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Abstract

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SYNTHESIS OF OPTICALLY ACTIVE DEPSIPEPTIDES

The class of depsipeptides ([1]) includes a great variety of natural compounds—various antibiotics, some alkaloids and proteins, and possibly individual enzymes, etc.

The study of general routes for the synthesis of various types of depsipeptides was begun by us several years ago in connection with the ever-increasing interest attracted by this new class of compounds ([2]). By the present time we have developed general methods for constructing a depsipeptide chain with a regular and irregular arrangement of residues of optically active α-hydroxy and α-amino acids, and have also demonstrated the possibility of cyclizing linear depsipeptides into cyclic ones.

For the synthesis of regularly constructed linear depsipeptides of type (VII), a route was chosen that provides for coupling the appropriately protected residues of α-amino acids (I) and α-hydroxy acids (II) by an ester bond, subsequent removal from the resulting esters (III) of either one (X) or the other (Y) protective group, and then coupling of the resulting fragments (IV) and (V) by an amide bond, with formation of tetradepsipeptides (VI). Further construction of the depsipeptide chain (VII) was carried out by repeated formation only of amide bonds.

$$\underset{\text{(I)}}{XX'NCHRCOOH} + \underset{\text{(II)}}{HOCHRCOY} \rightarrow \underset{\text{(III)}}{XX'NCHRCOOCHRCOY}$$

$$\underset{\text{(IV)}}{XX'NCHRCOOCHRCOOH} \qquad \underset{\text{(V)}}{H_2NCHRCOOCHRCOY}$$

$$\underset{\text{(VI)}}{XX'NCHRCO(OCHRHCONHCHRCO)_{nOCHRCOY}} \leftarrow \underset{\text{(VII)}}{XX'NCHRCO_2CHRCONHCHRCO_2CHRCOY}$$

$X{+}X' = C_6H_4(CO)_2$; $\quad X = H$, $X' =$ Cbo; $\quad Y = OCH_2Ph$ or OCH_2CN

It was found that the carboxyl of the hydroxy-acid component is advantageously protected by a benzyl group removable by hydrogenolysis, and sometimes also by the readily hydrolyzable cyanomethyl grouping. For protection of the amino group of the amino-acid component, the phthaloyl and carbobenzoxy groups proved suitable, since the former can subsequently be removed by boiling with 1 mole of an alcoholic solution of hydrazine hydrate, and the latter by hydrogen bromide in glacial acetic acid under the usual conditions of peptide synthesis; of course, the carbobenzoxy group can also be removed by hydrogenolysis.

Table 1

Compounds of the general formula $HOCHRCOY$ (II)

No.	R	Y	Configuration	b.p., °C (at 10 mm)	n_D^{20}	$[\alpha]_D^{20}$ (EtOH)	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
1	$CHMe_2$	OCH_2Ph	DL	132–134	1.5060		69.57	7.69	69.28	7.74	82
2	$CHMe_2$	OCH_2Ph	D	145–147	1.5060	+15.9	69.72	7.59	69.28	7.74	83
3	$CHMe_2$	OCH_2Ph	L			−16.5					
4	$CHMe_2$	OCH_2CN	DL	129–131	1.4450		53.32	7.23	53.49	7.06	60
5	Me	OCH_2Ph	DL	134–136	1.5145		66.60	6.80	66.66	6.66	55
6	Me	OCH_2Ph	L	134–135	1.5150	−15.4	66.71	6.87	66.60	6.66	60

* The ester was obtained with chloroacetonitrile under the usual conditions.

Table 2

Compounds of the general formula $XX'NCHRCOOCHR'COY$ (III–V)

No.	X and X′	Y	R and R′	Configuration	m.p. or b.p., °C	$[\alpha]_D^{20}$ (EtOH)	Method of preparation	Yield, %	Found, C, %	Found, H, %	Found, N, %	Calculated, C, %	Calculated, H, %	Calculated, N, %	Mol. wt., found	Mol. wt., calc.
1	X = H; X′ = Cbo	OCH$_2$Ph	R = R′ = $CHMe_2$	DL	187–190[1]	+40.5	A	57	68.44	7.15	3.38	68.08	7.08	3.17	337	317

No.	X and X'	Y	R and R'	Configuration	m.p. or b.p., °C	$[\alpha]_D^{20}$ (EtOH)	Method of preparation	Yield, %	Found C, %	Found H, %	Found N, %	Calculated C, %	Calculated H, %	Calculated N, %	Mol. wt., found	Mol. wt., calc.
2	$X = H$; $X' = Cbo$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	195–198[1]	+22.0	A	60	68.05	7.22	3.38	68.08	7.08	3.17	357	317
3	$X = H$; $X' = Cbo$	OH	$R = R' = CHMe_2$	D—	185–188[1]	—	A	74	61.77	7.34	7.48	61.53	7.17	7.17	—	—
4	$X = H$; $X' = Cbo$	OCH$_2$Ph	$R = R' = CHMe_2$	DL	197–200	—	A	60	61.81	6.78	7.48	61.53	6.72	7.17	—	—
5	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	oil	—	A, B, and G	75, 90, and 70	69.01	6.58	3.31	68.63	6.21	3.20	—	—
6	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	85–86[2]	+20.0	B and G	90 and 70	68.89	6.25	3.23	68.63	6.21	3.23	—	—
7	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$	L—	—	−24.5	B and G	—	—	—	—	—	—	—	—	—
8	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$	DL	oil	−5.0	B	95	68.68	8.22	3.20	68.63	6.21	3.23	—	—
9	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$;	DL	oil	—	A and B	60 and 90	67.47	7.75	3.36	67.47	5.66	3.42	—	—
10	$X' = C_6H_4(CO)_2$	OCH$_2$Ph	$R = R' = CHMe_2$;	D—	oil	+22.0	B	97	67.56	5.77	3.52	67.47	5.66	3.42	—	—
11	$X' = H$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	oil	—	NH_3/MeOH	70	NH_2	66.50	8.10	4.55	66.42	8.49	4.55	—	—
12	$X' = H$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	oil	+23.0	NH_2NH_2/MeOH	80	NH_2	66.53	8.25	4.75	66.42	8.19	4.55	—	—
13	$X' = H$	OCH$_2$Ph	$R = R' = CHMe_2$	D—	—	—	HBr/AcOH	50	—	—	—	—	—	—	—	—
14	$X' = H$	OCH$_2$Ph	$R = R' = CHMe_2$	L—	oil	−20.0	NH_3/MeOH	71	NH_2	66.71	8.05	4.49	66.20	8.20	4.55	337	317

No.	X and X'	Y	R and R'	Configuration	m.p. or b.p., °C	$[\alpha]_D^{20}$ (EtOH)	Method of preparation	Yield, %	Found C, %	Found H, %	Found N, %	Calculated C, %	Calculated H, %	Calculated N, %	Mol. wt., found	Mol. wt., calc.
15	$X = OCH_2C_6H_5$; $X' = H$		$R = L$; $R' = DCHMe_2$	oil		+43.0	NH_2NH_2	95	62.30	6.20	4.23	62.23	6.09	4.03	357	317
16	$X = OH$; $X' = C_6H_4(COOH)_2$		$R = D$; $R' = DCHMe_2$	amorph.		+2.0	Pd/C	92	62.31	6.20	4.00	62.23	6.09	4.03	—	—
17	$X = OH$; $X' = C_6H_4(COOH)_2$		$R = D$; $R' = DCHMe_2$	amorph.		+20.9	Pd/C	—	—	—	—	—	—	—	—	—
18	$X = OH$; $X' = C_6H_4(COOH)_2$		$R = L$; $R' = LCHMe_2$	—		−21.5	Pd/C	—	—	—	—	—	—	—	—	—
19	$X = OH$; $X' = C_6H_4(COOH)_2$		$R = DCHMe_2$; $R' = LCHMe_2$	140-141		+29.0	Pd/C	71	60.12	5.44	4.50	60.19	5.36	4.39	311	319
20	$X = OH$; $X' = H$		$R = DL$; $R' = CHMe_2$	140-141[2]		—	Pd/C	73	55.22	8.54	6.57	55.27	8.81	6.44	216	217
21	$X = OH$; $X' = H$		$R = D$; $R' = DCHMe_2$	141-142[2]		+22.0	Pd/C	70	55.46	8.95	6.71	55.27	8.81	6.44	216	217
22	$X = OH$; $X' = H$		$R = D$; $R' = LCHMe_2$	oil		−20.0	Pd/C	—	—	—	—	—	—	—	—	—
23	$X = OH$; $X' = H$		$R = DCHMe_2$; $R' = LCHMeEt$	130-131[2]		−50.0	Pd/C	85	50.84	7.75	7.35	50.78	7.98	7.40	182	189

[1] b.p. at $3 \cdot 10^{-2}$ mm.

[2] m.p. determined after recrystallization from a mixture of ether and ligroin.

The formation of an ester bond in the synthesis of compounds of type (III) proceeds rather with difficulty if the hydroxyl group of the α-hydroxy acid component is secondary, as is the case in most natural depsipeptides. In these cases, many of the frequently used methods for acylating alcohols cannot be employed, and, in order to create the ester bond, strong activation of the carboxyl group of the acylating amino-acid component is necessary; this is achieved by converting it into a mixed anhydride or an acid chloride. Sometimes activation of the hydroxyl group of the α-hydroxy acid component is also necessary, for example,

Linear and cyclic depsipeptides

Table 3

No.	X and X′	Y	R and R′	Configuration	Aggregation state	$[\alpha]_D^{20}$ (c; EtOH)	Method of preparation	Yield, %	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Mol. wt. (titration) found	Mol. wt. (titration) calc.
1	$X+X'=C_6H_4(COCl)_2$	OCH_2CHMe_2	$R=CHMe_2$; $R'=CH_2Ph$	D—D—D—	T. pl. 95°	+24.0	D	85	66.38	6.71	4.35	66.02	6.92	4.40	548	
2	»	»	»	L—L—L—		−24.3									548	
3	$X+X'=C_6H_4(COCl)_2$	OCH_2CHMe_2	$R=CHMe_2$; $R'=CH_2Ph$	D—L—D—	Oil	+20.0	D and Zh	98 and 50	64.89	6.64	4.58	65.11	6.62	4.60		
4	$X=H$; $X'=Cbo$	OCH_2CHMe_2	$R=CHMe_2$; $R'=Me$	D—D—D—		+11.0	E	70	63.95	6.40	—	65.10	6.55	—	518	
5	$X=H$; $X'=H$	OCH_2CHMe_2	$R=CHMe_2$; $R'=CH_2Ph$	D—D—D—		+54.5	NH_2	NH_2	63.86	8.48	5.81	64.01	8.35	5.53	416	
6	»	»	»	L—L—L—		−57.0									416	
7	$X=H$; $X'=H$	OCH_2CHMe_2	$R=CHMe_2$; $R'=Me$	D—L—D—	Oil	−9.0	NH_2	NH_2	62.76	7.95	5.85	62.76	8.04	5.85		
8	$X+X'=C_6H_4(COCl)_2$	OH	$R=CHMe_2$; $R'=Me$	D—D—D—	Amorph.	+41.0	Pd/C	90	61.60	7.01	5.40	61.71	7.04	5.40	520	
9	$X+X'=C_6H_4(COCl)_2$	OH	$R=CHMe_2$; $R'=Me$	D—L—D—	»	+10.0	Pd/C	82	60.21	6.72	5.18	60.20	6.60	5.18	520	

No.	X and X′ Y	R and R′	Configuration	Aggregation state	$[\alpha]_D^{20}$ (EtOH)	Method of preparation	Yield, %	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Mol. wt. (titration) found	Mol. wt. (titration) calc.
10	X = OH X′ = H	R = D– CHMe2; R′ = CHMe2	»	»	+59.0	Pd/C	90	57.93	8.72	6.74	57.67	8.72	6.73	422	
11	» OH	»	D L– L– L– L	»	−55.8									422	
12	X = OH X′ = H	R = D– CHMe2; R′ = Me	L– D	Amorphous	+40.8	Pd/C	74	55.43	8.29	7.38	55.63	8.33	7.21	400	388
13	X = OCH2Ph X′ = C6H4(CO)2	R = DL	DL	Amorphous	+57.3	D	98	63.30	7.29	5.40	63.80	7.60	5.40		
14	X = OCH2Ph X′ = C6H4(CO)2	R = [D– CHMe2; R′ = Me	D– D]2	»	+13.0	D	90	64.56	6.65	5.43	62.80	6.60	5.43		
15	X = OCH2Ph X′ = C6H4(CO)2	R = [D– CHMe2; R′ = Me	L– D]2	Amorphous	+13.0	D	97	62.90	7.00	5.45	62.56	7.21	5.72		
16	X = OCH2Ph H; X′ = Cbo	R = D– CHMe2; R′ = CHMe2	D– D	Oil	+51.0	E	84	66.44	6.63	5.20	66.65	7.46	5.18	303	316
17	X = OH X′ = H	R = D– CHMe2; R′ = CHMe2	D– D	Amorphous	+37.0	Pd/C	80	55.26	8.93		55.92	8.92			
18		R = [D– CHMe2	D– D]	Amorphous	+88.8	D	45	60.88	7.72	6.79	60.27	8.60	7.03	430	398

[1] To combine compound No. 10 with its optically inactive racemate, 2 mol of NaOH is insufficient; only one ester bond is split, with formation of valine and oxyisovaleric-valyl-oxyisovaleric acid. Under analogous conditions, compound No. 21 (Table 2), recrystallized from alcohol, gives mainly dioxane. Determined by the isothermal distillation method in dioxane.

by obtaining magnesium haloalcoholates. The ester bond was created by us by acylating the hydroxyl group of the hydroxy-acid components (II) with mixed anhydrides obtained from *N*-acylamino acids (I) by the action of benzenesulfochloride in an excess of pyridine (2 hours, 0°; method A), with anhydrides of *N*-acylamino acids in the presence of sulfuric acid (boiling for 2 hours in absolute benzene or ether; method B), with acid chlorides of *N*-acylamino acids in the presence of equimolecular amounts of pyridine (in absolute benzene or ether, 2 hours at 0°; method C), and also by the action of these same

acid chlorides into magnesium halide alcoholates, obtained by the action of EtMgBr on (II) in anhydrous ether (0°, then boiling for 2 hours; method G)*.

As hydroxy-acid components (II), chiefly benzyl esters of racemic and optically active α-hydroxyisovaleric** and lactic acids were used, obtained by passing HCl through solutions of the acids in anhydrous benzyl alcohol; the constants of the synthesized esters and the yields are given in Table 1. As amino-acid components (I), racemic and optically active phthaloylvalines, carbobenzoxyvalines, and anhydrides and acid chlorides of phthaloylvalines*** were used. The constants and yields of synthesized esters of type (III), as well as compounds of types (IV) and (V), obtained by removing one or both protecting groups from esters (III) by the methods indicated above, are given in Table 2.

To prove the optical purity of compounds of types (III)–(V), their protecting groups were removed, and the resulting esters with free carboxyl and amino groups were subjected to acid hydrolysis, followed by isolation of optically active α-amino and α-hydroxy acids, the optical purity of which was additionally checked with the aid of the corresponding enzymes (D-amino acid oxidase, dehydrogenase).

For joining fragments (IV) and (V) by an amide bond, the acid-chloride method (D) was used, carried out with Et_3N or pyridine, the mixed-anhydride method (E), using $ClCO_2Et$, and the azide method (Zh). In all cases the reactions were conducted under the usual conditions of peptide synthesis. The characteristics and yields of the synthesized substituted tetradepsipeptides, as well as tetradepsipeptides with free amino and carboxyl groups obtained after removal of the protecting groups, are given in Table 3. The optical purity of the latter was established by their partial alkaline hydrolysis, leading to selective cleavage of ester bonds and formation of compounds of the type HOCHRCONHCHRCOOH, from which substituted morpholines were obtained by thermal cyclization. On the other hand, complete acid hydrolysis followed by determination of the optical purity of the amino and hydroxy acids (see above) also confirmed the absence of noticeable racemization during the synthesis of tetradepsipeptides. In a manner analogous to the preparation of tetradepsipeptides (VI), the conversion of the latter into octadepsipeptides (VII; $n = 3$) was carried out; their characteristics and yields are given in Table 3. In the latter table, as an example, one tridepsipeptide of irregular structure is also given (VIII; $X = X' = H$; $Y = OH$), synthesized from carbobenzoxyvaline and the benzyl ester of valyloxyisovaleric acid, followed by hydrogenolysis.

Cyclization of linear depsipeptides was studied in greatest detail on the example of the D-D-D-D tetradepsipeptide (VI; $X = X' = H$; $Y = OH$; $R = R' = CHMe_2$) using the acid-chloride method (0°, anhydrous benzene, Et_3N, dilution 0.001 M/l); for the characteristics of the cyclotetradepsipeptide obtained, see Table 3.

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2. M. M. Shemyakin, *Angew. Chem.*, **72**, 342 (1960).

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* In obtaining optically active compounds of type (III) from phthaloylamino acids, method A should not be used, since it leads to racemization.
** D- and L-hydroxyisovaleric acids were obtained in yields of 75–80% with the aid of L- and D-*threo*-1-(p-nitrophenyl)-2-amino-1,3-propanediol.
*** The anhydride of D-phthaloylvaline was obtained with the aid of dicyclohexylcarbodiimide, m.p. 101–102°, and the acid chloride was obtained by the action of $SOCl_2$, m.p. 120–122°. $[\alpha]^{20} + 88.5°$ (c 1 in $CHCl_3$).

Note: Figure translations are in progress. See original paper for figures.