxycarbonylamino acid in 20 ml of anhydrous pyridine. The mixture was stirred at 0°C for 2 h and at 20°C for 2 h and was then poured into 100 ml of water, and the oil that separated out was extracted with ether. The ethereal extract was washed with 10% hydrochloric acid, water, saturated sodium bicarbonate solution, and water again, and was dried with magnesium sulfate. The solvent was distilled off and the residue was chromatographed on a column of neutral alumina (activity grade III), elution in the benzene−ethyl acetate (20 : 1) system giving compounds Ia-h.

2. N-Benzyloxycarbonylaminoacyloxy Acids (compounds IIa-e, Table 2). A solution of 0.03 mole of the appropriate tert-butyl ester of a N-benzyloxycarbonylaminoacyloxy acid (see Table 1) in 140 ml of absolute benzene was treated with 1.4 g of p-toluenesulfonic acid and the mixture was boiled for 1 h, cooled, washed with water to neutrality to Congo red, and extracted with 5% sodium bicarbonate solution. The bicarbonate solution was acidified with 5% hydrochloric acid, and the oil that separated out was extracted with ether. The ethereal extract was washed with water to a neutral reaction to Congo red, and dried with magnesium sulfate, and the solvent was distilled off. Compounds IIa-e were obtained.

3. tert-Butyl Esters of Aminoacyloxy Acids (compounds IIIa-e, Table 3). A solution of 0.02 mole of a tert-butyl ester of a N-benzyloxycarbonylaminoacyloxy acid (see Table 1) and 0.02 mole of citric or tartaric acid in 50 ml of methanol was hydrogenated in the presence of 1 g of palladium black in a current of hydrogen. After the end of hydrogenation, the catalyst was filtered off, the solvent was distilled off in vacuum, the residue was dissolved in water, the solution was extracted with ether, and the extract was cooled and re-extracted several times with 10% citric acid solution. The citric acid solution was washed with ether, cooled to 0-5°C, and neutralized with sodium bicarbonate. The oil that separated out was extracted with ether, and the ethereal extract was washed with water and dried with magnesium sulfate. Distillation of the solvent yielded the tert-butyl ester of the corresponding aminoacyloxy acid.

TABLE 4. tert-Butyl Esters of N-Benzyloxycarbonyltetradepsipeptides

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
IVa	Z-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	81	79—80 (petroleum ether)	+6 (*c* 0,12; ethanol)
IVb	Z-D. Ala-L. HyIv-L. Ala-D. HyIv-OBu^t	70	Oil	—3 *c* 0,1; ethanol)
IVc	Z-D. Val-Glyc-L. Val-Glyc-OBu^t	50	Oil	—2,5 (*c* 0,1; ethanol)
IVd	Z-L. Val-L. HyIv-L. Val-D. HyIv-OBu^t	83	98—99 (hexane)	—25 (*c* 1; ethanol)
IVe	Z-D. Val-L. HyIv-D. Val-D. HyIv-OBu^t	80	Oil	+28 (*c* 1; ethanol)
IVf	Z-L. Val-L. HyIv-D. Val-D. HyIv-OBu^t	89	93—94 (hexane)	+3 (*c* 2; ethanol)
IVg	Z-D. Val-L. HyIv-L. Val-L. HyIv-OBu^t	88	Oil	—32 (*c* 0,16; methanol)
IVh	Z-D. Val-D. HyIv-L. Val-D. HyIv-OBu^t	90	Oil	+30 (*c* 0,2; ethanol)
IVi	Z-D. Val-D. HyIv-L. Val-L. HyIv-OBu^t	84	94—95 (petroleum ether)	—1 (*c* 0,17; ethanol)

TABLE 5. N-Benzyloxycarbonyltetradepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
Va	Z-D. Val-L. HyIv-L. Val-D. HyIv-OH [4]	91	+2,7 (*c* 0,14; ethanol)
Vb	Z-D. Ala-L. HyIv-L. Ala-D. HyIv-OH	85	—11 (*c* 0,1; ethanol)
Vc	Z-D. Val-L. HyIv-L. Val-L. HyIv-OH	95	—23 (*c* 0,16; methanol)
Vd	Z-L. Val-L. HyIv-L. Val-D. HyIv-OH	92	—36 (*c* 2; ethanol)
Ve	Z-L. Val-L. HyIv-D. Val-D. HyIv-OH	90	—7 (*c* 1; ethanol)
Vf	Z-D. Val-Glyc-L. Val-Glyc-OH	90	+3 (*c* 0,1; ethanol)

TABLE 6. tert-Butyl Esters of Tetradepsipeptide

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
VIa	H-D-Val-L. HyIv-L. Val-D. HyIv-OBu^t [4]	81	
VIb	H-D. Ala-L. HyIv-L. Ala-D. HyIv-OBu^t	70	—16 (*c* 0,1; ethanol)
VIc	H-D. Val-D. HyIv-L. Val-L. HyIv-OBu^t	78	—27 (*c* 0,18; ethanol)
VId	H-L. Val-L. HyIv-L. Val-D. HyIv-OBu^t	87	— 6 (*c* 1; ethanol)
VIe	H-D. Val-L. HyIv-D. Val-D. HyIv-OBu^t	60	+25 (*c* 1; ethanol)
VIf	H-D. Val-L. HyIv-L. Val-L. HyIv-OBu^t	79	—47 (*c* 0,2 methanol)
VIg	H-D. Val-D. HyIv-L. Val-D. HyIv-OBu^t	85	+19 (*c* 0,19; ethanol)
VIh	H-D. Val-Glyc-L. Val-Glyc-OBu^t	60	—27 (*c* 0,1; ethanol)

4. tert-Butyl Esters of N-Benzyloxycarbonyltetradepsipeptides (compounds IVa-i, Table 4). A solution of 0.01 mole of the appropriate N-benzyloxycarbonylaminoacyloxy acid (see Table 2) in 15-20 ml of thionyl chloride was kept at 30-35°C for 30 min, and the excess of thionyl chloride was carefully distilled off in vacuum. The resulting acid chloride was dissolved in 40 ml of absolute benzene and, with stirring and cooling (3-5°C), was treated simultaneously, dropwise, with a solution of 0.015 mole of triethylamine in 30 ml of absolute benzene and a solution of 0.01 mole of a tert-butyl ester of an aminoacyloxy acid (see Table 3) in 30 ml of absolute benzene. The reaction mixture was stirred at 18-20°C for 2 h, washed with 5% hydrochloric acid, water, saturated sodium bicarbonate solution, and water again, and dried with magnesium sulfate, and the benzene was distilled off. The residue was chromatographed on a column of neutral alumina, the tert-butyl ester of the N-benzyloxycarbonyltetradepsipeptide being isolated by gradient elution in the benzene—ethyl acetate system.

5. N-Benzyloxycarbonyltetradepsipeptides (compounds Va-f, Table 5). A solution of 0.01 mole of the appropriate tert-butyl ester of a N-benzyloxycarbonyltetradepsipeptide (see Table 4) in 30 ml of trifluoroacetic acid was kept at 25-30°C for 20 min, and the trifluoroacetic acid was carefully distilled off in vacuum at 30-35°C. The residue was dissolved in ether and the resulting solution was washed with water until it was neutral to Congo red and was then extracted with saturated sodium bicarbonate solution. The bicarbonate extracts were acidified with 10% hydrochloric acid, the oil that separated out was extracted

TABLE 7. tert-Butyl Esters of N-Benzyloxycarbonyloctadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
VIIa	Z-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-OBu^t [4]	90	+16 (*c* 0.32; benzene)
VIIb	Z-(D. Ala-L. HyIv-L. Ala-D. HyIv)$_2$-OBu^t	80	—5 (*c* 0,1; ethanol)
VIIc	Z-D. Val-L. HyIv-L. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-OBu^t	92	+19 (*c* 0,24;benzene
VIId	Z-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	93	—20 (*c* 1; ethanol)
VIIe	Z-(L. Val-L. HyIv-L. Val-D. HyIv)$_2$-OBu^t	95	—30 (*c* 1;ethanol)
VIIf	Z-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-D. Val-D. HyIv-OBu^t	95	—3 (*c* 1;ethanol)
VIIg	Z-L. Val-L. HyIv-D. Val-D. HyIv-D. Val-L. H[illegible] Val-D. HyIv-OBu^t	85	+13 (*c* 1;ethanol)
VIIh	Z-(D. Val-L. HyIv-L. Val-L. HyIv)$_2$-OBu^t	92	—18 (*c* 0,14, benzene)
VIIi	Z-(D, Val-Glyc-L. Val-Glyc)$_2$-OBu^t	50	—3,5 (*c* 0,1; ethanol)

TABLE 8. N-Benzyloxycarbonyloctadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
VIIIa	Z-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-OH [4]	90	—13 (*c* 0,17;benzene)
VIIIb	Z-(D. Ala-L. HyIv-L. Ala-D. HyIv)$_2$-OH	83	—2,6 (*c* 0,1; ethanol)
VIIIc	Z-D. Val-L. HyIv-L. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-OH	92	—7 (*c* 0,14;benzene)
VIIId	Z-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OH	78	—18 (*c* 1;ethanol)
VIIIe	Z-(L. Val-L. HyIv-L. Val-D. HyIv)$_2$-OH	85	—32 (*c* 1; ethanol)
VIIIf	Z-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-D. Val-D. HyIv-OH	79	—12 (*c* 1; ethanol)
VIIIg	Z-L. Val-L. HyIv-D. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OH	83	—2 (*c* 1;ethanol)
VIIIh	Z-(D. Val-L. HyIv-L. Val-L. HyIv)$_2$-OH	84	—23 (*c* 0,13; benzene)
VIIIi	Z-(D. Val-Glyc-L. Val-Glyc)$_2$-OH	70	+1,8 (*c* 0,1; ethanol)

TABLE 9. tert-Butyl Esters of N-Benzyloxycarbonyldodecadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
IXa	Z-(D. Ala-L. HyIv-L. Ala-D. HyIv)$_3$-OBu^t	85	—1,6 (*c* 0,1; ethanol)
IXb	Z-D. Val-L. HyIv-L. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	96	+1,4 (*c* 0,13; benzene)
IXc	Z-L. Val-L. HyIv-L. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-OBu^t	95	—8 (*c* 1;ethanol)
IXd	Z-(L. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	89	—10 (c 1;ethanol)
IXe	Z-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-D. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	90	—23 (*c* 1;ethanol)
IXf	Z-L. Val-L. HyIv-D. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$OBu^t	93	+1 (*c* 0,1;ethanol)
IXg	Z-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-L. HyIv-OBu^t	95	—2,7 (*c* 0,13; ethanol)
IXh	Z-(D. Val-L. HyIv-L. Val-L. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv-OBu^t	93	—31 (*c* 0,14; benzene)
IXi	Z-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-D. HyIv-L. Val-L. HyIv-OBu^t	96	+27 (*c* 0,16; benzene)
IXj	Z-(D. Val-Glyc-L. Val-Glyc)$_3$-OBu^t	55	—22 (*c* 0,1; ethanol)

TABLE 10. Hydrobromide of Tetra- and Dodecadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
X a	HBr. H-D. Val-L. HyIv-L. Val-D. HyIv-OH [5]*	84	—43 (*c* 0,13; ethanol)
X b	HBr. H-(D. Ala-L. HyIv-L. Ala-D. HyIv)$_3$-OH	75	—5,8 (*c* 0,1; ethanol)
X c	HBr. H-L. Val-L. HyIv-L. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-OH	95	—14,5 (*c* 0,1; ethanol)
X d	HBr. H-(L. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv-OH	90	—20 (*c* 0,1; ethanol)
X e	HBr. H-L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-OH	93	—4 (*c* 1; ethanol)
X f	HBr. H-L. Val-L. HyIv-D. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-OH	95	+8 (*c* 1; ethanol)
X g	HBr. H-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-L. HyIv-OH	92	+5,3 (*c* 0,18; benzene)
X h	HBr. H-(D. Val-L. HyIv-L. Val-L. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv-OH	87	—56 (*c* 0,12; chloroform)
X i	HBr. H-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-D. HyIv-L. Val-L. HyIv-OH	94	+13,4 (*c* 0,18; benzene)
X j	HBr. H-D. Val-L. HyIv-L. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv-OH	88	+0,55 (*c* 0,11; chloroform)
X k	HBr. H-(D. Val-Glyc-L. Val-Glyc)$_3$-OH	80	

* mp 128°C (ether).

with ether, and the ethereal extract was washed with water until it was neutral to Congo red and was dried with magnesium sulfate. Distillation of the solvent yielded the corresponding compound (V).

6. tert-Butyl esters of tetradepsipeptides (compounds VIa-h, Table 6) were obtained by the hydrogenolysis of the corresponding tert-butyl esters of the N-benzyloxycarbonyltetradepsipeptides (see Table 4) under the conditions of experiment 3.

7. tert-Butyl esters of N-benzyloxycarbonyloctadepsipeptides (compounds VIIa-h, Table 7) were obtained by the condensation of the acid chloride derivatives of compounds of type (V) (see Table 5) with the tert-butyl esters of type (VI) (see Table 6) under the conditions of experiment 4.

8. tert-Butyl Ester of the N-Benzyloxycarbonyloctadepsipeptide VIIi (Table 7). A solution of 2.33 g (0.005 mole) of compound (Vf) (see Table 5) and 1.04 g (0.005 mole) of compound (VIh) (see Table 6) in 20 ml of tetrahydrofuran was treated with 1.14 g of N-hydroxysuccinimide in 5 ml of tetrahydrofuran. The reaction mixture was cooled to −10°C, treated with a cooled solution of 1.03 (0.005 mole) of dicyclohexylcarbodiimide in 5 ml of tetrahydrofuran and left at −10°C for 2 h and then at 20°C for 48 h. The dicyclohexylurea that had deposited was filtered off and the solvent was evaporated off to dryness. The residue was dissolved in ethyl acetate and the solution was washed with 5% hydrochloric acid, water, and 5% sodium bicarbonate solution and was dried with magnesium sulfate. Distillation of the solvent yielded compound (VII) in the amorphous state.

9. N-Benzyloxycarbonyloctadepsipeptides (compounds VIIIa-i, Table 8) were obtained from the corresponding tert-butyl esters of N-benzyloxycarbonyloctadepsipeptides (VIIa-i, see Table 7) under the conditions of experiment 5.

10. tert-Butyl ester of N-benzyloxycarbonyldodecadepsipeptides (compounds IXa-i, Table 9) were obtained by condensing the acid chloride derivatives of the N-benzyloxycarbonyloctadepsipeptides (VIIIa-h) (see Table 8) with the tert-butyl esters of tetradepsipeptides (VIa-c, f) (see Table 6) under the conditions of experiment 4.

11. The N-benzyloxycarbonyldodecadepsipeptide tert-butyl ester IXj (Table 9) was obtained from the N-benzyloxycarbonyloctadepsipeptide (VIIIi) (see Table 8) and the tetradepsipeptide tert-butyl ester (VIh) (see Table 6) under the conditions of experiment 8.

TABLE 11. Cyclododecadepsipeptides

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
XI	(D. Val-L. Lac-L. Val-D. HyIv)$_3$ Valinomycin [4]			
XIa	(D. Val-L. HyIv-L. Val-D. HyIv)$_3$ [5]	18	284 (dipropyl ether)	—
XIb	(D. Val-L. Lac-L. Val-D. Lac)$_3$ [4]			
XIc	(D. Ala-L. HyIv-L. Ala-D. HyIv)$_3$	17	Amorphous	—
XId	(D. Val-Glyc-L. Val-Glyc)$_3$	5	197—198 (ethanol)	
XIe	L. Val-L. HyIv-L. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$	18	221—222 (ethanol)	—15 (*c* 1; chloroform)
XIf	(L. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv	30	110—112 (pet. ether)	—5 (*c* 1; chloroform)
XIg	L. Val-L. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-D. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv	45	290—291 (ethanol)	+12 (*c* 1; chloroform)
XIh	L. Val-L. HyIv-D. Val-D. HyIv-(D. Val-L. HyIv-L. Val-D. HyIv)$_2$	60	205—207 (ethanol)	—8 (*c* 2; chloroform)
XIi	(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-L. HyIv-L. Val-L. HyIv	40	266—268 (ethanol)	—53 (*c* 0,1; chloroform)
XIj	(D. Val-L HyIv-L. Val-L. HyIv)$_2$-D. Val-L. HyIv-L. Val-D. HyIv	20	Amorphous	—32 (*c* 0,2; benzene)
XIk	(D. Val-L. HyIv-L. Val-D. HyIv)$_2$-D. Val-D. HyIv-L. Val-L. HyIv	65	235—236 (ethanol—dipropyl ether)	+21 (*c* 0,1; chloroform)
XIl	D. Val-L. HyIv-L. Val-L. HyIv-D. Val-D. HyIv-L. Val-D. HyIv-D. Val-L. HyIv-L. Val-D. HyIv	65	241 (ethanol—dipropyl ether)	—1,6 (*c* 0,1; chloroform)

12. Hydrobromides of the Tetra- and Dodecadepsipeptides (compounds Xa-k, Table 10). A solution of 0.002 mole of the N-benzyloxycarbonyltetradepsipeptide tert-butyl ester (IVa) (see Table 4) or a tert-butyl ester of a N-benzyloxycarbonyldodecadepsipeptide (IXa-j) (see Table 9) in 15-20 ml of a 30% solution of hydrogen bromide in glacial acetic acid was kept at 20-25°C for 1 h. The solvent was carefully distilled off in vacuum, and the residue was washed with absolute petroleum ether and dried in vacuum over phosphorus pentoxide. The corresponding compounds X were obtained.

13. The Cyclododecadepsipeptide (XIa) (Table 11). A solution of 0.99 g (0.002 mole) of the tetradepsipeptide hydrobromide (Xa) (see Table 10) in 10 ml of thionyl chloride was kept at 30°C for 30 min, and then the excess of thionyl chloride was carefully distilled off in vacuum at 30-35°C. The acid chloride remaining was dissolved in 120 ml of absolute benzene, and the solution was added with stirring (20°C, 5 h) simultaneously with a solution of 0.004-0.005 mole of triethylamine in 100 ml of absolute benzene to 700 ml of absolute benzene. After 24 h, the benzene was distilled off from the reaction mixture, which contained the corresponding cyclotetra-, cycloocta-, and cyclododecadepsipeptides formed, to a volume of 300 ml; the cyclotetradepsipeptide (XII) (see Scheme 1) partially precipitated. The suspension formed was washed with a 5% solution of hydrochloric acid, water, sodium bicarbonate solution, and water again. The reaction mixture was left at 20°C for 3-4 h, whereupon the cyclotetradepsipeptide precipitated completely; it was filtered off, the filtrate was dried with magnesium sulfate, and the solvent was distilled off. The residual mixture of cycloocta- and cyclododecadepsipeptides was treated with 10 ml of boiling ethanol. The cyclooctadepsipeptide (XIII) passed into solution, from which it precipitated on cooling, and the cyclododecadepsipeptide (XIa) remained in the residue. The latter was filtered off, washed several times with hot ethanol, and recrystallized from dipropyl ether [5].

14. Cyclododecadepsipeptides, Compounds (XIc, e-l) (Table 11). A solution of 0.001 mole of the hydrobromide of the appropriate dodecadepsipeptide (see Table 10) in 15 ml of thionyl chloride was kept at 30°C for 30 min, and the excess of thionyl chloride was carefully distilled off in vacuum at 30°C. The residual acid chloride was dissolved in 300 ml of absolute benzene and added with stirring (20°C, 10 h) simultaneously with a solution of 0.004 mole of triethylamine in 200 ml of absolute benzene to 1500 ml of absolute benzene. The reaction mixture was left overnight, the solvent was distilled off in vacuum to a volume of 300 ml, the solution was washed with 5% hydrochloric acid, water, saturated sodium bicarbonate solution, and water again, and was dried with magnesium sulfate, and the solvent was distilled off. The residue was chromatographed on a column of neutral alumina (activity grade III), the cyclodepsipeptides being isolated by gradient elution in the benzene–ethyl acetate system.

15. The Cyclododecadepsipeptide (XId) (Table 11). A solution of 0.0005 mole of the dodecadepsipeptide hydrobromide (Xk) (see Table 10) in 300 ml of tetrahydrofuran was treated with 0.00075 mole of triethylamine and, after 30 min, with a solution of 0.002 mole of N-hydroxysuccinimide in 10 ml of tetrahydrofuran. Then the solution was cooled to −10°C, and to it was added a solution of 0.001 mole of dicyclohexylcarbodiimide in 20 ml of tetrahydrofuran. The resulting mixture was left at −10°C for 2 h and then at 20°C for 48 h. The solvent was evaporated to a volume of 30 ml, and the dicyclohexylurea that precipitated was filtered off. The mother solution was evaporated to dryness, the residue was dissolved in ethyl acetate, and the solution was washed with 5% hydrochloric acid and with water and was dried with magnesium sulfate. After the solvent had been distilled off, compound (XId) remained, and it was recrystallized from ethanol.

SUMMARY

The synthesis of the "meso analogs" of valinomycin,

$$\left[\text{(D-alanyl-L-}\alpha\text{-hydroxyisovaleryl-L-alanyl-D-}\alpha\text{-hydroxyisovaleryl)}_3\right],$$

$$\left[\text{(D-valylglycolyl-L-valylglycolyl)}_3\right], \text{ and}$$

$$\left[\text{(D-valyl-L-}\alpha\text{-hydroxyisovaleryl-L-valyl-D-}\alpha\text{-hydroxyisovaleryl)}_3\right],$$

and also of a series of diastereoisomers of the last-mentioned meso compound has been described.

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