SYNTHESIS OF ANALOGS OF VALINOMYCIN WITH MODIFIED SIDE CHAINS AND DIFFERENT CONTENTS OF AMIDE AND ESTER GROUPS

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Wide-ranging investigations on both natural and synthetic depsipeptides, especially the antibiotic valinomycin and its analogs, have enabled a series of relationships between their structures and antimicrobial activities to be found [1, 2] and their capacity for the formation of complexes with alkali-metal ions and their influence on ionic transport through biological and artificial membranes to be determined. The conformations of valinomycin and its K^+complex in solution have been established, and information has been obtained which indicates a fundamental role of conformational factors for the exhibition by this cyclodepsipeptide of a capacity for complex formation and of an effect on the ionic permeability of membranes [3]. For a further study of the relationships between structure and function in a series of cyclodepsipeptides of the valinomycin group and to investigate the physicochemical bases of trans-membrane ionic transport, a series of valinomycin analogs has been synthesized (see Table 11), differing from one another by the nature of the hydroxy and amino acid residues and also by their contents of ester and amide linkages.

The synthesis of the depsipeptides was effected by the method developed by us previously [2, 4], which requires the creation first of the ester and then of the amide linkages. Compound XIa was obtained by Scheme 1 and compounds XIb-n by Scheme 2. The ester bonds between the N-protected amino acids and the hydroxy acid esters (apart from those of glycolic acid) were created by the method of mixed anhydrides with benzenesulfonyl chloride. For the synthesis of the glycolic acid esters acylated with acylamino acids, the latter were condensed with esters of bromoacetic acid by boiling in ethyl acetate in the presence of triethylamine [5]. Compound Il was obtained by the methylation of compound Ij (Table 1) with methyl iodide in the presence of silver oxide [6]. To link the protected amino acids or peptides by an amide bond, we used the phosphorazo method, the mixed-anhydride method with esters of chloroformic acid, and the carbodiimide and azide methods. The amide linkage between the C-terminal residues of the hydroxy acids of the N-acyl depsipeptides and the N-terminal amino acid residues of the esters of the peptides or depsipeptides, both in the synthesis of linear compounds and in their cyclization, was created by the acid chloride method [4]. The removal of the tert-butyl protective group was effected by boiling with p-toluenesulfonic acid in benzene or by the action of hydrogen bromide in glacial acetic acid or trifluoroacetic acid, and the benzyloxycarbonyl group was eliminated by hydrogenolysis, and also by the action of hydrogen bromide in glacial acetic acid. The yields and characteristics of all the linear and cyclic compounds synthesized are given in Tables 1-11.

EXPERIMENTAL

The individuality of all the compounds obtained was checked by thin-layer chromatography on alumina or silica. The analyses of all the compounds corresponded to the calculated figures. The molecular weights of all the cyclodepsipeptides were confirmed by mass spectroscopy.

1. Methyl Ester of N-Benzyloxycarbonyl-D-valyl-L-valine and tert-Butyl Ester of N-Benzyloxycarbonyl-L-valyl-D-valine (compounds Ib and c in Table 1). With cooling (−5°C), 1.43 ml (0.015 mole) of ethyl chloroformate was added to a solution of 3.75 g (0.015 mole) of N-benzyloxycarbonyl-D-valine and

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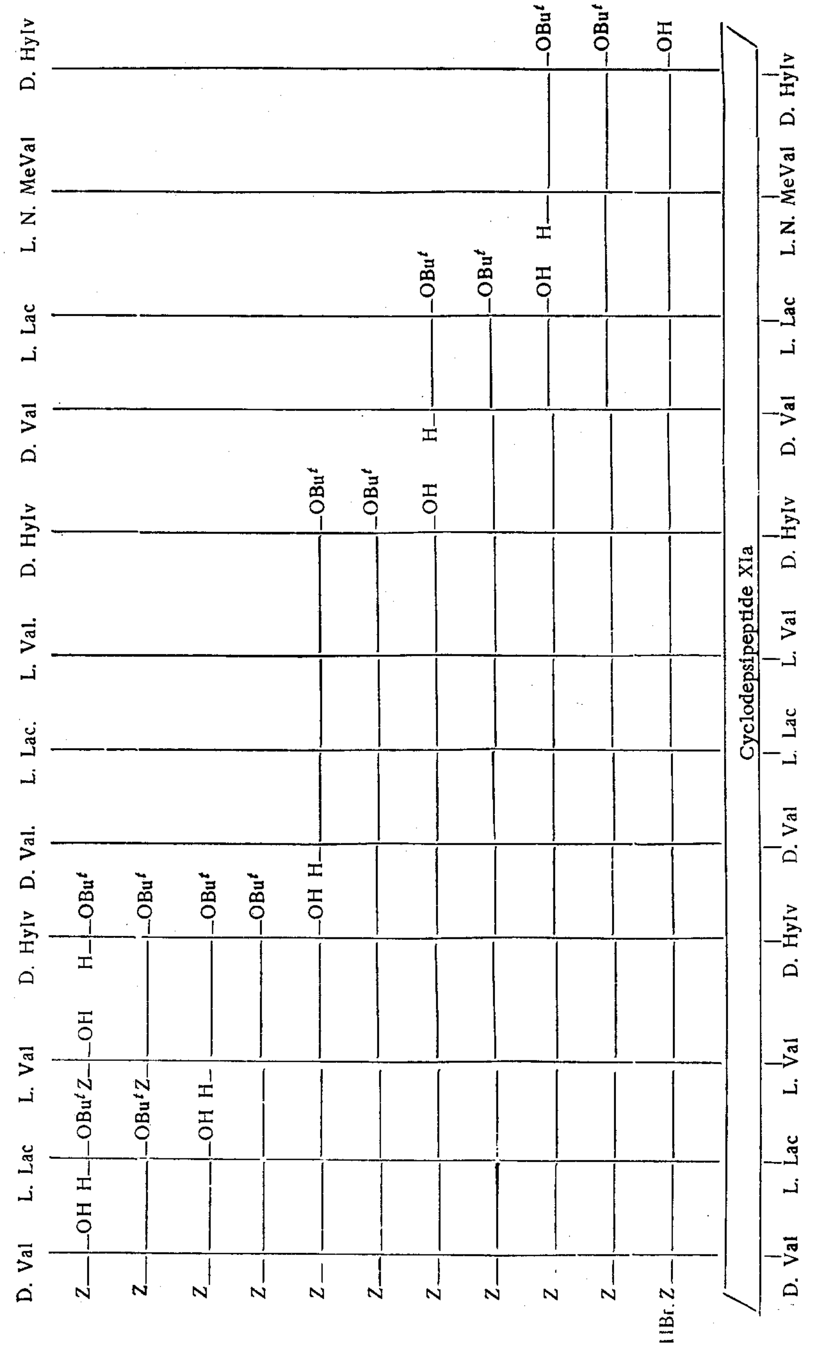
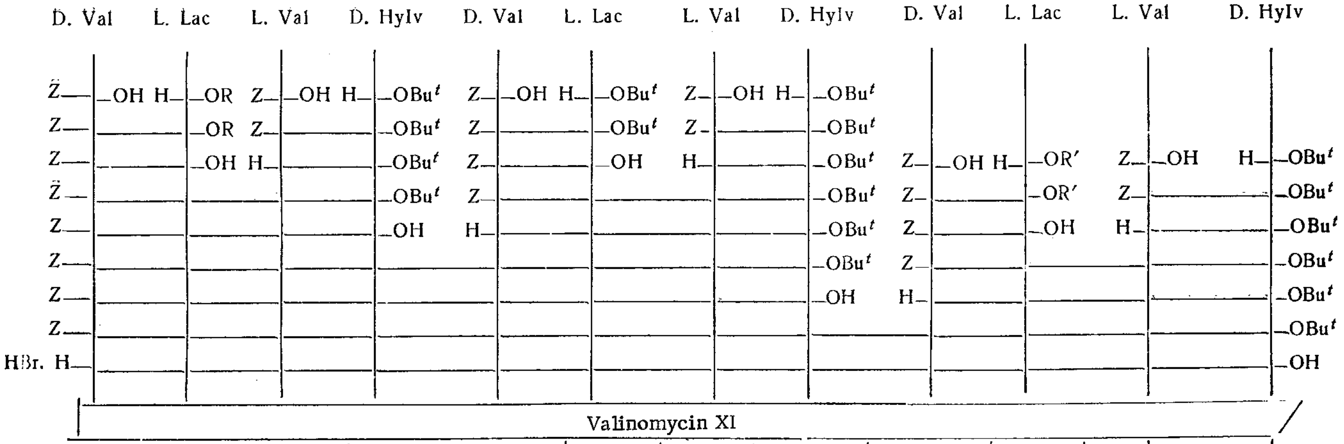
Scheme 1


D. Val
L. Lac
L. Val
D. Hylv
D. Val.
L. Lac.
L. Val.
D. Hylv
D. Val
L. Lac
L. N. MeVal
D. Hylv
Z
—OH H—
—OBu^{t}Z—
—OH
H—
—OBu^t
—OH H—
—OBu^t
—OH
H—
HBr. Z
Cyclodepsipeptide XIa
D. Val
L. Lac
L. Val
D. Hylv
D. Val
L. Lac
L. Val
D. Hylv
D. Val
L. Lac
L.N. MeVal
D. Hylv

Scheme 2



	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIb	D. Val	L. Lac	L. Ala	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIc	D. Val	L. Lac	L. Ala	D. Hylv	D. Val	L. Lac	L. Ala	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XId	D. Ala	L. Lac	L. Val	D. Hylv	D. Ala	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIe	D. Val	L. Lac	L. Ala	D. Hylv	D. Val	L. Lac	L. Ala	D. Hylv	D. Val	L. Lac	L. Ala	D. Hylv
XIf	D. Ala	L. Lac	L. Val	D. Hylv	D. Ala	L. Lac	L. Val	D. Hylv	D. Ala	L. Lac	L. Val	D. Hylv
XIg	D, Val	Glyc	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIh	D. Val	L. Lac	L. Val	Glyc	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIi	D. Val	L. Ala	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIj	D. Val	L. Ala	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Ala	L. Val	D. Hylv
XIk	D. Val	L. Val	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIl	D. Val	Gly	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIm	D. Val	L. Lac	L. Val	D. Val	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv
XIn	D. Val	L. Lac	L. Hylv	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv	D. Val	L. Lac	L. Val	D. Hylv

XIb-h, m, n R $=Bu^t$; XIi-l R $=Me$

XIb–i, k–n R'$=Bu^t$; XIj R'$=Me$

TABLE 1. Methyl and tert-Butyl Esters of N-Benzyloxycarbonyl Derivatives of Dipeptides and of Aminoacyloxy- and Hydroxyacyloxy Acids

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
Ia	Z-D. Val-L. Ala-OCH_3 [7]	90	150 (ethyl acetate – petroleum ether)	–5.4 (c 1; chloroform)
Ib	Z-D. Val-L. Val-OCH_3	78	162-163 (ethanol)	+6 (c 1; benzene)
Ic	Z-L. Val-D. Val-OBu^t	90	162-163 (ethanol)	–14 (c 2; chloroform)
Id	Z-D. Val-Gly-OCH_3 [8]	60	157-158 (ethanol)	+30 (c 1; methanol)
Ie	Z-D. Val-Glyc-OBu^t	84	Oil	+37 (c 0,1; benzene)
If	Z-L. Val-Glyc-OBu^t	82		–34 (c 0,1; benzene)
Ig	Z-D. Val-L. Lac-OBu^t [2]	85	47 (hexane)	–10 (c 2; ethanol)
Ih	Z-L. Ala-D. Hylv-OBu^t [2]	78	Oil	+8 (c 0,1;ethanol)
Ii	Z-D. Ala-L. Lac-OBu^t [2]	80		–15 (c 2; ethanol)
Ij	Z-L. Val-D. Hylv-OBu^t [9]	90		+8,4 (c 2; ethanol)
Ik	Z-L. Hylv-D. Hylv-OBu^t	70		+4,5 (c 2; benzene)
Il	Z-L. N. MeVal-D. Hylv-OBu^t [10]	55		–66 (c 1; ethanol)

2.1 ml (0.015 mole) of triethylamine in 20 ml of dry methylene chloride. After 15 min, a cooled suspension of 2.49 g (0.015 mole) of the hydrochloride of the methyl ester of L-valine and 2.1 ml (0.015 mole) of triethylamine in 10 ml of methylene chloride was added. The mixture was stirred at – 5°C for 0.5 h and at 20°C for 2 h and was then washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, and was dried with magnesium sulfate. After the solvent had been distilled off, compound (Ib) was obtained.

Compound (Ic) was obtained similarly from N-benzyloxycarbonyl-L-valine and the tert-butyl ester of D-valine.

2. Methyl Ester of N-Benzyloxycarbonyl-D-valylglycine (compound Id, Table 1). A suspension of 1.25 g (0.01 mole) of the hydrochloride of the methyl ester of glycine in 50 ml of pyridine cooled to 0°C was treated with 0.436 ml (0.005 mole) of phosphorus trichloride in 5 ml of pyridine; after 20 min, 2.5 g (0.01 mole) of N-benzyloxycarbonyl-D-valine was added and the reaction mixture was kept at 70-75°C for 3 h. Then it was cooled to 20°C, the precipitate that had deposited was filtered off, and the mother solution was evaporated to dryness. The dry crystalline residue was treated with 10% sodium carbonate solution, and the crystals were filtered off, washed with water, dried in vacuum, and recrystallized from ethanol.

3. tert-Butyl N-Benzyloxycarbonyl-D-valylglycolate and tert-Butyl N-Benzyloxycarbonyl-L-valylglycolate (compounds Ie, f, Table 1). A mixture of 1.75 g (0.007 mole) of N-benzyloxycarbonylvaline of the required configuration, 1.4 g (0.007 mole) of tert-butyl bromoacetate, and 1 ml (0.007 mole) of triethylamine in 20 ml of dry ethyl acetate was boiled for 3 h. Then the solution was cooled, washed with 5% hydrochloric acid, with saturated sodium bicarbonate solution, and with water, and was dried with magnesium sulfate and evaporated. The residue was chromatographed on a column of neutral alumina (activity grade III), compound (Ie) or (If) being eluted with a mixture of benzene and ethyl acetate (20 : 1).

4. tert-Butyl Esters of N-Benzyloxycarbonylaminoacyloxy- and -oxyacyloxy Acids (compounds Ig-k, Table 1). With stirring and cooling (0°C, 10 min), 0.02 mole of benzenesulfonyl chloride and, after 15 min, 0.02 mole of the tert-butyl ester of the appropriate hydroxy acid in 15 ml of pyridine were added to a solution of 0.02 mole of a N-benzyloxycarbonylamino or N-benzyloxycarbonyloxy 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 poured into 100 ml of cold water, and the oil that separated out was extracted with ether. The ethereal solution was washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and water, 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 with a mixture of benzene and ethyl acetate (20 : 1) giving compounds (Ig-k).

5. tert-Butyl N-Benzyloxycarbonyl-L-N-methylvalyl-D-α-hydroxyisovalerate (compound Il, Table 1). A solution of 4.09 g (0.01 mole) of tert-butyl-N-benzyloxycarbonyl-L-valyl-D-α-hydroxyvalerate in 300 ml of dimethylformamide was treated with 85 g of silver oxide and 155 ml of methyl iodide. The mixture was stirred for 96 h. Then 100 ml of dimethylformamide was added and, after filtration, the mother solution was treated with 600 ml of chloroform and was washed with a 5% solution of potassium cyanide and with water. Then it was dried with sodium sulfate, the solvent was distilled off, and the residue was chromato-

TABLE 2. N-Benzyloxycarbonyl Derivatives of Dipeptides and Aminoacyloxy Acids

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
II a	Z-D. Val-L. Val-OH [11]	73	179—180 (ethanol)	+24 (c 1; acetic acid)
II b	Z-D. Val-Gly-OH [8]	90	146 (methanol-water)	+21 (c 2; methanol)
II c	Z-D. Ala-L. Lac-OH [2]	78	137 (ethanol)	−6 (c 2; ethanol)
II d	Z-D. Val-L. Lac-OH [2]	80	Oil	+5 (c 1; ethanol)
II e	Z-D. Val-Glyc-OH	82	80 (benzene-hexane)	+40,2 (c 0,1; benzene)
II f	Z-D. Val-L. Ala-NH-NH_2	74	214—217 (methanol)	+29 (c 1; dimethylformamide)

TABLE 3. tert-Butyl Esters of Dipeptides and Aminoacyloxy and Hydroxyacyloxy Acids

No.	Compound	Yield, %	$[\alpha]_D^{20}$
IIIa	H-L. Val-D. Val-OBu^t	70	+23 (c 2; ethanol)
IIIb	H-L. Ala-D. Hylv-OBu^t [2]	78	+43 (c 0.15; ethanol)
IIIc	H-L. Val-Glyc-OBu^t	50	+33,8 (c 0,1; benzene)
IIId	H-L. N. MeVal-D. Hylv-OBu^t [10]	60	+24 (c 1; ethanol)
IIIe	H-L. Val-D. Hylv-OBu^t [9]	75	+40 (c 1,5; benzene)
IIIf	H-D. Val-L. Lac-OBu^t	80	−56 (c 2; ethanol)
IIIg	H-L. Hylv-D. Hylv-OBu^t	55	+35 (c 2; ethanol)

graphed on a column of neutral alumina (activity grade III), compound (II) being eluted with a mixture of benzene and ethyl acetate (20 : 1).

6. N-Benzyloxycarbonyl Derivatives of D-Valine-L-valine and D-Valylglycine (compounds IIa and b, Table 2). At 0-2°C, 10 ml of a 1 N solution of caustic soda was added to a solution of 2.7 g (0.0075 mole) of compound Ib in a mixture of 10 ml of methanol and 60 ml of acetone, and stirring was continued for 1 h. The solution was evaporated to a volume of 10 ml, and the residue was treated with 20 ml of water and extracted with ether. When the aqueous solution was acidified with 10% hydrochloric acid, compound (IIa) precipitated in the form of an oil which rapidly crystallized. The crystals were filtered off, washed with water, dried in vacuum, and recrystallized from ethanol.

Compound (IIb) was obtained similarly from compound (Id).

7. N-Benzyloxycarbonyl-D-valylglycolic Acid (compound IIe, Table 2). A solution of 3.09 g (0.01 mole) of compound (Ie) in 15 ml of trifluoroacetic acid was kept at 25-30°C for 20 min, and the trifluoroacetic acid was carefully distilled off under vacuum at 30-35°C. The residue was dissolved in ether, and the solution was washed with water to a neutral reaction to Congo red and extracted with saturated sodium bicarbonate solution. The bicarbonate extract was acidified with 10% hydrochloric acid and the oil that separated out was extracted with ether. The ethereal solution was washed with water to a neutral reaction to Congo red and was dried with magnesium sulfate. Distillation of the solvent yielded compound (IIe).

8. tert-Butyl Esters of Dipeptides and Aminoacyloxy- and Hydroxyacyloxy Acids (compounds IIIa-g, Table 3). A solution of 0.02 mole of a tert-butyl ester of a N-benzyloxycarbonyldepsipeptide (see Table 1) and 0.02 mole of citric acid in 50 ml of methanol was hydrogenated in a current of hydrogen in the presence of palladium black. After the end of the hydrogenation, the catalyst was filtered off, the solvent was distilled off in vacuum, the residue was dissolved in water, and the solution was extracted with ether and the ethereal extract was re-extracted with 1 N citric acid solution. The citric acid solution was washed with ether, cooled, and neutralized with sodium bicarbonate; the oil that separated out was extracted with ether, and the extract was washed with water and dried with magnesium sulfate. Distillation of the solvent yielded the tert-butyl esters of the corresponding compounds.

9. tert-Butyl Esters of N-Benzyloxycarbonyltetradepsipeptides (compounds IVa-g, Table 4). A solution of 0.01 mole of the appropriate N-benzyloxycarbonylaminoacyloxy acid (see Table 2) in 10 ml of thionyl chloride was kept at 30-35°C for 30 min, and the excess of thionyl chloride was carefully distilled off in

TABLE 4. tert-Butyl Esters of N-Benzyloxycarbonyltetradepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
IVa	Z-D. Val-L. Lac-L. Val-D. Hylv-OBu^t [2]	90	—2,1 (*c* 2; ethanol)
IVb	Z-D. Ala-L. Lac-L. Val-D. Hylv-OBu^t [2]	92	—5 (*c* 1; 5,ethanol)
IVc	Z-D. Val-L. Lac-L. Ala-D. Hylv-OBu^{t}*	88	—5,2 (*c* 0; 2,ethanol)
IVd	Z-D. Val-Glyc-L. Val-D. Hylv-OBu^t	85	+13 (*c* 1,5;benzene)
IVe	Z-D. Val-L. Lac-L. Val-Glyc-OBu^t	85	—17 (*c* 1;benzene)
IVf	Z-D. Val-L. Lac-L. Val-D. Val-OBu^t	80	—11 (*c* 2;chloroform)
IVg	Z-D. Val-L. Lac-L. Hylv-D. Hylv-OBu^t	85	+1,5 (*c* 2;ethanol)
IVh	Z-D. Val-L. Ala-L. Val-D. Hylv-OBu^t	57	—15 (*c* 1;methanol)
IVi	Z-D. Val-L. Val-L. Val-D. Hylv-OBu^t	73	+5 (*c* 1; benzene)
IVj	Z-D. Val-Gly-L. Val-D. Hylv-OBu^t	69	+15 (*c* 2; benzene)

*mp 97-98°C (petroleum ether).

TABLE 5. N-Benzyloxycarbonyltetradepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
Va	Z-D. Val-L. Lac-L. Val-D. Hylv-OH	95	—12 (*c* 1; ethanol)
Vb	Z-D. Ala-L. Lac-L. Val-D. Hylv-OH [2]	87	—14 (*c* 2; ethanol)
Vc	Z-D. Val-L. Lac-L. Ala-D. Hylv-OH*	92	—15 (*c* 0,2; ethanol)
Vd	Z-D. Val-Glyc-L. Val-D. Hylv-OH	84	+17,2 (*c* 1; benzene)
Ve	Z-D. Val-L. Lac-L. Val-Glyc-OH	82	—12 (*c* 1; benzene)
Vf	Z-D. Val-L. Lac-L. Val-D. Val-OH	72	—4 (*c* 2; ethanol)
Vg	Z-D. Val-L. Lac-L. Hylv-D. Hylv-OH	70	—11 (*c* 2; chloroform)
Vh	Z-D. Val-L. Ala-L. Val-D. Hylv-OH	72	—13,2 (*c* 1; ethanol)
Vi	Z-D. Val-L. Val-L. Val-D. Hylv-OH	81	+9 (*c* 1; benzene)
Vj	Z-D. Val-Gly-L. Val-D. Hylv-OH	75	+17 (*c* 1; ethanol)

*mp 64°C (ether).

vacuum. The acid chloride so obtained was dissolved in 40 ml of absolute benzene and, with stirring and cooling (3-5°C), the solution was added dropwise simultaneously with a solution of 0.015 mole of triethylamine in 30 ml of absolute benzene to a solution of 0.01 mole of the 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, saturated sodium bicarbonate solution, and water, and dried with magnesium sulfate, and the solvent was distilled off. The residue was chromatographed on a column of neutral alumina (activity grade III), compounds (IVa-g) being isolated by gradient elution in the benzene–ethyl acetate system.

10. tert-Butyl N-Benzyloxycarbonyl-D-valyl-L-alanyl-L-valyl-D-α-hydroxyisovalerate (compound IVh, Table 4). Hydrazide of N-Benzyloxycarbonyl-D-valyl-L-alanine (compound IIf, Table 2). A solution of 1.67 g (0.005 mole) of the methyl ester of N-benzyloxycarbonyl-D-valyl-L-alanine (compound Ia, Table 1) in 45 ml of methanol was treated with 0.7 ml of hydrazine hydrate, and the mixture was boiled for 3 h and left at 20°C for 24 h. Then it was evaporated to dryness, and the residual hydrazide was boiled with 25 ml of ethyl acetate and the mixture was filtered without cooling. This gave 1.25 g (74%) of the hydrazide of N-benzyloxycarbonyl-D-valyl-L-alanine.

A suspension of the resulting hydrazide in 25 ml of water was treated with 4 ml of 5 N hydrochloric acid, the resulting solution was cooled to −10°C, and to it was added a solution of 0.4 g (0.0053 mole) of sodium nitrite in 20 ml of water. The precipitate of azide that deposited was extracted with ethyl acetate, and the extract was cooled, washed with water and saturated sodium bicarbonate solution, dried with magnesium sulfate, and added to a solution of 1.4 g (0.0053 mole) of tert-butyl L-valyl-D-α-hydroxyisovalerate (compound IIIe, Table 3) in 20 ml of ethyl acetate. The reaction mixture was left at 20°C for 48 h, washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, and dried with magnesium sulfate. The amorphous compound IVh remaining after the solvent had been distilled off was reprecipitated from ethyl acetate with petroleum ether.

11. tert-Butyl Esters of N-Benzyloxycarbonyltetradepsipeptides (compounds IVi, j, Table 4). With ice cooling, 0.57 g (0.0028 mole) of dicyclohexylcarbodiimide was added to a solution of 1 g (0.0028 mole)

TABLE 6. tert-Butyl Esters of Tetradepsipeptides

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
VIa	H-D. Val-L. Lac-L. Val-D. Hylv-OBu^t [2]	72	97 (ether)	−32 (*c* 2; ethanol)
VIb	H-D. Val-L. Lac-L. Ala-D. Hylv-OBu^t	82	92—93 (ether)	—31 (*c* 0,2; ethanol)
VIc	H-D. Ala-L. Lac-L. Val-D. Hylv-OBu^t	74	62—63 (ether)	+16 (*c* 2; benzene)
VId	H-D. Val-L. Ala-L. Val-D. Hylv-OBu^t	80	132—134 (ethyl acet.)	—40 (*c* 1; ethanol)

TABLE 7. tert-Butyl Esters of N-Benzyloxycarbonyloctadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
VIIa	Z-(D. Val-L. Lac-L. Val-D. Hylv)$_2$-OBu^t	90	−1,7 (*c* 2; ethanol)
VIIb	Z-(D. Val-L. Lac-L. Ala-D. Hylv)$_2$-OBu^t	88	−1 (*c* 0,2; ethanol)
VIIc	Z-(D. Ala-L. Lac-L. Val-D. Hylv)$_2$-OBu^t	84	+16 (*c* 1; benzene)
VIId	Z-(D. Val-Glyc-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OBu^t	83	+7 (*c* 1; benzene)
VIIe	Z-(D. Val-L. Lac-L. Val-Glyc) (D. Val-L. Lac-L. Val-D. Hylv)-OBu^t	60	+12 (*c* 1; benzene)
VIIf	Z-(D. Val-L. Ala-L. Val-D. Hylv) (D. Val--L. Lac-L. Val-D. Hylv)-OBu^t	80	—3,5 (*c* 2; ethanol)
VIIg	Z-(D. Val-L. Val-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OBu^t	85	+15 (*c* 1; benzene)
VIIh	Z-(D. Val-Gly-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OBu^t	90	+10 (*c* 1; benzene)
VIIi	Z-(D. Val-L. Lac-L. Val-D. Val) (D. Val-L. Lac-L. Val-D. Hylv)-OBu^t	72	+15 (*c* 2; chloroform)
VIIj	Z-(D. Val-L. Lac-L. Hylv-D. Hylv) (D. Val--L. Lac-L. Val-D. Hylv)-OBu^t	85	—1,7 (*c* 2; chloroform)

TABLE 8. N-Benzyloxycarbonyloctadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
VIIIa	Z-(D. Val-L. Lac-L. Val-D. Hylv)$_2$-OH	85	—1,6 (*c* 0,2; ethanol)
VIIIb	Z-(D. Val-L. Lac-L, Ala-D, Hylv)$_2$-OH	89	−6,4 (*c* 0.2; ethanol)
VIIIc	Z-(D. Ala-L. Lac-L. Val-D. Hylv)$_2$-OH	80	+7 (*c* 1; ethanol)
VIIId	Z-(D. Val-Glyc-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OH	79	+4 (*c* 1; ethanol)
VIIIe	Z-(D. Val-L. Lac-L. Val-Glyc) (D. Val-L. Lac-L. Val-D. Hylv)-OH	75	—6 (*c* 2; benzene)
VIIIf	Z-(D. Val-L. Ala-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OH	82	—11 (*c* 2; ethanol)
VIIIg	Z-(D. Val-L. Val-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OH	80	+13 (*c* 1; benzene)
VIIIh	Z-(D. Val-Gly-L. Val-D. Hylv) (D. Val-L. Lac-L. Val-D. Hylv)-OH	75	+10 (c 1; benzene)
VIIIi	Z-(D. Val-L. Lac-L. Val-D. Val) (D. Val-L. Lac-L, Val-D. Hylv)-OH	80	
VIIIj	Z-(D. Val-L. Lac-L. Hylv-D. Hylv) (D. Val-L. Lac L. Val-D. Hylv)-OH	72	—7 (*c* 2; ethanol)

of N-benzyloxycarbonyl-D-valyl-L-valine (compound IIa, Table 2) and 0.77 g (0.0028 mole) of tert-butyl L-valyl-D-α-hydroxyisovalerate (compound IIIe, Table 3) in 10 ml of tetrahydrofuran. The mixture was kept at 0°C for 30 min and at 20°C for 48 h, the dicyclohexylurea that had separated out was filtered off, and the solvent was evaporated to dryness. The residue was dissolved in ether, and the ethereal solution was washed with 5% hydrochloric acid, with saturated sodium bicarbonate solution and with water, and was dried with magnesium sulfate. The solvent was distilled off and the residue of compound IVi was reprecipitated from ethyl acetate with petroleum ether.

Compound (IVj) was obtained from compounds (IIb) (Table 2) and (IIIe) (Table 3) under similar conditions.

12. N-Benzyloxycarbonyltetradepsipeptides (compounds Va-j, Table 5) were obtained from the corresponding tert-butyl esters of N-benzyloxycarbonyltetradepsipeptides (see Table 4) under the conditions of experiment 7.

TABLE 9. tert-Butyl Esters of N-Benzyloxycarbonyldodecadepsipeptides

No.	Compound	Yield, %	$[\alpha]_D^{20}$, deg
IXa	Z-(D. Val-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. N. MeVal-D. HyIv)-OBu^t	85	—15 (*c* 2; benzene)
IXb	Z-(D. Val-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. Ala-D. HyIv)-OBu^t	93	+2,1 (*c* 0,2; ethanol)
IXc	Z-(D. Val-L. Lac-L. Ala-D. HyIv)$_2$ (D. Val-L. Lac-L. Val-D. HyIv)-OBu^t	90	—11,8 (*c* 0,2; ethanol)
IXd	Z-(D. Ala-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. Val-D. HyIv)-OBu^t	82	+3 (*c* 1; ethanol)
IXe	Z-(D. Val-L. Lac-L. Ala-D. HyIv)$_3$-OBu^t	91	+7,5 (*c* 0,2; ethanol)
IXf	Z-(D. Ala-L. Lac-L. Val-D. HyIv)$_3$-OBu^t	88	+18 (*c* 1; benzene)
IXg	Z-(D. Val-Glyc-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OBu^t	90	+12 (*c* 1; benzene)
IXh	Z-(D. Val-L. Lac-L. Val-Glyc) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OBu^t	85	+17 (*c* 2; benzene)
IXi	Z-(D. Val-L. Ala-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OBu^t	85	+5 (*c* 2; benzene)
IXj	Z-(D. Val-L. Ala-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)-(D. Val-L. Ala-L. Val-D. HyIv)-OBu^t	80	—49 (*c* 1; chloroform)
IXk	Z-(D. Val-L. Val-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OBu^t	90	+14 (*c* 1; benzene)
IXl	Z-(D. Val-Gly-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OBu^t	83	+18 (*c* 1; benzene)
IXm	Z-(D. Val-L. Lac-L. Val-D. Val) (D. Val-L. Lac-L. Val-D. HyIv)$_2$OBu^t	87	—17 (*c* 2; ethanol)
IXn	Z-(D. Val-L. Lac-L. HyIv-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$OBu^t	85	+2 (*c* 2; ethanol)

TABLE 10. Hydrobromides of Dodecadepsipeptides

No	Compound	Yield, %	$[\alpha]_D^{20}$, deg
Xa	HBr. H-(D. Val-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. N. MeVal-D. HyIv)-OH	80	—
Xb	HBr. H-(D. Val-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. Ala-D. HyIv)-OH	79	—18 (*c* 0,2; ethanol)
Xc	HBr. H-(D. Val-L. Lac-L. Ala-D. HyIv)$_2$ (D. Val-L. Lac-L. Val-D. HyIv)-OH	86	+40 (*c* 0,2; ethanol)
Xd	HBr. H-(D. Ala-L. Lac-L. Val-D. HyIv)$_2$ (D. Val-L. Lac-L. Val-D. HyIv)-OH	80	—1,6 (*c* 0,1; chloroform)
Xe	HBr. H-(D. Val-L. Lac-L. Ala-D. HyIv)$_3$-OH	83	—16,7 (*c* 0,2; ethanol)
Xf	HBr. H-(D. Ala-L. Lac-L. Val-D. HyIv)$_3$-OH	78	—8 (*c* 2; ethanol)
Xg	HBr. H-(D. Val-Glyc-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	84	—11,5 (*c* 1; ethanol)
Xh	HBr. H-(D. Val-L. Lac-L. Val-Glyc) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	87	—10 (*c* 1; ethanol)
Xi	HBr. H-(D. Val-L. Ala-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	82	—14 (*c* 2; ethanol)
Xj	HBr. H-(D. Val-L. Ala-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)-(D. Val-L. Ala-L. Val-D. HyIv)-OH	80	—31 (*c* 1; ethanol)
Xk	HBr. H-(D. Val-L. Val-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	85	—
Xl	HBr. H-(D. Val-Gly-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	80	—15 (*c* 1; ethanol)
Xm	HBr. H-(D. Val-L. Lac-L. Val-D. Val) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	85	+4 (*c* 2; ethanol)
Xn	HBr. H-(D. Val-L. Lac-L. HyIv-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)$_2$-OH	86	—15 (*c* 2; ethanol)

TABLE 11. Cyclododecadepsipeptides

No.	Compound	Yield, %	mp, °C	$[\alpha]_D^{20}$, deg
XI	$\overline{\text{(D. Val-L. Lac-L. Val-D. HyIv)}_3}$ [2]			
XIa	$\overline{\text{(D. Val-L. Lac-L. N. MeVal-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	30	142—143 (hexane)	—12 (*c* 1; chloroform)
XIb	$\overline{\text{(D. Val-L. Lac-L. Ala-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	23	152—153 (petroleum ether)	+38 (*c* 0,1; benzene)
XIc	$\overline{\text{(D. Val-L. Lac-L. Ala-D. HyIv)}_2\text{ (D. Val-L. Lac-L. Val-D. HyIv)}}$	36	Amorphous	+2 (*c* 0,1; benzene)
XId	$\overline{\text{(D. Ala-L. Lac-L. Val-D. HyIv)}_2\text{ (D. Val-L. Lac-L. Val-D. HyIv)}}$	20		+3,6 (*c* 0,1; ethanol)
XIe	$\overline{\text{(D. Val-L. Lac-L. Ala-D. HyIv)}_3}$	34		+19 (*c* 0,1; benzene)
XIf	$\overline{\text{(D. Ala-L. Lac-L. Val-D. HyIv)}_3}$	19		+14 (*c* 1; benzene)
XIg	$\overline{\text{(D. Val-Glyc-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	36	159 (petroleum ether)	+31 (*c* 1; benzene)
XIh	$\overline{\text{(D. Val-L. Lac-L. Val-Glyc) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	30	172—173 (petroleum ether)	+24 (*c* 2; benzene)
XIi	$\overline{\text{(D. Val-L. Ala-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	25	192 (petroleum ether)	+40 (*c* 1; ethanol)
XIj	$\overline{\text{(D. Val-L. Ala-L. Val-D. HyIv)}_2\text{ (D. Val-L. Lac-L. Val-D. HyIv)}}$	22	203 (hexane	+5 (*c* 1; chloroform)
XIk	$\overline{\text{(D. Val-L. Val-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	34	203 (hexane)	+26 (*c* 1; ethanol)
XIl	$\overline{\text{(D. Val-Gly-L. Val-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	20	100—101 (hexane)	+43 (*c* 1; benzene)
XIm	$\overline{\text{(D. Val-L. Lac-L. Val-D. Val) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	22	173 (water – ethanol)	+16 (*c* 1; chloroform)
XIn	$\overline{\text{(D. Val-L. Lac-L. HyIv-D. HyIv) (D. Val-L. Lac-L. Val-D. HyIv)}_2}$	30	132 (petroleum ether)	+17 (*c* 1; chloroform)

13. tert-Butyl esters of tetradepsipeptides (compounds VIa-d, Table 6) were obtained by the hydrogenolysis of the corresponding tert-butyl esters of N-benzyloxycarbonyltetradepsipeptides (see Table 4) under the conditions of experiment 8.

14. tert-Butyl esters of N-benzyloxycarbonyloctadepsipeptides (compounds VIIa-j, Table 7) were obtained by condensing the acid chloride derivatives of compounds (Va-j) (see Table 5) with the tert-butyl esters of compounds (VIa-d) (see Table 6) under the conditions of experiment 9.

15. N-Benzyloxycarbonyloctadepsipeptides (compounds VIIIa-j, Table 8) were obtained from the tert-butyl esters of N-benzyloxycarbonyloctadepsipeptides (VIIa-j) (see Table 7) by the method described in experiment 7.

16. tert-Butyl N-benzyloxycarbonyl(D-valyl-L-lactyl-L-valyl-D-α-hydroxyisovaleryl)$_2$-D-valyl-L-lactate (Scheme 1) was obtained in the amorphous state from the acid chloride derivative of compound (VIIIa) (Table 8) and tert-butyl D-valyl-L-lactate (compound IIIf, see Table 3) by the method described in experiment 9. Yield 90%, $[\alpha]_D^{20}$ +8° (c 1; benzene).

17. N-Benzyloxycarbonyl(D-valyl-L-lactyl-L-valyl-D-α-hydroxyisovaleryl)$_2$-D-valyl-L-lactic acid was obtained from the tert-butyl ester of the N-benzyloxycarbonyldecadepsipeptide obtained in experiment 16 under the conditions of experiment 7. Yield 88%, amorphous, $[\alpha]_D^{20}$ +12° (c 1; benzene).

18. tert-Butyl Esters of N-Benzyloxycarbonyldodecadepsipeptides (compounds IXa-n, Table 9). Compound (IXa) was obtained from the acid chloride derivative of the N-benzyloxycarbonyldecadepsipeptide obtained in experiment 17 and the tert-butyl ester (IIId) (see Table 3), and compounds (IXb-n) were obtained from the acid chloride derivatives of the N-benzyloxycarbonyloctadepsipeptides (VIIIa-j) (see Table 8) and the tert-butyl esters of the tetradepsipeptides (VIa-f) (see Table 6) under the conditions of experiment 9, in the amorphous state.

19. Hydrobromides of Dodecadepsipeptides (compounds Xa-n, Table 10). A solution of 0.002 mole of a tert-butyl ester of a N-benzyloxycarbonyldodecadepsipeptide (IXa-n) (see Table 9) in 15 ml of a 30% solution of hydrogen bromide in glacial acetic acid was kept at 20°C for 1 h. The solvent was distilled off, and the residue was washed with absolute ether and dried in vacuum over phosphorus pentoxide. Compounds (IXa-n) were obtained in the amorphous state.

20. Cyclododecadepsipeptides (compounds XIa-n, Table 11). A solution of 0.001 mole of a hydrobromide of a dodecadepsipeptide (Xa-n) (see Table 10) in 10 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 a temperature not exceeding 30°C. The residual acid chloride derivative of a dodecadepsipeptide was dissolved in 300 ml of absolute benzene and, with stirring (20°C, 10 h), was added 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 stirred for another 12 h, the solvent was distilled off, the residue was dissolved in chloroform, and the solution was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water, and was dried with magnesium sulfate. The chloroform was distilled off and the residue was chromatographed on a column of neutral alumina (activity grade III), the cyclodepsipeptide being isolated by gradient elution in the benzene—ethyl acetate system. The process was monitored by means of a Pye gas-liquid chromatograph with an argon ionization detector.

SUMMARY

The synthesis of analogs of valinomycin with individual hydroxy acid and amino acid residues of different types in the molecule and different contents of amide and ester groups has been effected by a method developed previously [2, 4].

LITERATURE CITED

1. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, N. F. Loginova, I. D. Ryabova, and I. A. Pavlenko, Experientia, 21, 548 (1965); M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin, G. L. Zhdanov, and I. D. Ryabova, Experientia, 19, 566 (1963); I. I. Mikhaleva, I. D. Ryabova, T. A. Romanova, T. I. Tarasova, V. T. Ivanov, Yu. A. Ovchinnikov, and M. M. Shemyakin, Zh. Obshch. Khim., 38, 1229 (1968).
2. M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, Yu. B. Shvetsov, and L. A. Fonina, Zh. Obshch. Khim., 36, 1391 (1966).

3. 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. Commun., 29, 834 (1967); M. M. Shemyakin, V. K. Antonov, L. D. Bergelson, V. T. Ivanov, G. G. Malenkov, Yu. A. Ovchinnikov, and A. M. Shkrob, in: The Molecular Basis of Membrane Function (D. C. Tosteson, editor), Prentice-Hall, Inc., Englewood Cliffs, N. J. (1969), p. 173; V. I. Ivanov, I. A. Laine, N. D. Abdulaev, L. B. Senyavina, E. M. Popov, Yu. A. Ovchinnikov, and M. M. Shemyakin, Biochem. Biophys. Res. Commun., 34, 803 (1969); 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. Membrane Biol., 1, 402 (1969).
4. M. M. Shemyakin, N. A. Aldanova, E. I. Vinogradova, and M. Yu. Feigina, Tetrahedron Lett., 1963, 1921; M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, N. A. Aldanova, Yu. A. Ovchinnikov, and A. A. Kiryushkin, Zh. Obshch. Khim., 34, 1782 (1964); M. M. Shemyakin, E. I. Vinogradova, M. Yu. Feigina, and N. A. Aldanova, Zh. Obshch. Khim., 34, 1798 (1964).
5. G. Kupryszewski, Rocz. Chem., 36, 1593 (1962).
6. B. C. Das, S. D. Gero, and E. Ledere, Biochem. Biophys. Res. Commun., 29, 211 (1967).
7. E. I. Vinogradova, V. M. Lipkin, Yu. B. Alakhov, M. Yu. Feigina, and Yu. B. Shvetsov, Zh. Obshch. Khim., 39, 777 (1968).
8. W. Grassman and E. Wünsch, Ber., 91, 449 (1958).
9. R. O. Studer, P. Quitt, E. Böhni, and K. Vogler, Monatsh. Chem., 96, 461 (1963).
10. P. A. Plattner, K. Vogler, R. O. Studer, P. Quitt, and W. Keller-Schierlein, Helv. Chem. Acta, 46, 927 (1963).
11. M. A. Nyman and R. M. Herst, J. Org. Chem., 15, 108 (1950).