RUSSIAN CHEMICAL REVIEWS
Uspekhi Khimii

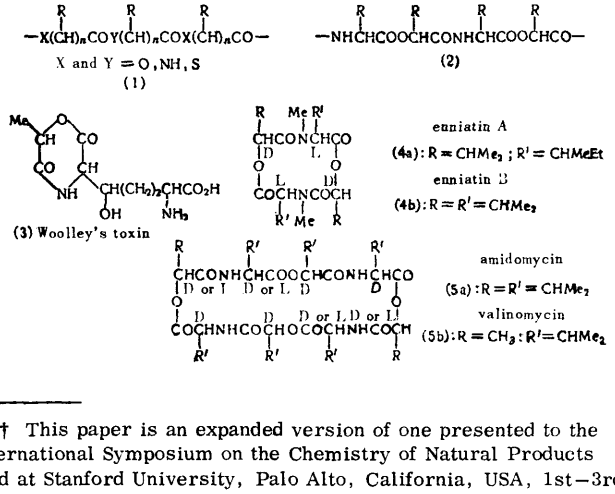
March 1962

# THE CHEMISTRY OF DEPSIPEPTIDES†

M. M. Shemyakin

*Depsipeptides* is a term we have applied[1,2] to a group of compounds of type (1) made up of residues of hydroxy-acids and amino-acids linked together by amide and ester bonds. Various representatives of this group are frequently met among natural products, and recently intense research has started on methods for their synthesis. Thiodepsipeptides, made up of residues of mercapto- and amino-carboxylic acids, are related to depsipeptides in structure and modes of synthesis.

Not long ago Russell[3] suggested the name *peptolides* for compounds of type (1), but this was unsuitable because it is applicable only to cyclic and not to linear compounds. Therefore Russell[4] soon gave up his term, regarding the name *depsipeptides* as more correct.



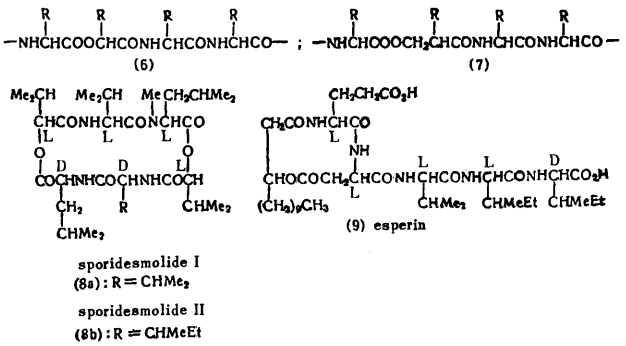

Natural and synthetic depsipeptides are now known which possess both linear and cyclic structures, and can be divided into several types. The first group of depsipeptides contain a regular alternation of residues of α-amino and α-hydroxy-acids (2). All natural compounds in this group are cyclodepsipeptides. The simplest of them is the phytopathogenic toxin (3) described in 1955 by Woolley[5], which proved to be a cyclodidepsipeptide. Being a derivative of dioxomorpholine, it is analogous to dioxopiperazine in the cyclopeptide series. This group also includes several depsipeptide antibiotics — the cyclotetradepsipeptides enniatin A (4a) and enniatin B (4b), the structure of which has been investigated by Plattner and others[6-17], and also the two cyclooctadepsipeptides amidomycin and valinomycin. According to Vining's results[18-20] amidomycin possesses the structure (5a), and valinomycin, which has been studied by Brockmann[21,22], is probably (5b), although the sequence of hydroxy-acid and amino-acid residues in the latter was not completely elucidated. There are still several little known antibiotics which are evidently related to the above compounds — enniatin C,[11] sambucinin, avenacein, fructigenin, lateritiin II,[12,14] baccatin A,[16] and fusafungin[17] — but these have not been obtained in a pure form, and their individuality still remains obscure‡.

The second group of depsipeptides comprises compounds having an irregular alternation of hydroxy-acid and amino-acid residues. It can include compounds containing α-hydroxy-acids, *e.g.* type (6), and also those containing β-hydroxy-acids, type (7). Among natural compounds of the former type are sporidesmolides I and II, investigated by Russell[3,4] in 1960, which are metabolic products of the fungus *Sporidesmium bakeri*. No pharmacological, or in particular antibiotic, activity has yet been detected in these compounds. They are both cyclohexadepsipeptides, sporidesmolide I possessing the structure (8a), while

† This paper is an expanded version of one presented to the International Symposium on the Chemistry of Natural Products held at Stanford University, Palo Alto, California, USA, 1st–3rd March, 1961.

‡ It has been shown quite recently that baccatin A is a mixture of enniatins A and B.[23]

sporidesmolide II is evidently its homologue with the structure (8b).



(5) (7)

(9) esperin

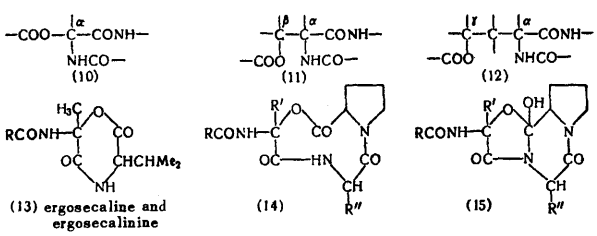
sporidesmolide I
(8a): R = CHMe$_2$

sporidesmolide II
(8b): R = CHMeEt

Depsipeptides of this group which contain β-hydroxy-acid residues, type (7), include the antibiotic esperin, whose structure (9) has recently been elucidated by Japanese workers[24]§.

The third group of depsipeptides are characterised by the presence of one or more residues of an aminohydroxy--acid, containing both the amine and hydroxyl functions in the same molecule. This group can be subdivided into compounds containing residues of α-amino-α-hydroxy--acids (10), α-amino-β-hydroxy-acids (11), α-amino-γ--hydroxy-acids (12), etc.

The first subgroup includes among natural products two new ergot alkaloids — ergosecaline and ergosecalinine — discovered in 1959 by Japanese workers[26], for which the cyclodidepsipeptide structure (13) has been proposed. However, the long known ergotamine and ergotoxine groups of alkaloids can also be included in this subgroup if they are accepted as having the cyclotridepsipeptide formula (14) of Jacobs and Craig[27] and of Barger[28] or the isomeric Stoll formula (15),[29,30] which is produced from it by transannular interaction between one of the amide groups and an ester group.



(10) (11) (12)

(13) ergosecaline and ergosecalinine (14) (15)

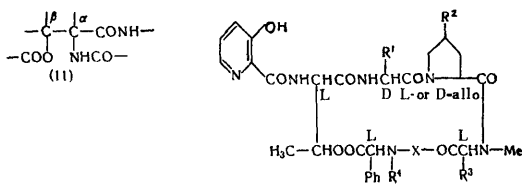
| R-Lysergic acid | R′ | R″ | R-Isolysergic acid |
|---|---|---|---|
| Ergocristine | CHMe$_2$ | CH$_2$Ph | ergocristinine |
| Ergotamine | Me | CH$_2$Ph | ergotaminine |
| Ergokryptine | CHMe$_2$ | CH$_2$CHMe$_2$ | ergokryptinine |
| Ergocornine | CHMe$_2$ | CHMe$_2$ | ergocorninine |
| Ergosine | Me | CH$_2$CHMe$_2$ | ergosinine |

§ According to Todd[25] the peptide antibiotic ostreogrycin A, the structure of which has not yet been finally established, contains an ester link formed by the hydroxyl group of a δ-hydroxy--acid residue.

Quite recently a new antibiotic serratamolide has been described[78], which has proved to be a cyclotetradepsipeptide composed of two L-serine residues and two residues of a β-hydroxy-acid (3-hydroxydecanoic acid).

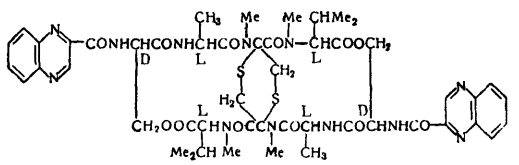
However, the question of the structure of the peptide part of the ergot alkaloids has not yet been finally settled, and forms a special subject of investigation by my colleagues and myself.

The second subgroup embraces a large number of diverse substances of type (11) which contain, in addition to residues of various α-amino-acids joined by amide links, one or more α-amino-β-hydroxy-acid (or α-amino-β--mercapto-acid) residues linked with other amino-acid residues not only by an amide but also by an ester (or thioester) link¶. The natural products include several interrelated antibiotics — etamycin (16a),[32-34] staphylomycin S (16b),[35,36] and ostreogrycin B (16c)[37,38]† — the molecules of which all contain one threonine residue incorporated in the depsipeptide ring not only by an amide but also by an ester link, the amino-group of the threonine being acylated by a hydroxypicolinic-acid residue. Still another closely related antibiotic is echinomycin (17),[39-41] the depsipeptide ring of which contains two serine residues incorporated in the ring by ester and amide links.



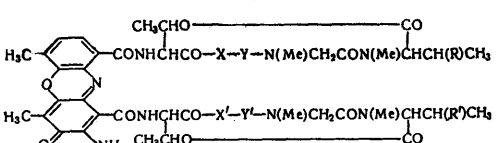
(11)

(16a): etamycin; R$^1$ = iso-Bu; R$^2$ = OH; R$^3$ = H; R$^4$ = Me; X = L-DiMeLeu-L-Ala
(16b): staphylomycin S; R$^1$ = Et; R$^2$ = H; R$^3$ = CH$_2$C$_6$H$_5$; R$^4$ = H; X = L-oxopipecolinic acid
(16c): ostreogrycin B; R$^1$ = Et; R$^2$ = H; R$^3$ = CH$_2$C$_6$H$_4$NMe$_2$-p; R$^4$ = H; X = L-olinic acid



(17) echinomycin

All actinomycin antibiotics of general formula (18), which have been studied in greatest detail by Brockmann[42,43], contain two cyclodepsipeptide groups, each of the rings always including one threonine residue, while the other α-amino-acid residues can vary greatly.



(18) actinomycins

| Actinomycin | X and X′ | Y and Y′ | R and R′ | Actinomycin | X and X′ | Y and Y′ | R and R′ |
|---|---|---|---|---|---|---|---|
| I ($X_0\beta$) | Val | Pro; HyPro | $CH_3$ | $E_1$ | alleu | Pro | $CH_3$; $C_2H_5$ |
| II ($F_8$) | Val | Sar | $CH_3$ | $E_2$ | alleu | Pro | $C_2H_5$ |
| III ($F_9$) | Val | Sar; Pro | $CH_3$ | $F_1$ | alleu; Val | Sar | $CH_3$ |
| IV ($C_1$) | Val | Pro | $CH_3$ | $F_2$ | alleu; Val | Sar; Pro | $CH_3$ |
| V ($X_2$) | Val | Pro; γ-OPro | $CH_3$ | $F_3$ | alleu | Sar | $CH_3$ |
| VI ($C_2$) | alleu*; Val | Pro | $CH_3$ | $F_4$ | alleu | Sar; Pro | $CH_3$ |
| VII ($C_3$) | alleu | Pro | $CH_3$ | $X_1\alpha$ | Val | Sar; γ-OPro | $CH_3$ |
| | | | | $X_0\delta$ | Val | Pro; HyPro | $CH_3$ |

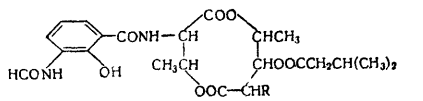
* Alleu = alloisoleucine (Ed. of Translation).

¶ Compounds of type (11) are sometimes termed *O*-peptides.[31] However, this name cannot in general be applied to depsipeptides, since *O*-peptides actually mean depsides.

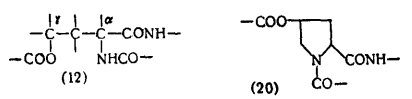
† According to Todd's most recent results[25], two further antibiotics, ostreogrycins $B_1$ and $B_2$, can be added to these compounds.

Antimycin $A_1$ (19a) and antimycin $A_3$ (19b), the structures of which were established in 1960,[44-46] differ substantially and stand apart from the above compounds. Both these antibiotics contain a threonine residue, but, in contrast to all the previous depsipeptides, three ester links are present for every peptide link.

The subgroup of depsipeptides of type (12), the molecules of which contain $\alpha$-amino-$\gamma$-hydroxy-acid residues, are of peculiar interest, since they include the proteins of connective tissue, procollagen and collagen. The amino--acid residues in these proteins are joined together not only by peptide but also by ester links, and it has recently been shown[47] that the latter are formed between the hydroxyl group in hydroxyproline and the carboxyl group of glutamic or aspartic acid (20).

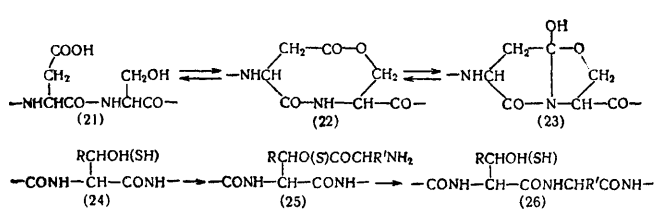


antimycin $A_1$ (19a) : R = $(CH_2)_5CH_3$
antimycin $A_3$ (19b) : R = $(CH_2)_3CH_3$



(12) (20)

Thus the class of depsipeptides includes the most varied representatives of natural products, extending from alkaloids and various antibiotics to several proteins. Moreover, depsipeptide groupings can evidently arise in the course of biochemical changes. Thus from Bernhard's results[48] it is quite possible that the action of esterases is associated with the ability of their active centre (21) to undergo changes leading to the formation of a cyclodepsipeptide grouping (22) and the tautomeric or isomeric cyclol structure (23). According to Brenner[49,50], on the other hand, the synthesis and the change in structure of some protein molecules of the type (24) may be associated with the intermediate formation of the corresponding depsipeptides and thiodepsipeptides (25), which then rearrange under the influence of enzymes to produce a normal peptide chain (26):

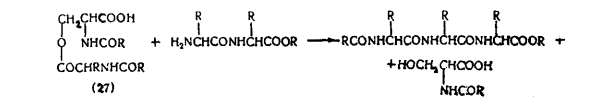


(21) (22) (23)

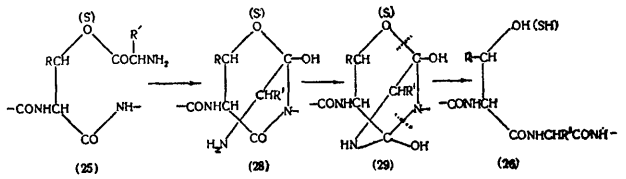
(24) (25) (26)

An important general property of all depsipeptides is that, under conditions of alkaline hydrolysis, they are readily cleaved only at the ester linkages. This fact affects fundamentally the procedures and methods used to study depsipeptides compared with those applicable to peptides. The possibility of the alkaline cleavage of depsipeptides into fragments at precisely located sites in the molecule greatly facilitates the investigation of their structure, in particular the determination of the optical purity of synthetic depsipeptides.

Little work has yet been done on the relation of the ester and the amide links in depsipeptides to the corresponding enzymes, although several facts suggest that interesting features can be expected here. Thus Botvinik has shown recently[51-54] that, under the influence of chymotrypsin, depsipeptides of type (27) not only undergo hydrolysis at the ester linkage but also, in the presence of esters of amino-acids or dipeptides, transfer their aminoacyl residue to the latter with formation of esters of the correspond ing dipeptides or tripeptides.



(27)



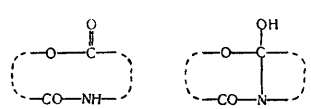
(25) (28) (29) (26)

Another characteristic feature of the same particular group of depsipeptides of type (25), containing residues of $\alpha$-amino-$\beta$-hydroxy- or $\alpha$-amino-$\beta$-mercapto-acids, is their tendency to undergo the above-mentioned rearrangement into the compounds (26), which according to Brenner[49,50] results from intramolecular reactions, first between an amide and an ester group (28), and then between an amide and an amino-group (29).

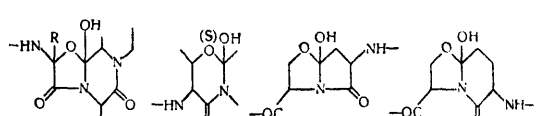
Such a tendency of amide and ester groups to undergo intramolecular reaction may perhaps be a general property of both linear and especially cyclic depsipeptides. With the latter (30) such transannular interaction should lead to the formation of bicyclic compounds of type (31). This question has been raised several times in the literature, by Witkop[55] in connection with the ergot alkaloids (32), by Brenner[49,50] when discussing the rearrangement (33) which he discovered, and by Bernhard[48] in connection with the mechanism of the action of esterases (34).

Experimentally, however, the possibility of intramolecular interaction between amide and ester groups remains so far completely unproven.

We are now studying this question with a series of model compounds analogous to those which have been cited, and especially with the ergot alkaloids, where the general method for synthesising $\alpha$-substituted $\alpha$-amino-acids and their peptides, which we worked out a few years ago[56-59], constituted a prerequisite for the synthesis[60,79] and study of the peptide moiety of the ergot alkaloids‡.



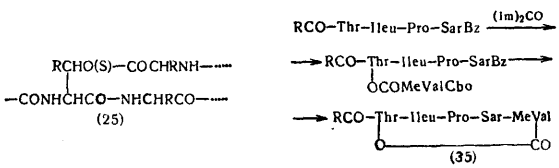
(30) (31)



ergot alkaloids (32) Brenner's rearrangement (33) esterases (34)

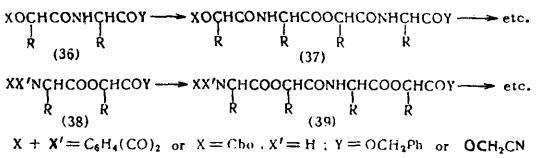
‡ Quite recently Swiss investigators have published a preliminary communication on the synthesis of one of the ergot alkaloids — ergotamine[61].

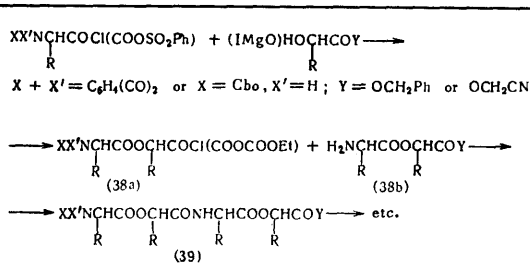
The general question of the synthesis of depsipeptides has not arisen until recently, although in isolated cases concerning depsipeptides of type (25), incorporating residues of α-amino-β-hydroxy- or α-amino-β-mercapto-acids (serine, threonine, cysteine), the desired compounds were synthesised. It was usually found that an ester (thioester) link was formed only after the peptide links, and it evidently proved best to use the carbodiimide and mixed anhydride methods (Shchukina[62-64], Brenner[65-67], and others[68-70]), which enable depsipeptides and thiodepsipeptides of type (25) to be obtained in high yield and in crystalline form. In the successful synthesis of actinomycin $C_3$ by Brockmann[71,72] the ester link of the cyclodepsipeptide part of the molecule (35) was formed at an intermediate stage by means of *NN'*-carbonyldiimidazole, cyclisation being effected by formation of a peptide link.




An experimental investigation of general paths for the synthesis of various types of depsipeptides was begun under the direction of Shemyakin and Shchukina a few years ago in view of the ever increasing interest aroused by this new class of compounds. By the present time Vinogradova, Lur'e-Feigina, Aldanova, and Oladkina[2,73] have worked out general methods for building up a depsipeptide chain with either a regular or an irregular arrangement of residues of optically active α-amino- and α-hydroxy-acids, and have shown the possibility of converting linear into cyclic depsipeptides.

Linear depsipeptides based on a regular alternation of α-amino-acid and α-hydroxy-acid residues can be synthesised in two fundamentally different ways. The first is to combine appropriate residues of a hydroxy- and an amino-acid by an amide link (36), remove either one (X) or the other (Y) protective group, and then join the resulting fragments together by an ester link (37); the whole depsipeptide chain is then built up by the repeated formation of ester links alone. In the second method substituted residues of an amino- and a hydroxy-acid would be combined by an ester link (38), then either one (X) or the other (Y) protective group would be removed and the resulting fragments connected by an amide link (39); here the further building up of the whole depsipeptide chain will be achieved by the repeated formation of amide links alone. Since methods of forming an amide link, and also procedures for introducing and removing protective groups, are quite well developed in peptide chemistry, the second path was preferred. In this case, however, it was necessary to reckon with the permanent presence in the molecules of labile ester groupings, which restricts the choice of methods applicable to the synthesis of a depsipeptide chain.




The choice of protective groupings should be governed by the possibility of their subsequent removal without affecting the ester links of the depsipeptide. It was found that, in preparing compounds of types (38) and (39), it was advisable to protect the carboxyl of the α-hydroxy-acid component by converting it into a benzyl or a cyanomethyl ester. If necessary, the cyanomethyl ester of the depsipeptide could be hydrolysed under mild alkaline conditions without greatly affecting the ester bonds of the depsipeptide itself, whereas the benzyl ester could be more suitably cleaved by hydrogenolysis§. The amino-group could be most suitably protected with a phthaloyl or a benzyloxycarbonyl group, since the former could be removed with hydrazine, and the latter with hydrogen bromide, under conditions which had little effect on the ester links of the depsipeptides; a benzyloxycarbonyl group could also be removed, of course, by hydrogenolysis. The removal of protective groups is not accompanied by racemisation.

Formation of an ester link in the synthesis of compounds of type (38) takes place with some difficulty, since the hydroxyl group of the α-hydroxy-acid component is usually secondary, and therefore many methods which are often employed for the acylation of alcohols cannot be utilised here. Production of such an ester link requires strong activation of the carboxyl group of the acylating amino-acid component, which is achieved by converting it into a mixed anhydride or the acid chloride. By itself, strong activation of the carboxyl is not dangerous with respect to racemisation of *N*-acylamino-acids: in the absence of bases, racemisation does not occur even with phthaloyl-D-valyl chloride, in which the α hydrogen atom should possess considerable reactivity owing to the presence of two strongly electron-accepting groups. However, acylation of the hydroxyl group of the α-hydroxy-acid component, by either anhydrides or chlorides of *N*-acylamino-acids, frequently takes place only in the presence of bases (pyridine, triethylamine), which strongly favour racemisation. Thus in the preparation of a mixed anhydride by the action of benzenesulphonyl chloride on phthaloyl-D-valine in the presence of excess of pyridine, complete racemisation of the phthaloyl-D-valine has occured even before it reacts with the α-hydroxy-acid component. Nevertheless, racemisation can be avoided if acylation with chlorides of phthalimido-acids is carried out in the presence of strictly equimolecular quantities of pyridine. Acylation can also be accomplished in the absence of bases, but then the hydroxyl group of the α-hydroxy-acid component must first have been activated, for example, by preparing one of the alkoxymagnesium halides. In the case of benzyloxycarbonylamino--acids, acylation can be carried out by the mixed anhydride method (with benzenesulphonyl chloride) and in excess of pyridine, since, in contrast to the phthalimido-acids, no

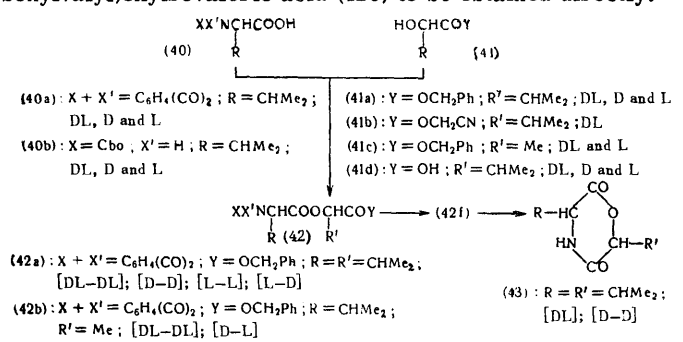
§ Recently we have begun to make extensive use of protection of the carboxyl group by converting it into a t-butyl ester, which is stable under alkaline conditions but unstable in acid media.

racemisation is observed at all here. The method suggested not long ago by Gibian and Lübke[74,75] and subsequently used by Schwyzer[76] for preparing compounds of type (38) by acting on diazoacetic esters and amides with *N*-acylamino-acids cannot be of general significance, since it provides no opportunity for synthesising depsipeptides containing residues of optically active hydroxy-acids¶.

Among methods of forming an amide link in preparing linear depsipeptides of type (39) the most promising proved to be the mixed anhydride method and especially the acid chloride method. Their use does not cause racemisation, because it is only the carboxyl of the hydroxy-acid residue of compounds of type (38a) which undergoes activation, whereas the amino-acid component of compounds of type (38b) does not require activation and its racemisation is excluded. This makes it possible to use the above two methods to synthesise various tetra- and octa-depsipeptides in high yields without appreciable racemisation.

Thus the scheme which we have worked out enables the preparation of optically active depsipeptides to be accomplished under far harsher conditions than the synthesis of the corresponding peptides. As a result, the preparation of depsipeptides is considerably simpler, and it does not involve the complications usually associated with the synthesis of optically active peptides.

It will be useful to consider in greater detail a number of actual examples of the synthesis of depsipeptides. Preparation of the first fragment of a depsipeptide chain — of racemic and optically active compounds of type (42) — was effected initially starting from phthaloylvaline (40a) or benzyloxycarbonylvaline (40b) and benzyl (41a) or cyanomethyl (41b) $\alpha$-hydroxyisovalerate, or also benzyl lactate (41c). The racemic compounds (42a)–(42d), which are either crystalline solids or oils which can be distilled in a vacuum, were readily synthesised in yields of 65–70% by the mixed anhydride method (by the action of benzenesulphonyl chloride and excess of pyridine at 0°–2°). The same procedure was employed for the condensation of benzyloxycarbonylvaline (40b) with $\alpha$-hydroxyisovaleric acid (41d), which enabled a 70% yield of $\alpha$-(*N*-benzyloxycarbonylvalyl)oxyisovaleric acid (42e) to be obtained directly.




In the synthesis of optically active compounds of type (42), however, this method can be used only when benzyloxycarbonylamino-acids are used as starting materials. Thus benzyl $\alpha$-(benzyloxycarbonyl-D-valyloxy)-D-isovalerate (42c) has been obtained in an optically pure state in 65% yield, whereas condensation under the same conditions of phthaloyl-D-valine (40a) with benzyl D-$\alpha$-hydroxyisovalerate (41a) or L-lactate (41c) was accompanied by complete racemisation of the phthaloyl-D-valine. Variation of the reaction conditions (quantity of pyridine, temperature, sequence in which the components were introduced) did not eliminate the racemisation. If the protective group is a phthaloyl residue, optically active compounds of type (42) can be obtained in a different way, by condensing phthalimido-acid chlorides with esters of $\alpha$-hydroxy-acids in the presence of one mole of pyridine in benzene. Benzyl phthaloyl-D-valyl-L-lactate (42b), for example, was obtained under these conditions in 95% yield. Good results were achieved also by the action of phthalimido-acid chlorides on the alkoxymagnesium halides formed by esters of $\alpha$-hydroxy-acids, benzyl $\alpha$-(phthaloyl-D-valyloxy)-D-isovalerate (42a) being synthesised in 70% yield.

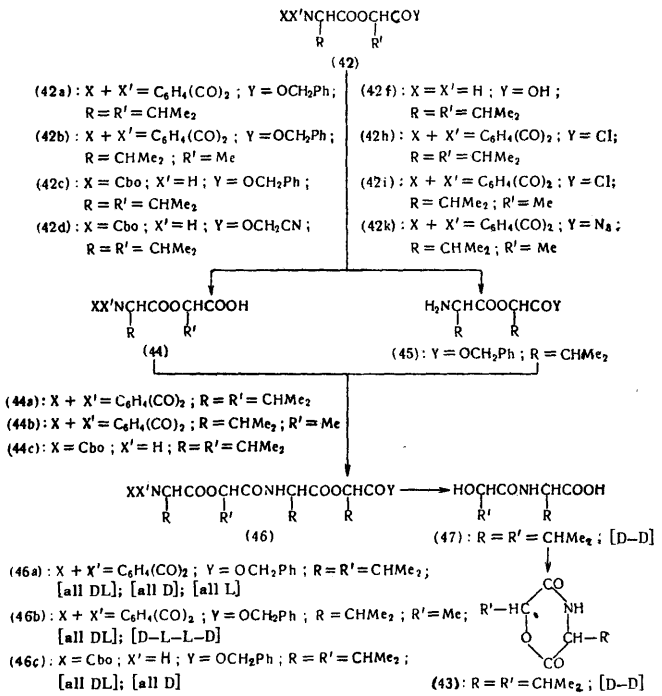
In order to demonstrate the optical activity of the compounds of type (42) obtained, their protective groups were removed, and then the following two procedures were used: (1) thermal cyclisation into easily sublimed substituted morpholines (43); (2) acid hydrolysis with subsequent isolation of optically active $\alpha$-amino- and $\alpha$-hydroxy-acids, the optical purity of the D-$\alpha$-amino-acids being checked additionally with D-amino-acid-oxidase, and that of L-lactic acid with the corresponding dehydrogenase. Thus the compounds (42a, D–D) and (42c, D–D) yielded *via* (42f, D–D) a morpholine (43, D–D) identical with that isolated previously in an investigation of the structure of the antibiotic amidomycin, and acid hydrolysis of the compounds (42f, D–D) and (42g, D–L) led to the isolation of the corresponding optically active amino- and hydroxyl-acids uncontaminated with racemates.

The depsipeptide chain was built up further by splitting off the protective groups from the carboxyl or the amino-group of compounds of type (42) and then condensing the fragments (44) and (45) into racemic and optically active tetradepsipeptides (46). The benzyl group in the compounds (42a) and (42b) was eliminated by hydrogenolysis under normal conditions, when the acids (44a) and (44b) were obtained in yields reaching 80%. But hydrogenolysis of the compound (42c), of course, led to the formation of the compound (42f) containing free amino- and carboxyl groups. The phthaloyl group in (42a) was eliminated by heating with an alcoholic solution of one mole of hydrazine hydrate; under these conditions benzyl $\alpha$-valyloxyisovalerate (45) is formed with a yield of ~80%. This same aminoester was obtained in 60% yield by eliminating the benzyloxycarbonyl group from compound (42c) by the action of HBr in glacial acetic acid. The acid chloride method was used to join fragments (44) and (45) by an amide link: the action of thionyl chloride on (44a) and (44b) yielded the corresponding acid chlorides (42h) and (42i), reaction of which with the aminoester (45) in the presence of triethylamine or pyridine led to the formation of substituted tetradepsipeptides of type (46). Thus 75% yields of the optically active tetradepsipeptides (46a, all D) and (46a, all L) have been obtained in the crystalline state by this method, while the optically active tetradepsipeptide (46b, D–L–L–D) separated as an oil in almost quantitative yield. This last compound has also been obtained by the azide method *via* the acid chloride (42i) and the azide (42k), but the yield is only

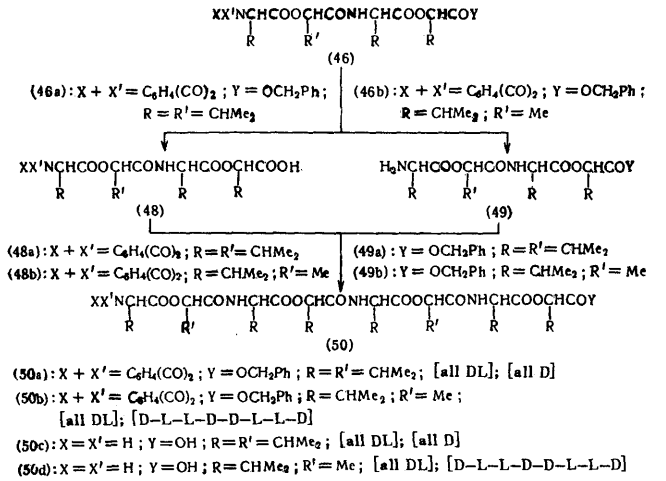
¶ The same drawback is possessed by the method, published at the end of 1961, for preparing tridepsipeptides by the condensation of acylamino-acids, aldehydes (ketones), and esters of $\alpha$-isocyanocarboxylic acids[77].

50%. The compounds (46a, all D) and (46c, all D) were also synthesised, with yields of ~70%, by the mixed anhydride method, by treating (44a) or (44c) under normal conditions with ethyl chloroformate followed by the aminoester (45). Attempts to use the cyanoethyl ester (42d) to synthesise the tetradepsipeptide (46c), however, led to negative results, as this ester proved to be insufficiently reactive to condense with the aminoester (45).

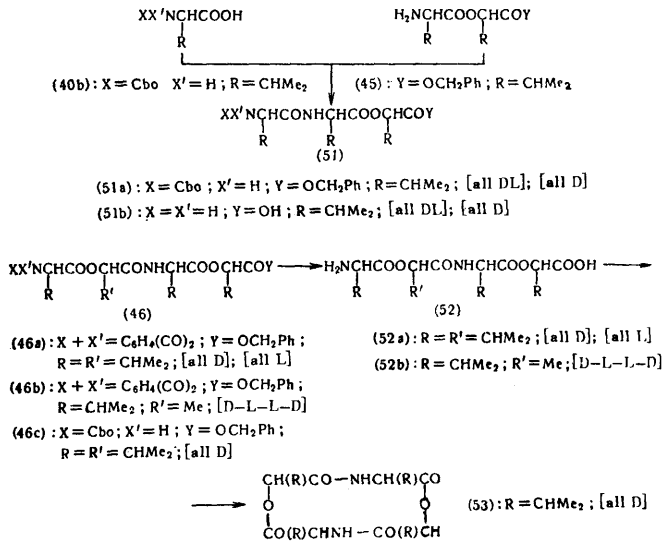
The optical purity of tetradepsipeptides of type (46) was determined by partial alkaline hydrolysis leading to a selective cleavage of the ester links and the formation of compounds of type (47) containing free hydroxyl and carboxyl. Thermal cyclisation of these compounds with simultaneous sublimation in a vacuum results in formation of the substited morpholines (43). The optically active tetradepsipeptide (46a, all D), for example, yielded the morpholine (43, D–D), identical with that isolated previously in studying the structure of amidomycin. On the other hand, complete acid hydrolysis of the tetradepsipeptide (46b, D–L–L–D) with subsequent determination of D-valine with D-amino-oxidase and of L-lactic acid with the corresponding dehydrogenase also confirmed the absence of appreciable racemisation during synthesis of tetradepsipeptides in this way.




The tetradepsipeptides (46) were converted into racemic and optically active octadepsipeptides (50) in a similar manner to that in which they had been formed from compounds of type (42). Hydrogenolysis of the compounds (46a) and (46b) yielded the phthalimido-acids (48a) and (48b), and elimination of the phthaloyl group from (46a) and (46b) by means of hydrazine led to the aminoesters (49a) and (49b), which were condensed with (48a) and (48b) respectively by the acid chloride method, removal of the protective groups from the resulting compounds (50a) and (50b) being effected under the same conditions as with the corresponding substituted tetradepsipeptides. In this way, for example, an 80% yield of the octadepsipeptide (50a, all D) was obtained in the crystalline state. The above process for lengthening a depsipeptide chain with regularly alternating residues of α-hydroxy- and α-amino-acids can be continued further.




The above synthetic path can also be used to obtain linear depsipeptides having an irregular arrangement of α-amino-acid and α-hydroxy-acid residues. Thus benzyloxycarbonylvaline (40b) was condensed by the mixed anhydride method with the aminoester (45) to give an 80% yield of the compounds (51a, all DL) and (51a, all D), hydrogenolysis of which led to the tridepsipeptides (51b, all DL) and (51b, all D) containing two amino-acid residues together. Depsipeptides having any alternation of α-amino- and α-hydroxy-acid residues can be synthesised in this way.




Linear tri-, tetra-, and octa-depsipeptides having free amino- and carboxy-end-groups can serve as starting materials for the synthesis of cyclodepsipeptides. Such

unsubstituted linear depsipeptides can be prepared in various ways. Thus hydrogenolysis of the optically active tetradepsipeptide (46c, all D) gave an 80% yield of α-(D-valyloxy)-D-isovaleryl-α-(D-valyloxy)-D-isovaleric acid (52a), which can be obtained also, though in lower yield, from the tetradepsipeptide (46a, all D) by removing the protective groups in stages, first the phthaloyl group (by means of hydrazine) and then the benzyl group (by hydrogenolysis). The cyclisation of linear depsipeptides, for example of the tetradepsipeptide (52a) into the cyclotetradepsipeptide (53), is most simply accomplished by the acid chloride method, the acid chloride of this tetradepsipeptide being cyclised in very dilute benzene solution in the presence of triethylamine.

The influence of various structural and especially steric factors on the cyclisation of linear depsipeptides, ring-closure by formation of an ester link, and also several other problems of the chemistry of depsipeptides having regular and irregular alternations of various amino- and hydroxy-acids form the subject of our current investigations.

The methods which we have worked out can be further utilised for the synthesis of various natural depsipeptides, in particular antibiotics. Furthermore, these methods open up the possibility of synthesising a new type of analogues of biologically active peptides in which some of the peptide links are replaced by ester links, *i.e.* in which residues of various α-amino-acids are replaced by residues of the corresponding α-hydroxy-acids. In this connection it is of particular interest to introduce α-hydroxy-acid residues into peptides which exhibit enzyme or hormone activity, since it is quite possible that, among such analogues, substances will be found which possess a strong antagonistic effect. At the present time our interests in this field are concentrated on two peptides — glutathione, which displays a broad spectrum of biological activity, and bradykinin, which possesses appreciable hypotensive activity.


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# ORGANOPHOSPHORUS COMPOUNDS† OBTAINED FROM α-OXIDES

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† In this translation names of these compounds have been changed to conform to the 1952 rules of the Chemical Society and American Chemical Society, where authors' intentions are clear. In the Russian text derivatives of phosphonous and phosphinous acids are both referred to as phosphinites (Ed. of Translation).