The Chemistry of Natural Depsipeptides

by
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and
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AKADÉMIAI KIADÓ, BUDAPEST

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M. M. SHEMYAKIN

AND

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THE CHEMISTRY OF NATURAL DEPSIPEPTIDES

Depsipeptides constitute a large and rapidly expanding class of peptide-related compounds, which are built up of hydroxy and amino acid residues joined by amide and ester linkages. Various members of this class are quite frequently encountered among natural products, particularly in substances of microbiological origin. Most of these are cyclodepsipeptides with considerably varying ring size up to 36-membered cyclododecadepsipeptides. Many of the naturally occurring depsipeptides are biologically active. These include an appreciable number of antibiotics, some alkaloids, and, apparently, certain proteins.

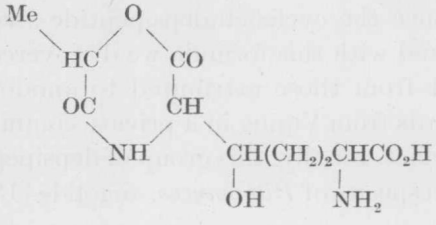
In the past years we devised general methods for the synthesis of optically active linear and cyclic depsipeptides with any desired sequence of the amino acid and hydroxy acid residues. Simultaneously we studied some of their properties, including the stereochemical aspects of their ring closure. Furthermore, new methods for their structural study were developed, among which the mass spectrometric approach deserves special mention.

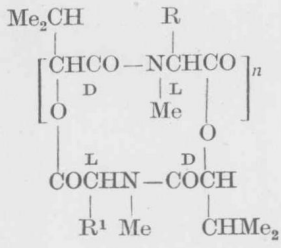
All these studies led to the syntheses in 1962–64 of a number of naturally occurring depsipeptides; in the course of this work it was discovered that formulae proposed for some of them had been erroneous and these were corrected. Parallelly, work was begun on the relations between chemical constitution and physiological action of antibiotic depsipeptides. Probable biogenetic pathways to a number of these compounds were also outlined.

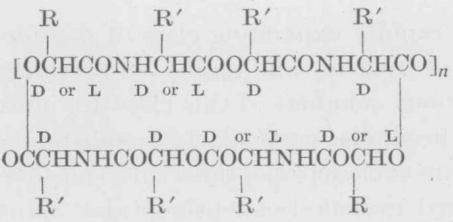
*

The naturally occurring depsipeptides known at present may be divided into a number of groups.

I. Woolley's toxin (1955)







Enniatin A

II. R = R¹ = CHMeEt, $n = 1$; Plattner et al. (1947–48)

III. R = R¹ = CHMeEt, $n = 2$; Shemyakin et al. (1963); Vogler et al. (1963)

Enniatin B

IV. R = R¹ = $CHMe_2$, $n = 1$; Plattner et al. (1947–48)

V. R = R¹ = $CHMe_2$, $n = 2$; Shemyakin et al. (1963); Plattner, Vogler et al. (1963)

Valinomycin

VI. R = CH_3, R′ = $CHMe_2$, $n = 1$; Brockmann et al. (1955–57)

VII. R = CH_3, R′ = $CHMe_2$, $n = 2$; Shemyakin et al. (1963)

Amidomycin

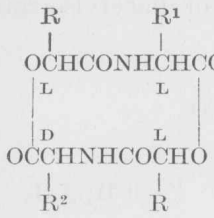
VIII. R = R′ = $CHMe_2$, $n = 1$, Vining, Taber (1957)

Formula VIII is wrong; Shemyakin et al. (1963)

Amidomycin is an artefact; Vining (1963)

To the first group belong cyclodepsipeptides with regularly alternating α-amino and α-hydroxy acid residues. The simplest of these is Woolley's phytopathogenic toxin [191] with the cyclodidepsipeptide formula (I). Here also belong two antibiotics, namely enniatin A and enniatin B, to which Plattner [45, 90–94] had ascribed a cyclotetradepsipeptide structure (II and IV), but which we [152–155] and simultaneously Plattner–Vogler's team [95, 96, 100, 101] have recently shown to be the cyclohexadepsipeptides (III and V). Latterly, mass spectrometric studies have revealed the existence in naturally occurring enniatin mixtures of a "mixed" type of enniatins, in particular enniatin A_1 (R = CHMeEt, R¹ = $CHMe_2$, $n = 2$) and B_1 (R = $CHMe_2$, R¹ = CHMeEt, $n = 2$) [62]. The group further includes the antibiotic valinomycin for which Brockmann had proposed the structure of the cyclooctadepsipeptide (VI) [24, 32], whereas it is actually the cyclododecadepsipeptide (VII) [35], as we have directly shown by its synthesis [130, 131]. Research in this group of compounds was not without its comic turns. For instance with amidomycin, Vining and Taber [170, 171, 183] had suggested for this substance the cyclooctadepsipeptide structure (VIII). On synthesizing the compound with this formula we discovered that it had properties entirely different from those attributed to amidomycin [158, 159], only to find out afterwards from Vining in a private communication that this compound was an artefact. Finally, this group of depsipeptides. includes also a metabolite of certain species of *Pithomyces*, angolide [13, 103]

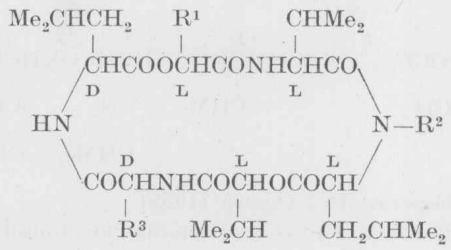
This compound is a cyclotetradepsipeptide, its structure (IX) being elucidated by Russell [106] and confirmed mass spectrometrically both by us [60, 61] and by Shannon [74], and then through its total synthesis [61].



Angolide

IX. $R = CHMe_2$, $R^1 = CHMeEt$
$R^2 = CHMeEt$-*allo*
Russell (1965)
Shemyakin (1964)

To the second group of depsipeptides belong substances with irregular amino acid and hydroxy acid sequences. This group contains compounds with both α- and β-hydroxy acid residues. Among its members there are four cyclohexadepsipeptides, sporidesmolides I, II, III and IV, biologically inactive metabolites isolated by Russell from the fungus *Pithomyces chartarum* and *Pithomyces maydicus* [11, 14, 104, 105, 107]. To sporidesmolide I Russell assigned the formula X, whose validity we demonstrated soon after by direct synthesis [82, 142, 145, 146]. In the case of sporidesmolide II, Russell who had proposed the structure XI, did not elucidate the stereoisomerism of the isoleucine residue. We found it to be *allo*isoleucine, so that the final structure is represented by XII as we confirmed it by the synthesis of sporidesmolide II [89, 143, 146]. The structure of sporidesmolide III (XIII) was elucidated by Russell and Shannon mass spectrometrically [108] and confirmed by us synthetically [58]. Russell also established the formula of sporidesmolide IV (XIV) [13, 14], whose total synthesis we carried out [59].



Sporidesmolide I

X. $R^1 = R^3 = CHMe_2$, $R^2 = Me$;
Russell (1960); Shemyakin et al. (1962)

Sporidesmolide II

XI. $R^1 = CHMe_2$, $R^2 = Me$, $R^3 =$
$=$ CHMeEt; Russell (1960)

XII. $R^1 = CHMe_2$, $R^2 = Me$, $R^3 =$
CHMeEt-*allo*; Shemyakin et al. (1963)

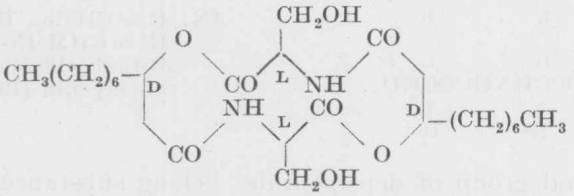
Sporidesmolide III

XIII. $R^1 = R^3 = CHMe_2$, $R^2 = H$;
Russell (1964); Shemyakin et al. (1965)

Sporidesmolide IV

XIV. $R^1 = CH_2CHMe_2$, $R^2 = Me$, $R^3 =$
$CHMe_2$; Russell (1964); Ovchinnikov et al. (1965)

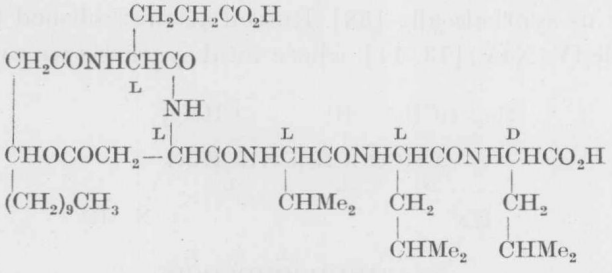
To this group of depsipeptides, but containing β-hydroxy acid residues, belong two antibiotics, serratamolide and esperin. For the former Wasserman [187] proposed the structure of a cyclotetradepsipeptide (XV), which we have recently confirmed by the synthesis of diacetylserratamolide [139, 140] and serratamolide itself [5, 63].



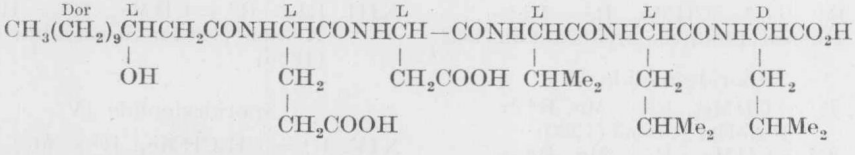
Serratamolide

XV. Wasserman et al. (1961)
Shemyakin et al. (1964-1965)

As for esperin Ito and Ogawa [54] formulated its structure (XVI), leaving open the question of the configuration of the hydroxy acid residue. On subjecting esperin to alkaline hydrolysis, they isolated esperinic acid (XVII). We synthesized two stereoisomers corresponding to this formula, one containing L- and the other D-β-hydroxytridecanoic acid. However, both stereoisomers differed considerably from esperinic acid, which thus places questionable the correctness of the formula (XVI) proposed for esperin [85].

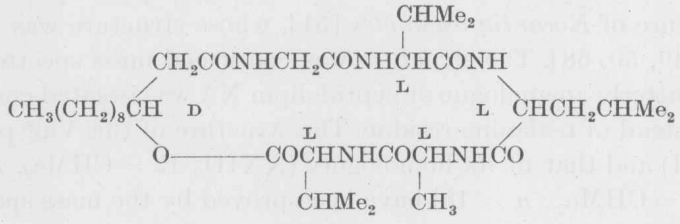


XVI. Esperin; Ito, Ogawa (1959)
Formula XVI is questionable; Ovchinnikov et al. (1966)



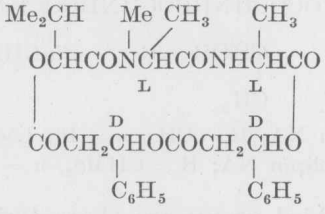
XVII. Esperinic acid; Ito, Ogawa (1959)
Formula XVII is wrong; Ovchinnikov et al. (1966)

This type of depsipeptides also includes isariin, a metabolite of the fungus *Isarea cretacea*, described by Vining [184],who also established its structure (XVIII) mass spectrometrically [190].



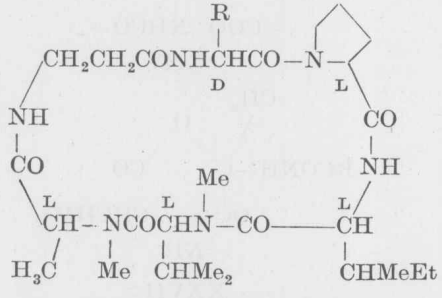
XVIII. Isariin; Vining (1966)

Still another depsipeptide called pithomycolide was found among the metabolic products of *Pithomyces chartarum*. It was established by Briggs [20] that pithomycolide is a 17-membered cyclopentadepsipeptide (XIX), containing two D-β-hydroxy-β-phenylpropionic acid residues.



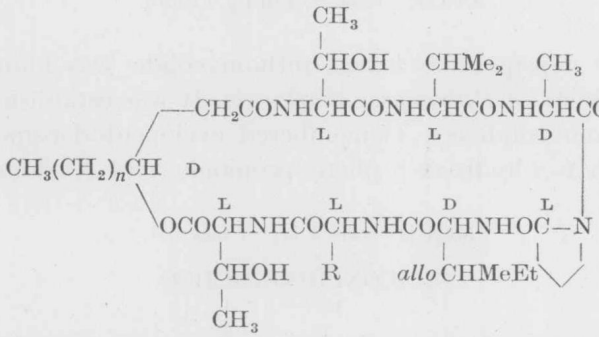
XIX. Pithomycolide; Briggs (1964)

To depsipeptides of the second group belong also the destruxins, possessing insecticide properties. These were studied by Japanese workers [64, 172], who proposed the structure XX for destruxin B [173], confirmed by its total synthesis [67] and recently structure XXI for destruxin A [169].



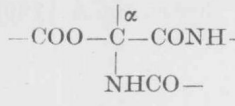
XX. Destruxin B; R = CH_2CHMe_2; Tamura (1964)
XXI. Destruxin A; R = $CH_2CH=CH_2$; Tamura (1966)

Finally, this group of depsipeptides also includes the quite recently discovered compounds related to the lipoproteins whose molecules contain residues of the higher hydroxy acids as well as amino acid residues. To date compounds of this type best known chemically are peptidolipin NA, isolated from a culture of *Nocardia asteroides* [51], whose structure was formulated as XXII [49, 50, 68]. The structure was confirmed mass spectrometrically [10]. Just latterly an analogue of peptidolipin NA was isolated containing an L-valine instead of L-alanine residue. The structure of this Val^6-peptidolipin NA (XXIII) and that of its homologues (XXIII; R = $CHMe_2$, $n = 17$ and XXIII; R = $CHMe_2$, $n = 18$) have been proved by the mass spectrometric method [52].

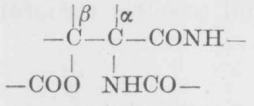


XXII. Peptidolipin NA; R = CH_3, $n = 16$; Lederer (1964–1965)
XXIII. Val^6-Peptidolipin NA; R = $CHMe_2$, $n = 16$; Lederer (1966)

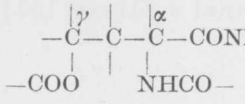
Depsipeptides of the third group are characterized by the presence of one or more hydroxyamino acid residues with both the hydroxyl and amino functions in the same molecule. This group may be subdivided into compounds containing α-hydroxy- (XXIV), β-hydroxy- (XXV) and γ-hydroxy- (XXVI) -α-amino acid residues. To the first group belong two new ergot



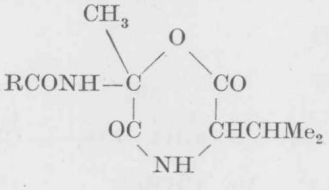
XXIV



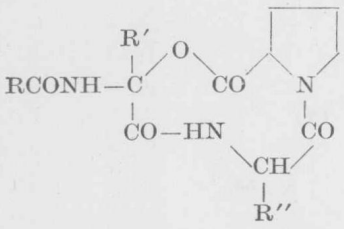
XXV



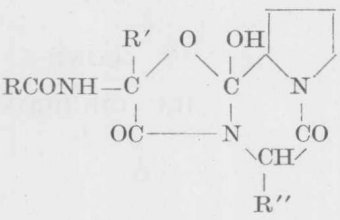
XXVI



XXVII
Ergosecaline
Ergosecalinine



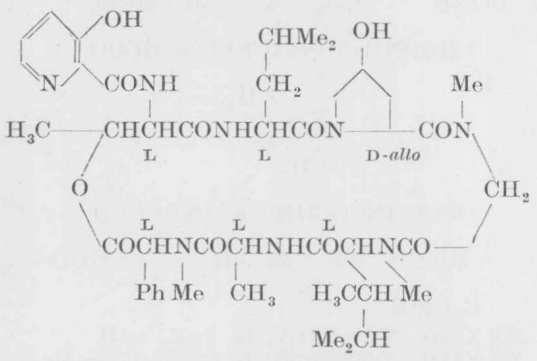
XXVIII



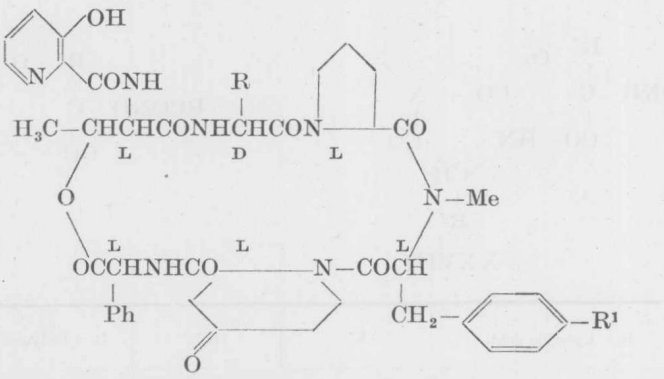
XXIX

R = Lysergic acid	R′	R″	R = Isolysergic acid
Ergocristine	$CHMe_2$	CH_2Ph	Ergocristinine
Ergotamine	Me	CH_2Ph	Ergotaminine
Ergokryptine	$CHMe_2$	CH_2CHMe_2	Ergokryptinine
Ergocornine	$CHMe_2$	$CHMe_2$	Ergocorninine
Ergosine	Me	CH_2CHMe_2	Ergosinine

alkaloids of the type XXVII, to which Japanese investigators have ascribed a cyclodidepsipeptide structure [1], as well as the long-known ergot alkaloids of the ergotamine and ergotoxine groups, which are cyclols (XXIX) isomeric with the corresponding cyclotridepsipeptides (XXVIII) [53, 166]. The second subgroup (XXV) embraces a large number of antibiotics whose molecules contain one or two serine or threonine residues incorporated in the depsipeptide ring by means of an amide and ester bond. The best known compound of this series is etamycin (XXX) [9, 124, 125] and also the compounds structurally related to it, staphylomycin S (XXXIa) and S_1 (XXXIb) [180—182], ostreogricin B (XXXIc), B_1 (XXXId) and B_2 (XXXIe) [41, 174, 175, 188] also called, respectively, vernamycins B_α, B_γ and B_β [16], as well as vernamycin B_δ (XXXIf) [16] and doricin [17].

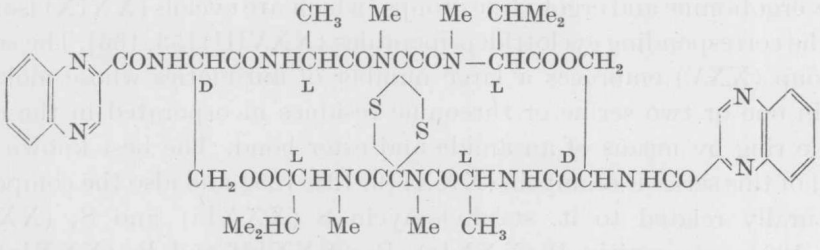


XXX. Etamycin; Sheehan et al. (1958)

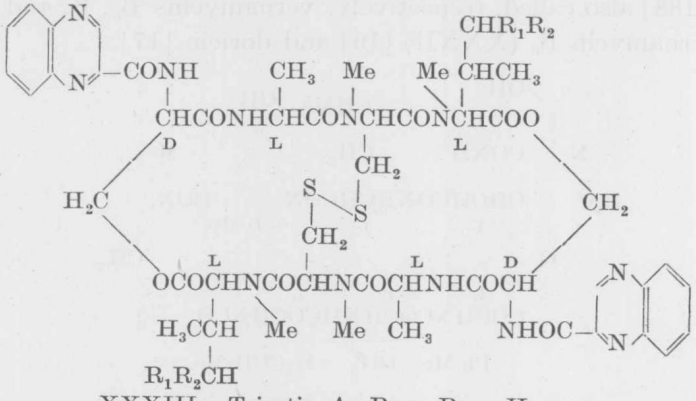


XXXIa. Staphylomycin S; R = Et; R^1 = H; Vanderhaeghe et al. (1960)
XXXIb. Staphylomycin S_1; R = Me; R^1 = H; Vanderhaeghe et al. (1965)
XXXIc. Ostreogricin B; R = Et; R^1 = NMe_2; Todd (1960)
XXXId. Ostreogricin B_1; R = Me; R^1 = NMe_2; Todd (1962)
XXXIe. Ostreogricin B_2; R = Et; R^1 = NHMe; Todd (1962)
XXXIf. Vernamycin B_δ; R = Me; R^1 = NHMe; Bodanszky et al. (1963)

To this subgroup should also be referred telomycin [122, 123], echinomycin (XXXII) [40, 56, 57] and the closely related quinomycins B and C [77, 80, 179], the triostins A, B and C (XXXIIIa—XXXIIIc) [77—79, 179],

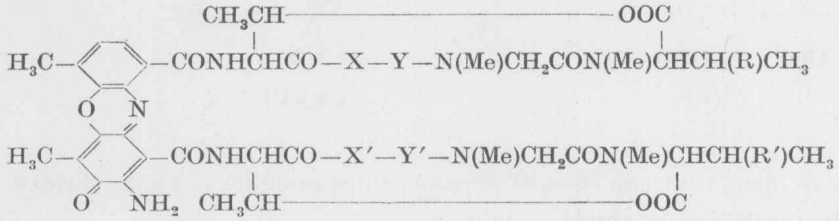


XXXII. Echinomycin; Prelog (1957)



XXXIIIa. Triostin A; $R_1 = R_2 = H$
XXXIIIb. Triostin B; $R_1 = H$; $R_2 = Me$
XXXIIIc. Triostin C; $R_1 = R_2 = Me$

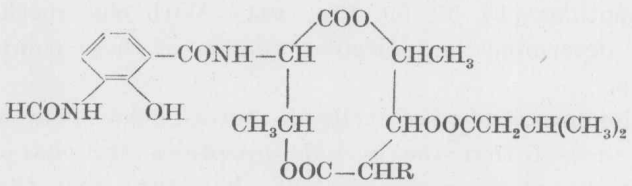
and a large group of actinomycins of the general formula (XXXIV) [21, 138].



XXXIV. Actinomycins

Actinomycin	X and X′	Y and Y′	R and R′	Actinomycin	X and X′	Y and Y′	R and R′
I (X_0)	Val	Pro; HyPro	CH_3	E_1	*a*Ileu	Pro	CH_3; C_2H_5
II (F_8)	Val	Sar	CH_3	E_2	*a*Ileu	Pro	C_2H_5
III (F_9)	Val	Sar; Pro	CH_3	F_1	*a*Ileu; Val	Sar	CH_3
IV (C_1)	Val	Pro	CH_3	F_2	*a*Ileu; Val	Sar; Pro	CH_3
V (X_2)	Val	Pro; *γ*-Opro	CH_3	F_3	*a*Ileu	Sar	CH_3
				F_4	*a*Ileu	Sar; Pro	CH_3
VI (C_2)	*a*Ileu; Val	Pro	CH_3	X_1	Val	Sar; *γ*-Opro	CH_3
VII (C_3)	*a*Ileu	Pro	CH_3	X_0	Val	Pro; HyPro	CH_3

A somewhat special position is occupied by the antimycins A_1 and A_3 (XXXV) in which there are three ester bonds to each peptide bond [12, 167, 189]. The type XXVI subgroup of depsipeptides is of particular interest, since it includes the connective tissue proteins, procollagen and collagen. Besides peptide bonds, these contain ester linkages formed by means of the hydroxyl group of hydroxyproline (XXXVI) [36].



XXXVa. Antimycin A_1; R = $(CH_2)_5CH_3$
XXXVb. Antimycin A_3; R = $(CH_2)_3CH_3$