SYNTHESIS AND SOME PROPERTIES OF TOPOCHEMICAL ANALOGS OF VALINOMYCIN

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Among the membrane-active compounds forming complexes with alkali-metal cations and increasing the cationic permeability of membranes, a central position is occupied by the depsipeptide antibiotic valinomycin (I) (see [1] and the references there given). The popularity of this compound which is used as an instrument for the study of various biochemical processes connected with the transport of ions through membranes is explained by the fact that the effectiveness and selectivity of the action which it exerts have no equals among compounds with similar biological activity.

We have previously [2] established the conformation of valinomycin and its K^+ complex in solution (see [3]) and have shown the decisive role of the conformational characteristics of the molecule of this depsipeptide in the display of complex-forming properties and its effect on the ionic permeability of membranes. For a more detailed investigation of the various aspects of the molecular mechanism of the action of valinomycin it appeared desirable, in addition to studying the membrane activity of the antibiotic itself [1, 4], to perform the synthesis of various analogs of it in order, by using them, to determine the role of various structural factors both in the formation of the conformations of valinomycin and its complexes and in the functioning of the cyclodepsipeptides of the valinomycin group on artificial and biological membranes.

The present paper describes the preparation of seven new analogs of valinomycin [compounds (2)-(8), see Fig. 1]. In contrast to the case of the analogs obtained previously [5, 6], for the synthesis of compounds (2)-(8) we used the topochemical principle of modifying biologically active compounds [7] which provides not for local changes in individual sections of the depsipeptide chain but the transformation of the initial molecule as a whole. Thus, of the compounds synthesized, enantiovalinomycin (2) is distinguished from (1) by the opposite configuration of all the asymmetric centers, retrovalinomycin (3) by the reversed direction of acylation, and the so-called "pseudovalinomycin" (5) by the formal replacement of all the amide groups by ester groups and of the ester groups by amide groups. Finally, the analogs (4), (6), (7), and (8) were obtained by a combination of the features mentioned.

The synthesis of the analogs (2)-(8) was effected according to schemes (1)-(5) with the aid of the usual methods employed previously for obtaining a large number of diverse cyclodepsipeptides [8]. The ester bonds were created in the initial stages of the synthesis by the benzenesulfonyl chloride method; the esters formed in this process with yields of 75-80% were oils which were purified by chromatography on alumina. The further extension of the chain and cyclization were effected by the formation of amide bonds by the acid chloride method. The protected linear depsipeptides were isolated with yields of 80-90% in the form of chromatographically homogeneous oils or amorphous powders and did not require further purification. The constants of the intermediate compounds are given in Table 1. The cyclization of the linear dodecadepsipeptides was performed after the elimination of the protective groups under conditions of high dilution, and the final crystalline cyclodepsipeptides were isolated after chromatography on alumina with yields of 20-30%. The structures and individuality of compounds (2)-(8) were shown by thin-layer chromatography on alumina, mass spectrometric measurement of molecular weights, IR and NMR spectroscopy, and elementary analyses. Their antimicrobial activities and some physicochemical properties (complex-formation constants, etc.) are given in Tables 2 and 3; for comparison the analogous characteristics of valinomycin are also given.

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TABLE 1. Constants of Derivatives of Linear Depsipeptides

Compound	mp	$[\alpha]_D^{C_2H_5OH}$, deg	c	Compound	mp	$[\alpha]_D^{C_2H_5OH}$	c
(11)	Amorphous	+ 0,8	0,2	(47)	Amorphous	+19	0,2
(12)	Amorphous	− 4,3	0,2	(48)	101-102°	+20,9	0,2
(13)	Oil	−36,2	0,2	(49)	101-102°	−21,7	0,2
(14)	Amorphous	+ 2,0	0,2	(50)	Amorphous	+ 2,2	0,1
(15)	Amorphous	− 2,7	1,0	(51)	Amorphous	− 2,9	0,2
(16)	Amorphous	− 0,9	0,2	(52)	Amorphous	− 7	0,1
(17)	Amorphous	−18	0,2	(53)	Amorphous	+ 7,5	0,2
(22)	72-73°	+ 4,7	0,2	(54)	Amorphous	+ 3	0,2
(23)	73-74°	− 5,5	1,0	(55)	Amorphous	− 3,4	0,2
(24)	Amorphous	−12,5	0,2	(56)	Amorphous	+ 9,4	0,2
(25)	Amorphous	+11,5	0,2	(57)	Amorphous	− 8,8	0,2
(26)	92-93°	+33,3	0,2	(59)	93-94°	+ 8,4	0,2
(27)	92-93°	−33,3	0,2	(60)	Amorphous	− 3,9	0,2
(28)	Amorphous	+11,3	0,2	(61)	Oil	−26	0,1
(29)	Amorphous	−10,5	0,2	(62)	Amorphous	+ 0,1	0,2
(30)	Amorphous	− 3,4	0,2	(63)	Amorphous	− 0,1	0,2
(31)	Amorphous	+ 3	1,0	(64)	Amorphous	+ 4,9	0,2
(32)	Amorphous	+ 8,5	0,2	(65)	Amorphous	−15,3	0,2
(33)	Amorphous	− 9	1,0	(66)	Oil	− 2,3	0,2
(34)	Amorphous	+10,5	0,2	(67)	Oil	+ 6,7	0,2
(35)	Amorphous	−11,2	0,2	(69)	Oil	− 3,5	2,0
(40)	Oil	−47	2,0	(70)	Amorphous	− 5,2	0,2
(41)	Oil	+45	2,0	(71)	Oil	− 6,1	0,2
(42)	Oil	−35	0,2	(72)	Amorphous	+14,2	0,1
(43)	Oil	+37	0,2	(73)	Amorphous	− 6,5	0,2
(44)	105-106°	+ 5,3	0,2	(74)	Amorphous	− 9,0	0,2
(45)	104-105°	− 5	0,2	(75)	Amorphous	−11,4	0,2
(46)	Amorphous	−18	0,2				

TABLE 2. Antimicrobial Activity of Compounds (1)-(8)

Compound	Minimum concentration inhibiting growth γ/ml												
	Staph. aureus 209P	Staph. aureus, UV-3	Str. faecalis	Sarcina lutea	Bac. mycoides	Bac. subtilis	E. coli	Mycob. phlei	Cand. albicans	Sacch. cereviseae	Botrytis cinereae	Nigrosp. oryzae	Sclerotinia libertiana
(1)	>25	0,7–0,8	0,2–0,3	2	>25	>25	>25	0,3	0,7	0,7	1–1,5	1–1,5	0,8–1
(2)	>25	0,7–0,8	0,2–0,3	2	>25	>25	>25	0,3	0,7	0,7	1–1,5	1–1,5	0,8–1
(3)	>25	>25	>25	>25	>22	>25	>25	>25	>25	>25	>25	>25	>25
(4)	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25
(5)	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
(6)	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
(7)	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25
(8)	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25

TABLE 3. Physicochemical Constants of Compounds (1)-(8)

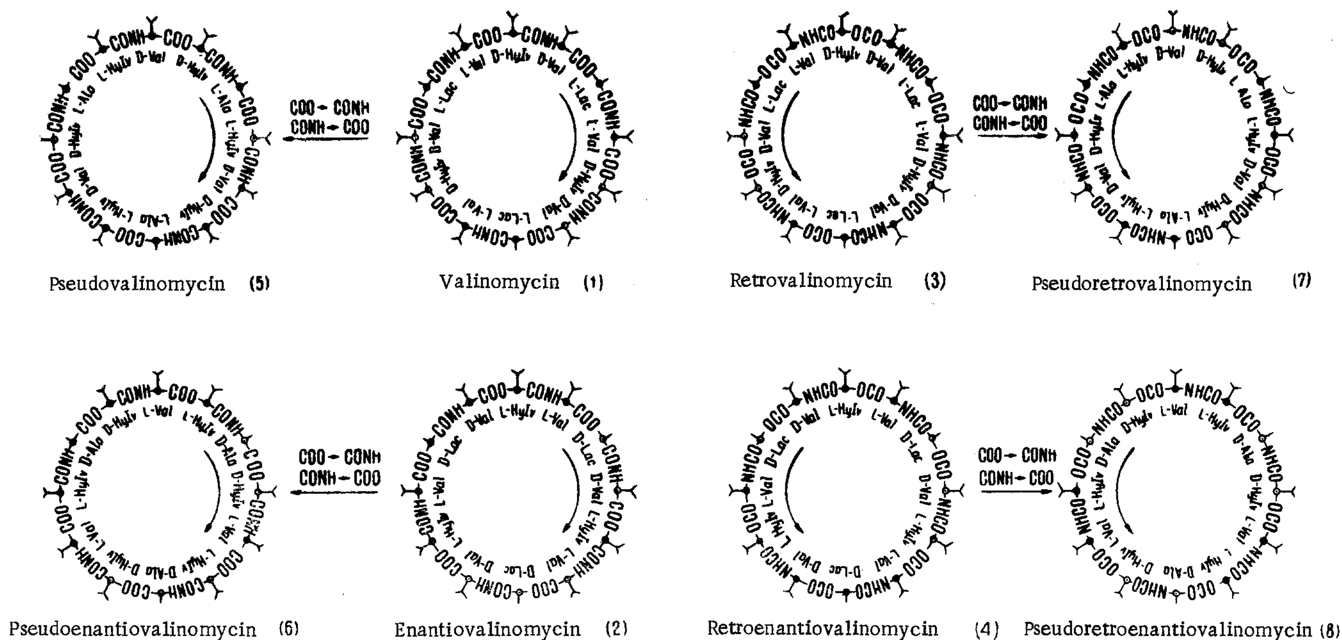
Compound	mp, °C	$[\alpha]_D$, deg	Complex-formation constant† (K·10^{-5} l/mole, KCl, EtOH, 25°C)	R_f‡	Found, %			Formula	Calculated, %		
					C	H	N		C	H	N
(1)	190 [22], 187 [16],	+32,8 (c 1,0; C_6H_6)	20 [1]	0,72				$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(2)	187–188	−30,4 (c 0,2; C_6H_6)	20 [1]	0,72	58,60	8,31	7,57	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(3)	125*, 247–248	+13,0 (c 0,2; C_2H_5OH)	<0,001	0,31	58,29	8,18	7,41	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(4)	125 245–246	−12,5 (c 0,2; C_2H_5OH)	<0,001	0,31	58,21	8,25	7,38	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(5)	278–279	+6,8 (c 0,2; C_2H_5OH)	<0,001	0,32	58,40	8,20	7,56	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(6)	280–281	−6,2 (c 0,2; C_2H_5OH)	<0,001	0,32	58,21	8,23	7,62	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(7)	233–234	−7,6 (c 0,2; C_6H_6)	26	0,71	58,26	8,22	7,60	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56
(8)	233–244	+7,2 (c 0,2; C_6H_6)	26	0,71	58,24	8,19	7,71	$C_{54}H_{90}N_6O_{18}$	58,36	8,16	7,56

*The first figure represents the softening temperature, after which the substance hardened again; the second figure is the melting point.

†The complex-formation constant was determined by the conductometric method [1].

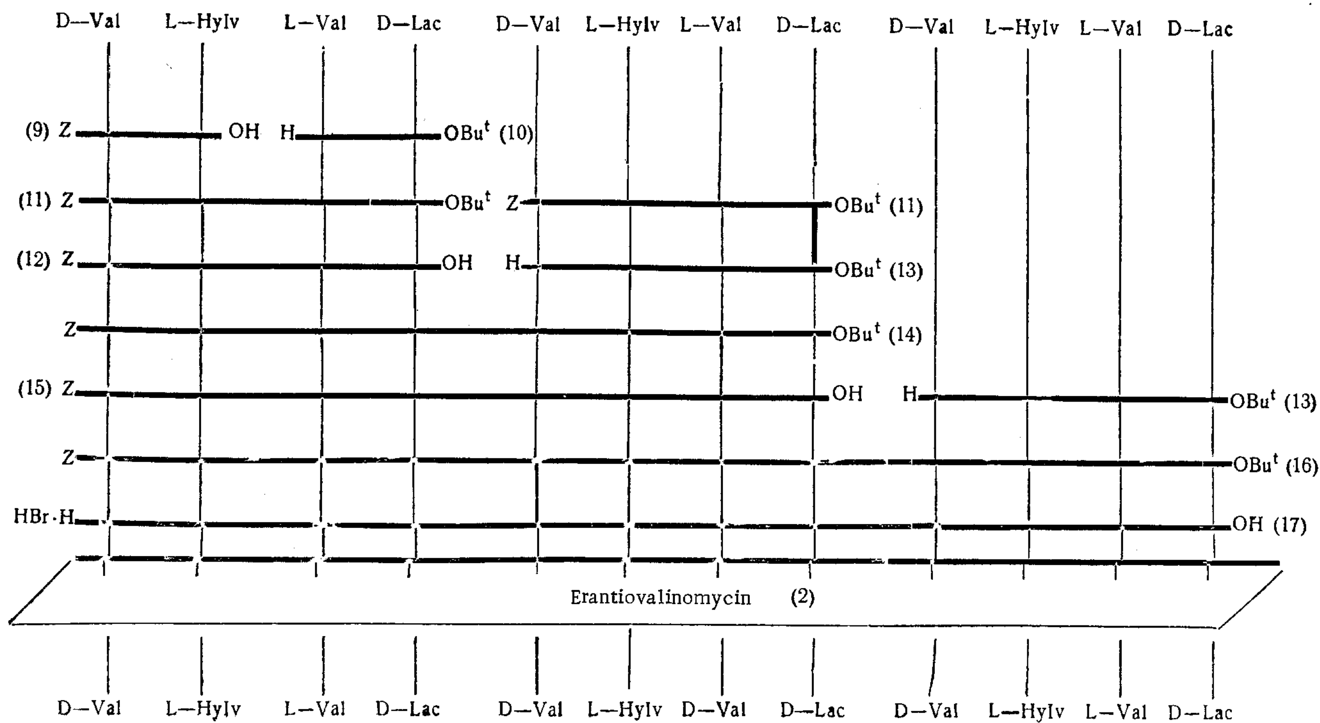
‡Thin-layer chromatography on alumina (activity grade II) in the benzene–ethyl acetate–methanol (40 : 20 : 1) system, mol. wt. 1111.

As can be seen from Table 2, compounds (3), (4), (5), and (6) do not form complexes with Na^+ and K^+ and do not possess antimicrobial activity. Pseudoretrovalinomycin (7) and its antipode (8) also do not



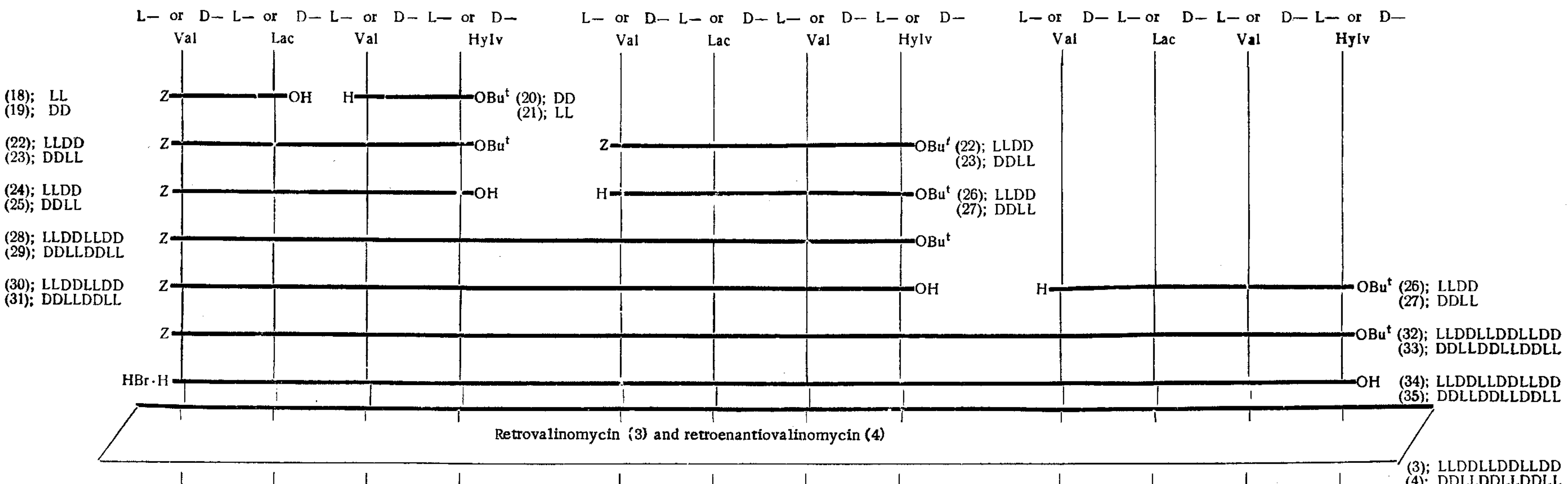
Structure of the antibiotic valinomycin (1) and its topochemical analogs (2)-(8).

Scheme 1

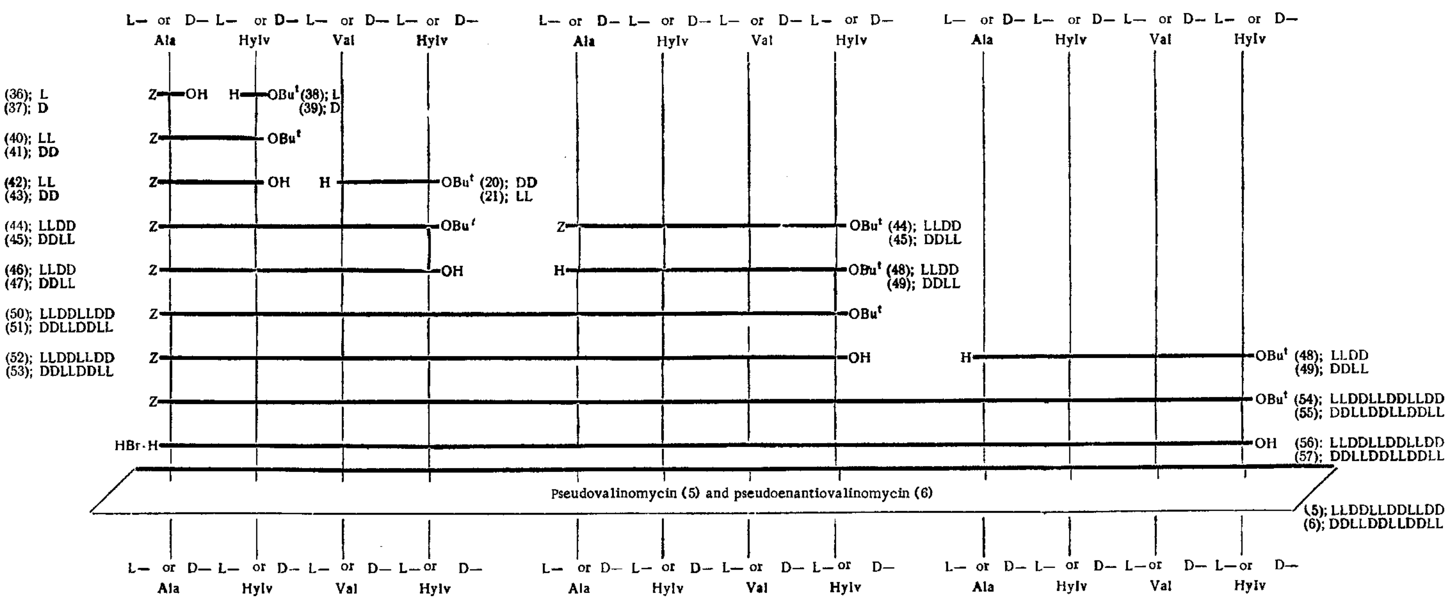


suppress the growth of microorganisms under standard nutritional conditions [9]; however, they form K^+ complexes with stability constants larger than those of valinomycin and any of its known analogs. Because of this, compounds (7) and (8) are of considerable interest from the point of view of studies being carried out at the present time on the relationship between membrane activity, physicochemical properties, and conformations among valinomycin analogs. So far as concerns enantiovalinomycin (2), it, like enantioenniatins A, B, and C [7, 10], does not differ from the initial antibiotic in its physicochemical and biological properties (apart from its optical rotation). This feature of the cyclodepsipeptide antibiotics permits the assumption that their functioning is apparently not determined by their interaction with asymmetric re-

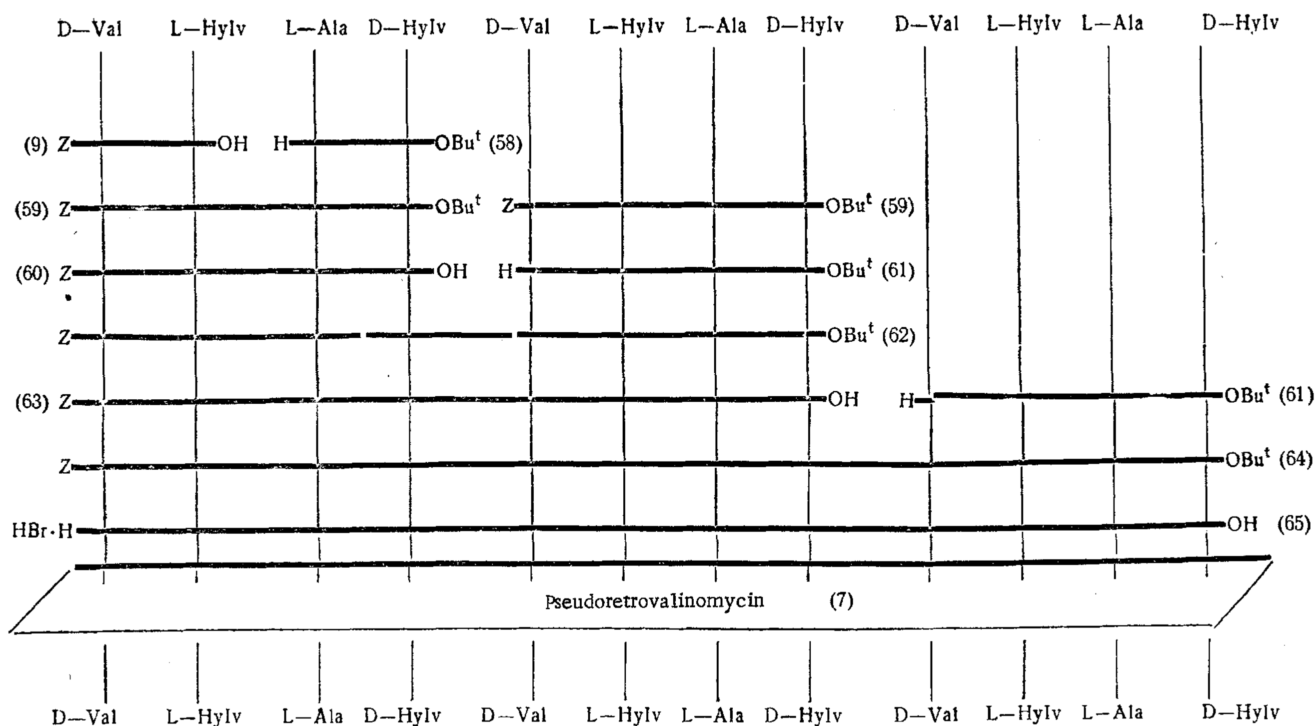
Scheme 2



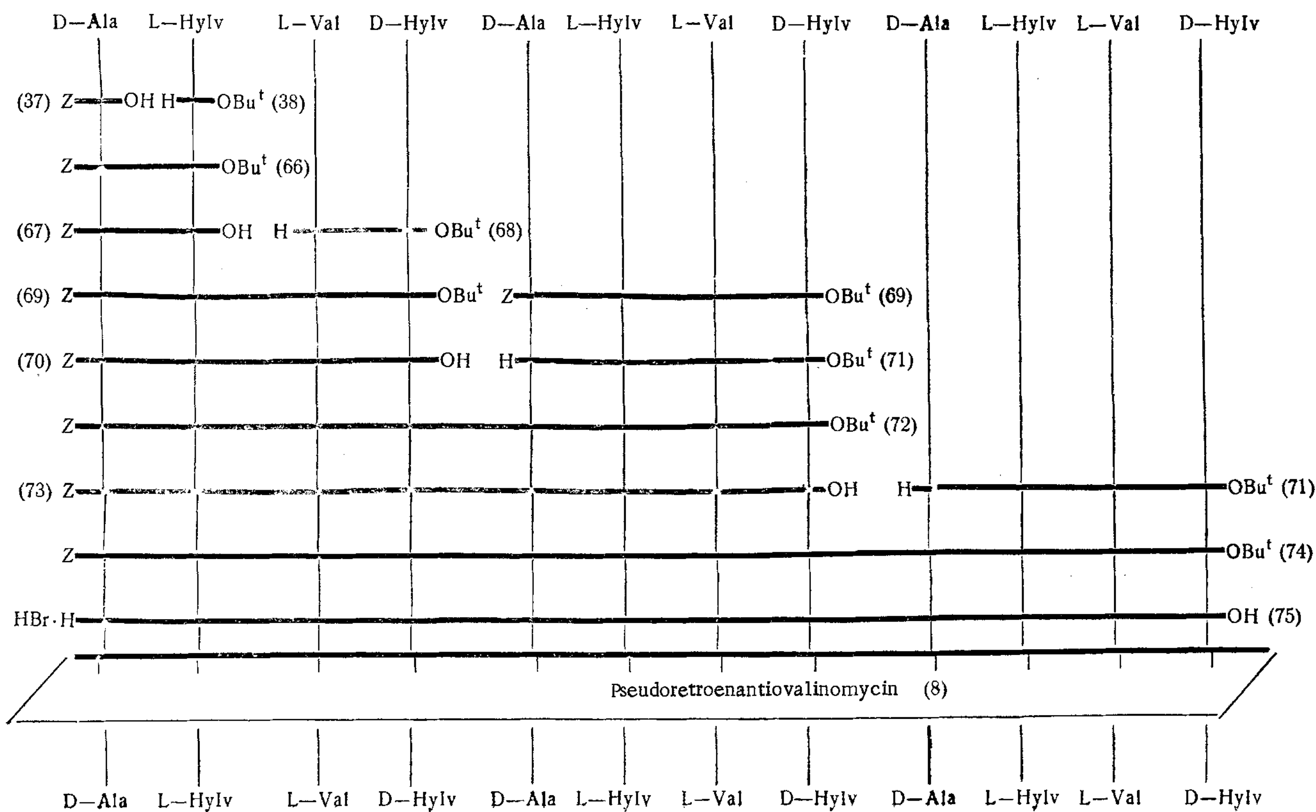
Scheme 3



Scheme 4



Scheme 5



ceptors. In this respect, the membrane-active cyclodepsipeptides differ markedly from other biologically active peptides (for example, oxytocin [11], bradykinin [12], Asn^1-Val^5-angiotensin II [13]) and depsipeptides (actinomycin C_1 [14]) in which the inversion of the configuration of all the centers is accompanied by a complete loss of activity.

In addition to compounds (2)-(8), we have also obtained an analog of valinomycin labeled with ^{15}N in which one of the three L-valine residues has been replaced by [^{15}N]-L-valine. The synthesis was carried out by analogy with the synthesis of valinomycin described previously [15, 16], starting from [^{15}N]-L-valine obtained by the reaction of L-α-bromoisovaleric acid with $^{15}NH_3$. The analog synthesized was used for the assignment of the signals from the L- and D-valine residues in the NMR spectra of valinomycin [1, 2]. More detailed information on the physicochemical investigations of valinomycin and the compounds described in the present paper, together with results of a study of their effect on membranes, will be published in subsequent papers.

EXPERIMENTAL

All the melting points are uncorrected. The individuality of the compounds obtained was checked by thin-layer chromatography on alumina (activity grade II) or silica gel. The elementary analyses of all the compounds agreed with the calculated C, H, and N contents.

[^{15}N]-L-Valine. A mixture of 5.1 mmoles of L-α-bromoisovaleric acid [17] and 33.5 ml of a 0.95 N solution of $^{15}NH_3$ in absolute dioxane was shaken in a sealed tube at room temperature for 9 days. The reaction mixture was evaporated to dryness, the residue was dissolved in water, and the solution was passed through Dowex 50 ×8 resin (H^+ form) which was then washed with water and with 3%, 5%, and 10% aqueous pyridine. The ninhydrin-positive fraction was evaporated to dryness and the residue was reprecipitated from water with acetone, giving 0.2 g (34%) of [^{15}N]-L-valine $[\alpha]^{20}_{213}$ + 1200° (c 0.5; H_2O); for "Reanal" L-valine, $[\alpha]^{20}_{213}$ + 1290° (c 0.5; H_2O).

tert-Butyl Esters of N-Benzyloxycarbonylaminoacyloxy Acids (40), (41), and (66). With stirring (−5°C, 15 min), 80 mmoles of benzylsulfonyl chloride was added to a solution of 80 mmoles of an N-benzyloxycarbonylamino acid (36) or (37) [18] in 80 ml of anhydrous pyridine. After 15 min, a solution of 80 mmoles of a tert-butyl ester of a hydroxy acid (38) or (39) [19] in 40 ml of pyridine was added. The mixture was stirred at 0°C for 2 h and then at 20°C for 12 h and was poured into 400 ml of water and extracted with ether; the extract was washed with 10% HCl, with water, and with saturated $NaHCO_3$ solution, dried with $MgSO_4$, and evaporated in vacuum. The residue was chromatographed on neutral alumina (activity grade II) in the benzene–ethyl acetate system (gradient elution), giving the tert-butyl esters of the N-benzyloxycarbonylaminoacyloxy acids (40), (41), and (66) with a yield of 75-80%.

The N-Benzyloxycarbonylaminoacyloxy Acids (42), (43), and (67). A solution of 40 mmoles of a tert-butyl ester of an N-benzyloxycarbonylaminoacyloxy acid (40), (41), or (66) in 200 ml of absolute benzene was treated with 1.6 g of p-toluenesulfonic acid, and the mixture was boiled for 2 h, cooled, and extracted with saturated $NaHCO_3$ solution. The bicarbonate extract was acidified with 10% HCl and extracted with ether. The ethereal extract was washed with water, dried with $MgSO_4$, and evaporated. The oil obtained was kept at 40°C/0.5 mm for 2 h. This gave the corresponding N-benzyloxycarbonylaminoacyloxy acid (42), (43), or (67) with a yield of 85-90%.

tert-Butyl Esters of the N-Benzyloxycarbonyltetradepsipeptides (11), (22), (23), (44), (45), (59), and (69). A solution of 20 mmoles of a benzyloxycarbonylaminoacyloxy acid (9), (18), (19) [5], (42), (43), or (67) in 12 ml of $SOCl_2$ was kept at 20°C for 40 min and then the excess of $SOCl_2$ was distilled off in vacuum and the residual acid chloride was dissolved in 80 ml of absolute benzene. With stirring and cooling to +5°C, half this solution was added to a solution of 20 mmoles of the corresponding amino ester (10), (58) [5], (20), (21) [20], or (68) [21] and 1.5 ml of dry triethylamine in 60 ml of absolute benzene, and then another 1.5 ml of triethylamine and the second half of the acid chloride solution were added. The reaction mixture was stirred with cooling for 30 min and at 20°C for 3 h, and was washed with 1 N H_2SO_4, water, and saturated $NaHCO_3$ solution and dried with $MgSO_4$, and the solvent was distilled off. This gave the protected tetradepsipeptides (11), (22), (23), (44), (45), (59), and (69) with yields of 80-90%.

N-Benzyloxycarbonyltetradepsipeptides (12), (24), (25), (46), (47), (60), and (70). A solution of 10 mmoles of a protected tetradepsipeptide (11), (22), (23), (44), (45), (59), or (69) in 30 ml of trifluoroacetic acid was kept at 20°C for 40 min, and then the solvent was carefully distilled off in vacuum. The residue was dissolved in ether and the ethereal solution was extracted with saturated $NaHCO_3$ solution. The bicarbonate extracts were acidified with 10% HCl and extracted with ether, and the ethereal extract was dried with $MgSO_4$ and evaporated. This gave the corresponding N-benzyloxycarbonyltetradepsipeptide (12), (24), (25), (46), (47), (60), or (70) in the form of a colorless oil with a yield of 85-90%.

tert-Butyl Esters of Tetradepsipeptides (13), (26), (27), (48), (49), (61), and (71). The hydrogenation of 20 mmoles of the tert-butyl ester of a protected tetradepsipeptide (11), (22), (23), (44), (45), (59), or (69) in solution in 50 ml of methanol was carried out in the presence of a palladium catalyst (from 0.12 g of PdO), a current of hydrogen being passed through the solution for 4 h. The catalyst was filtered off, the solvent was distilled off in vacuum, the residue was dissolved in ether, and the solution was washed with saturated $NaHCO_3$ solution and with water and was then extracted repeatedly with 10% citric acid solution. The combined citric acid extracts were neutralized with sodium bicarbonate, after which the oil that had deposited was extracted with ether and dried with $MgSO_4$. After the solvent had been distilled off, the corresponding amino ester (13), (26), (27), (48), (49), (61), or (71) was obtained with a yield of 70-80%.

The tert-butyl ethers of N-benzyloxycarbonyloxytetradepsipeptides (14), (28), (29), (50), (51), (62), and (72) were isolated from the tert-butyl esters of the tetradepsipeptides (13), (26), (27), (48), (49), (61), and (71), respectively, and the appropriate N-benzyloxycarbonyltetradepsipeptides (12), (24), (25), (46), (47), (60), and (70) by the method described in experiment 4 with yields of 85-90%.

The N-benzyloxycarbonyloctadepsipeptides (15), (30), (31), (52), (53), (63), and (74) were obtained in the amorphous state from the protected octadepsipeptides (14), (28), (29), (50), (51), (62), and (72), respectively, by the method described in experiment 5, with yields of 85-90%.

The tert-butyl esters of N-benzyloxycarbonyldodecadepsipeptides (16), (32), (33), (54), (55), (64), and (74) were obtained in the form of amorphous powders from the acid chlorides of the N-benzyloxycarbonyloctadepsipeptides (15), (30), (31), (52), (53), (63), and (73), respectively, and the appropriate tetradepsipeptide tert-butyl esters (13), (26), (27), (48), (49), (61), and (71) by the method described in experiment 4, with yields of 90-95%.

Dodecadepsipeptide Hydrobromides (17), (34), (35), (56), (57), (65), and (75). A solution of 5 mmoles of a protected dodecadepsipeptide (16), (32), (33), (54), (55), (64), or (74) in 5 ml of glacial acetic acid was treated with 30 ml of a 35% solution of HBr in glacial acetic acid. The solution was left at 20°C for 1 h, the solvent was carefully distilled off in vacuum, and the residue was washed several times with absolute ether and dried in vacuum over P_2O_5. The corresponding hydrobromide (17), (34), (35), (56), (57), (65), or (75) was obtained in the form of an amorphous powder. Yield 85-90%.

Cyclization of the Linear Dodecadepsipeptides. A solution of 3 mmoles of one of the dodecadepsipeptide hydrobromides (17), (34), (35), (56), (57), (65), and (75) in 30 ml of freshly distilled $SOCl_2$ was kept at 20°C for 1 h, and then the excess of $SOCl_2$ was carefully distilled off in vacuum, the residue was treated with 20 ml of absolute benzene, and the solution was again evaporated in vacuum. The residual acid chloride was dissolved in 800 ml of absolute benzene, and the resulting solution was gradually added simultaneously with a solution of 30 mmoles of triethylamine in 800 ml of absolute benzene to 2.5 liters of absolute benzene with continuous stirring (20°C, 12 h). Then the mixture was left for 20 h and was evaporated to a volume of 500 ml. The reaction mixture was washed with 5% HCl, water, and saturated $NaHCO_3$ solution and was dried with $MgSO_4$ and evaporated. The residue was chromatographed on a column of neutral alumina (activity grade III), the cyclodecadepsipeptides (2), (3), (4), (5), (6), (7), and (8) being isolated by gradient elution in the benzene–ethyl acetate system with yields of 20-30%.

SUMMARY

1. The synthesis of seven topochemical analogs of the antibiotic valinomycin has been effected.

2. The complex-formation and antimicrobial properties of the analogs obtained have been studied.

3. The synthesis of valinomycin enriched with the isotope ^{15}N in one L-valine residue has been effected.

LITERATURE CITED

1. M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, E. I. Vinogradova, A. M. Shkrob, G. G. Malenkov, A. V. Evstratov, I. A. Laine, E. I. Melnik, and I. D. Ryabova, J. Membr. Biol., 1, 402, 1969.
2. V. T. Ivanov, I. A. Laine, N. D. Abdulaev, L. B. Senyavina, E. M. Popov, Yu. A. Ovchinnikov, and M. M. Shemyakin, Biochem. Biophys. Res. Communs, 34, 803, 1969.

3. M. Pinkerton, L. K. Steinrauf, and P. Dawkins, Biochem. Biophys. Res. Communs, 35, 512, 1969; M. Ohnishi and D. W. Urry, Biochem. Biophys. Res. Communs, 36, 194, 1969; M. Ohnishi and D. W. Urry, Science, 168, 1091, 1970.
4. B. Pressman and D. H. Haynes, The Molecular Basis of Membrane Function, Ed. D. C. Tosteson, Prentice Hall, Inc. Englewood Cliffs, 1969, p. 221; M. M. Shemyakin, V. K. Antonov, L. D. Bergelson, V. T. Ivanov, G. G. Malenkov, Yu. A. Ovchinnikov, and A. M. Shkrob, The Molecular Basis of Membrane Function, Ed. D. C. Tosteson, Prentice Hall, Inc. Englewood Cliffs, 1969, p. 173.
5. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, Yu. B. Shvetsov, and L. A. Fonina, ZhOKh, 36, 1391, 1966.
6. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, N. F. Loginova, I. D. Ryabova, and I. A. Pavlenko, Exper., 21, 548, 1965; R. B. Merrifield, B. F. Gisin, D. C. Tosteson, and M. Tieffenberg, The Molecular Basis of Membrane Function, Ed. D. C. Tosteson, Prentice Hall, Inc. Englewood Cliffs, 1969, p. 211.
7. M. M. Shemyakin, Yu. A. Ovchinnikov, and V. T. Ivanov, Angew. Chem., 81, 523, 1969.
8. M. M. Shemyakin and Yu. A. Ovchinnikov, Recent Developments in the Chemistry of Natural Carbon Compounds, Eds. R. Bognar, V. Bruckner, and G. Fodor, Vol. 2, Publ. House Hung. Acad. Sci., Budapest, 1967, p. 2.
9. I. I. Mikhaleva, I. D. Ryabova, T. A. Romanova, T. I. Tarasova, V. T. Ivanov, Yu. A. Ovchinnikov, and M. M. Shemyakin, ZhOKh, 38, 1228, 1968.
10. M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, and A. V. Evstratov, Nat., 213, 413, 1967; M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, A. M. Shkrob, I. I. Mikhaleva, A. V. Evstratov, and G. G. Malenkov, Biochem. Biophys. Res. Communs, 29, 834, 1967; Yu. A. Ovchinnikov, V. T. Ivanov, V. K. Antonov, A. M. Shkrob, I. I. Mikhaleva, A. V. Evstratov, G. G. Malenkov, E. I. Melnik, and M. M. Shemyakin, Peptides, Proc. 9th Europ. Symp., North Holland Publ. Co., Amsterdam, 1968, p. 56.
11. G. Flouret and V. du Vigneaud, J. Am. Chem. Soc., 87, 3775, 1965.
12. J. M. Stewart, and D. W. Woolley, Nat., 206, 619, 1965; K. Vogler, P. Lanz, W. Lergier, and W. Haefely, Helv. Chim. Acta, 49, 390, 1966.
13. K. Vogler and R. O. Studer, Helv. Chim. Acta, 48, 1407, 1965; J. Ph. Bonjour and G. Petters, Exper., 26, 517, 1970.
14. H. Brockmann and W. Schramm, Tetrah. Lett., 2331, 1966.
15. M. M. Shemyakin, N. A. Aldanova, E. I. Vinogradova, and M. Yu. Feigina, Izv. AN SSSR, Ser. Khim., 1966, 2143.
16. M. M. Shemyakin, N. A. Aldanova, E. I. Vinogradova, and M. Yu. Feigina, Tetrah. Lett., 1963, 1921.
17. Yu. A. Ovchinnikov, V. T. Ivanov, and A. A. Kiryushkin, Izv. AN SSSR, OKhN, 2046, 1962; E. Fischer and H. Scheibler, Ber., 41, 889, 1908.
18. M. Bergmann and L. Zervas, Ber., 65, 1192, 1932.
19. Pl. A. Plattner, K. Vogler, R. O. Studer, P. Quitt, and W. Keller-Schierlein, Helv. Chim. Acta, 46, 927, 1963.
20. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, Yu. A. Ovchinnikov, and A. A. Kiryushkin, ZhOKh, 34, 1782, 1964.
21. P. Quitt, E. Böhni, and K. Vogler, Mon., 96, 461, 1965.
22. H. Brockmann and G. Schmidt-Kastner. Chem. Ber., 88, 57, 1955.