7. ERGOT ALKALOIDS AND OTHER METABOLITES OF THE GENUS *CLAVICEPS*

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7.1. INTRODUCTION

Both parasitic and saprophytic ergot is a producer of vast number of compounds from which alkaloids represent the most important group. Over 80 ergot alkaloids (EA) have as yet been isolated from diverse natural material, mainly from *Claviceps* strains, but also from other fungi and higher plants. Besides alkaloids and some other secondary metabolites (pigments and mycotoxins), ergot produces also some unusual primary metabolites of the lipidic and sacharidic nature.

7.2. ERGOT ALKALOIDS

Only alkaloids isolated from different *Claviceps* species are described in this chapter. EA produced by other fungi and higher plants are the subject of the Chapter 18. Beside this limitation, nearly 70 ergot alkaloids, produced by genus *Claviceps,* are discussed here.

7.2.1. Ergot Alkaloid Structure

All the EA are biosynthetically derived from L-tryptophane, that means indole is the base of their structure. Although the most of EA contains a tetra-cyclic **ergoline** system (Figure 1), there are some exceptions whose structure is created only by two or three cycles. Natural alkaloids can be divided into three groups according to their structure: The first, structurally simplest group, contains alkaloids of clavine type, the second group are simple amides of lysergic and paspalic acids and the third, most complex group is created by the alkaloids of peptidic type. Biosynthetically, the peptidic EA can be understand as tetrapeptides containing lysergic acid as the first member of the peptidic chain. The other amino acids of the tetrapeptide are variable, which provides the basis for a great diversity of this group of EA. Structurally, two group of peptidic alkaloids can be distinguished: ergopeptines and ergopeptams.

7.2.2. Ergot Alkaloid Nomenclature

EA nomenclature is very complex and systematic names are used only for semisynthetic derivatives or for exact chemical description. New natural

compounds were usually given a trivial name by their discoverers which were later generally accepted.

Trivial names mark the milestones in the history of ergot research and their etymology unravels interesting facets of the ergot story. Most of the trivial names of EA stem from the botanical names of their producers or the host plant, e.g., agroclavine and pyroclavine *(Agropyrum)*, elymoclavine and molliclavine *(Elymus mollis)*, setoclavine and penniclavine *(Pennisetum)*, paspalic acid *(Paspalum)*, festuclavine *(Festuca)*, ergosecaline *(Secale)*, etc. Other trivial EA names are connected with the circumstances of their discovery, e.g., ergokryptine remained obscured (*κρυπτός*) for a long time (however, some authors and even official pharmacopaeias use incorrectly name "ergocriptine"), ergobasine was considered to be very basic or lysergic acid was a product of the **lys**is of **ergo**t alkaloids. Still other names were connected with the pharmacological properties, e.g., ergotoxine or ergo**metri**ne (endo**metri**um uteri). Some scientists embodied parts of their private life in the EA names, e.g., Stoll's ergo**cristi**ne according to a girl named **Cristi**ne or Flieger's ergo**anna**me according to his daughter **Anna**. Sometimes, the discoverers wanted to make a compliment to a person or company closely associated with EA, e.g., ergo**lad**inine (**Ladi**slav Cvak) or ergo**gal**ine (**Gal**ena).

The rational approach to the nomenclature created hybrids bearing prefixes nor-, iso-, dihydro- and suffixes -inine, -ol, -am, etc. Other trivial names were coined also for some products of chemical modification, e.g., prefix lumifor the products of photochemically initiated water addition or aci- for ergopeptine isomers possessing acidic properties (see Chapter 8). Another such rational approach, but not generally accepted, is the use of the name **ergolene** for 8,9- or 9,10-didehydroergolines.

The systematic nomenclature of EA and their derivatives is based on general principles of chemical nomenclature. Three types of nomenclature are used. The first is the nomenclature according to Chemical Abstracts using the name **ergoline** (Figure 1) for the tetra-cyclic system which is present in most of EA and the name **ergotaman** (Figure 2) for the hepta-cyclic system of EA of peptidic type. The second type of systematic names, valid for peptidic alkaloids only, uses the name **ergopeptine** (Figure 3) for the whole hepta-cyclic system of these alkaloids including all the substituents present in natural EA of this type. The last one, the most complicated but the most rational, is the nomenclature based on IUPAC rules for nomenclature of heterocyclic compounds. According to this nomenclature the ergoline system can be described as 7-methyl4,6,6a,7,8,9,10,10a-octahydro-indolo[4, 3-fg]quinoline. Examples of all those types of nomenclature can be found in the Chapter 13.

7.2.3. Ergot Alkaloid Stereochemistry

Although ergot alkaloids contain several chiral centres of various configuration, there is one fixed configuration in all the natural EA, i.e., *5R* having relation to

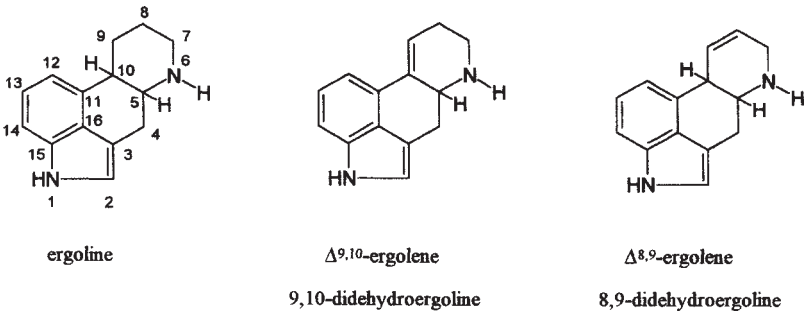


Figure 1 Ergoline and ergolene structures and their numbering

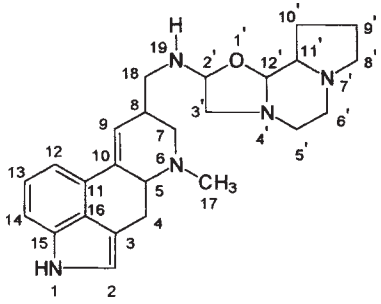


Figure 2 Ergotaman skeleton and its numbering[1]

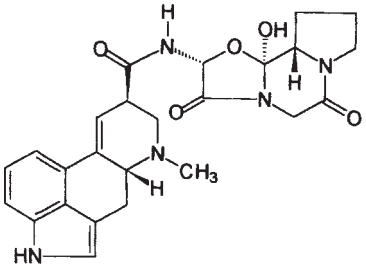


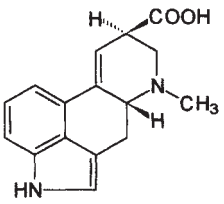
Figure 3 Ergopeptine skeleton

EA biosynthetic precursor L-tryptophane. Only EA prepared by total synthesis or products prepared by isomerisation of natural alkaloids under harsh

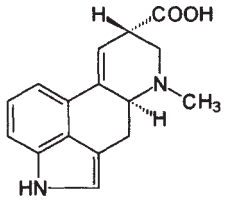
[1] Carbon on C-8 (e.g., carbonyl of lysergic acid) is usually numbered as C-17, however, according to Chemical Abstracts nomenclature C-17 is the Me on N-6, and the carbon on C-8 is numbered as C-18.

conditions (e.g. hydrolysis or hydrazinolysis) can have 5*S* configuration. Natural 5*R* EA are sometimes specified as D isomers, which is incorrect. The only *d*- and *l*-denomination for some derivatives e.g., *d*-lysergic acid can be accepted.

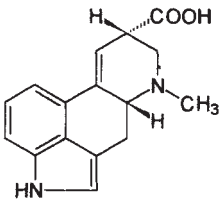
The prefix *iso*- in EA nomenclature is strictly confined to the position 8, i.e., lysergic acid for the 5*R*, 8*R* and isolysergic acid for the 5*R*, 8*S* derivatives. Stoll originally designated roman numbers for the stereochemistry at C5-C10: I for 5, 10-*trans*-isomers, e.g., dihydrolysergic acid-I and II for 5, 10-*cis*-isomers, e.g., dihydrolysergic acid-II. This system was used for many natural and semisynthetic alkaloids (e.g., chanoclavines), but in the case of agroclavine-I (5, 10-*cis*-isomer) it was used incorrectly and its name is misleading (see Chapter 18). The stereochemistry of lysergic and dihydrolysergic acids is demonstrated in the Figure 4.



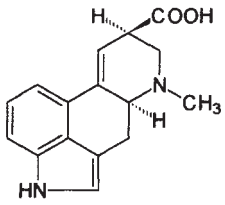
d-lysergic acid (5*R*, 8*R*)



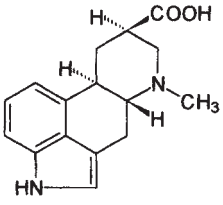
l-lysergic acid (5*S*, 8*S*)



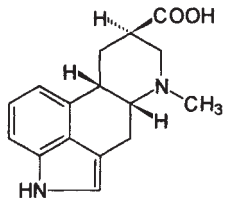
d-isolysergic acid (5*R*, 8*S*)



l-isolysergic acid (5*S*, 8*R*)



d-dihydrolysergic acid-I (5*R*, 8*R*, 10*S*)



d-dihydrolysergic acid-II (5*R*, 8*R*, 10*R*)

Figure 4 Lysergic acid and dihydrolysergic acid stereoisomers (only two, most important dihydrolysergic acid stereoisomers are presented)

Because of the ergoline system is only slightly puckered, the steroid chemistry nomenclature using designation α- for a substituent below and ß- for that above the plane is convenient and is therefore used very often for semisynthetic derivatives e.g., 10α-methoxydihydrolysergol.

7.2.4. Clavine Alkaloids

The clavine alkaloids are tricyclic (secoergolines) or tetracyclic (ergolines) compounds with relation to L-tryptophan. The ergoline (secoergoline) skeleton of clavine alkaloids is usually substituted in positions 8 and/or 9 with simple substituents e.g. methyl, hydroxyl, hydroxymethyl or a double bond is present in the positions 8,9 or 9,10. Some clavine alkaloids are the primary products of EA biosynthesis e.g. chanoclavine, agroclavine, elymoclavine and they serve as the biosynthetic precursors of other EA. Although some clavines are produced by various strains of *Claviceps* under parasitic conditions (e.g. chanoclavine-I, agroclavine, elymoclavine), most of the clavine alkaloids were isolated from the saprophytic cultures of some *Claviceps* species originating from the Far East. Particularly Abe and his group of Japanese scientists contributed substantially to the discovery of clavine alkaloids. A number of clavine alkaloids are produced outside of *Claviceps* genus, some of them are identical with that from *Claviceps*, some other are different—see Chapter 18. According to their structures the clavine alkaloids can be divided into two main groups, i.e., 6,7-secoergolines and ergolines and besides one smaller group containing alkaloids with modified ergoline structure.

6, 7-Secoergolines

The basic biosynthetic precursors of 6, 7-secoergolines are chanoclavine-I and chanoclavine-I-aldehyde. All the other secoergolines and $\Delta^{8,9}$–6,7-secoergolenes are the biosynthetic by-products or the products of their further biotransformations. All the natural secoergolines (including secoergolenes) and their occurrence in the nature are summarised in the Table 1. Structures of all the EA of this group are in the Figure 5.

Ergolines

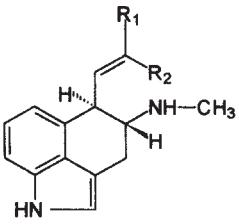
Agroclavine is the biosynthetic precursor of the other ergolines and ergolenes, which is further transformed either to other $\Delta^{8,9}$-ergolenes (e.g. elymoclavine, molliclavine-I) or is isomerised to $\Delta^{9,10}$-ergolenes (e.g. lysergol, penniclavine, setoclavine), or alternatively is reduced to ergolines (e.g. festuclavine, dihydrolysergol). All the clavine alkaloids, with the structure of $\Delta^{8,9}$-ergolene, $\Delta^{9,10}$-ergolene and ergoline, isolated from different strains of *Claviceps* genus are summarised in Table 2. Structures of all clavine alkaloids of this group are on Figure 6.

Table 1 6, 7-secoergolines

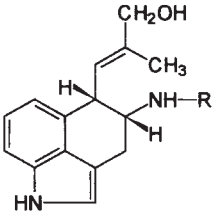
Alkaloid	*Structure*	*Source*	*Growing*	*References*
Chanoclavine-I	1	*Claviceps* sp. from *Pennisetum typhoideum*	saprophytic	Hofmann *et al.*, 1957
		Claviceps purpurea	parasitic, on rye	Stauffacher and Tscherter, 1964
		Claviceps paspali	saprophytic	Gröger, 1965
		Claviceps gigantea	parasitic, on maize	Agurell and Ramstad, 1965
Chanoclavine-II	2	*Claviceps purpurea*	parasitic, on rye	Stauffacher and Tscherter, 1964
Isochanoclavine-I	3	*Claviceps purpurea*	parasitic, on rye	Stauffacher and Tscherter, 1964
Dihydrochano-clavine-I	4	*Claviceps paspali*	saprophytic	Voigt and Zier, 1970
Dihydro-isochano-clavine-I	5	*Claviceps paspali*	saprophytic	Voigt and Zier, 1970
Norchano-clavine-II	6	*Claviceps purpurea*	saprophytic	Cassady *et al.*, 1973
Paliclavine	7	*Claviceps paspali* from *Paspalum dilatatum*	saprophytic	Tscherter and Haut, 1974
6,7-Secoagro-clavine	8	*Claviceps purpurea*	saprophytic	Horwell and Verge, 1979
Chanoclavine-I-aldehyde	9	*Claviceps purpurea*	saprophytic	Maier *et al.*, 1980a,b
Chanoclavine-I-monofructoside	10	*Claviceps fusiformis*	saprophytic	Flieger *et al.*, 1990
Chanoclavine-I-difructoside	11	*Claviceps fusiformis*	saprophytic	Flieger *et al.*, 1990

Alkaloids with Modified Ergoline Structure

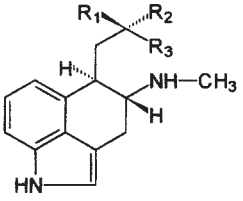
Many EA with modified ergoline skeleton have been found in the nature but most of them outside of *Claviceps* genus (e.g. aurantioclavine, cycloclavine, rugulovasine A and B). Only four such modified ergolines were isolated from ergot: 4-dimethylallyltryptophan and *N*-methyl-4-dimethylallyltryptophan are the biosynthetic precursors of the other EA, Clavicipitic acid is the biosynthetic by-product having still the carboxyl group of tryptophan and paspaclavine is a modified alkaloid of the clavine type. The occurrence of these alkaloids in ergot is summarised in the Table 3. Structures of all the modified ergolines isolated from *Claviceps* are in the Figure 7.



1 chanoclavine-I, $R_1 = CH_2OH$, $R_2 = CH_3$
3 isochanoclavine-I, $R_1 = CH_3$, $R_2 = CH_2OH$
8 secoagroclavine, $R_1 = CH_3$, $R_2 = CH_3$
9 chanoclavine-I aldehyde, $R_1 = CHO$, $R_2 = CH_3$
10 chanoclavine-I *O*-β-D-fructofuranoside
11 chanoclavine-I *O*-β-D-fructofuranosyl-(2→1)-O-β-D-fructofuranoside



2 chanoclavine-II, $R = CH_3$
6 norchanoclavine-II, R = H



4 dihydrochanoclavine-I, $R_1 = CH_2OH$, $R_2 = H$, $R_3 = CH_3$
5 dihydroisochanoclavine-I, $R_1 = H$, $R_2 = CH_2OH$, $R_3 = CH_3$
7 paliclavine, $R_1 = C(CH_3)=CH_2$, $R_2 = H$, $R_3 = OH$

Figure 5 Clavine alkaloids: 6,7-secoergolines

7.2.5. Simple Derivatives of Lysergic and Paspalic Acids

Elymoclavine is the biosynthetic precursor of paspalic acid, which is further isomerised to lysergic acid. Lysergic acid can be transformed to its derivatives: simple amides and more complex derivatives—alkaloids of peptidic type. Lysergic

Table 2 Ergolines

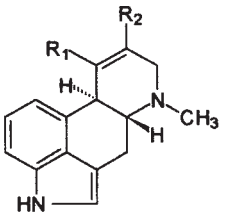
Alkaloid	*Structure*	*Source*	*Growing*	*References*
Agroclavine	12	*Claviceр* sp. from *Agropyrum semicostatum*	saprophytic	Abe, 1948; Abe *et al.*, 1951
		Claviceps sp. from *Pennisetum typhoideum*	saprophytic	Stoll *et al.*, 1954
Elymoclavine	13	*Claviceps* sp. from *Elymus mollis*	saprophytic	Abe *et al.*, 1952
Penniclavine	14	*Claviceps* sp. from *Festuca rubra*	saprophytic	Abe and Yamatodani, 1954
Festuclavine	15	*Claviceps* sp. from *Festuca rubra*	saprophytic	Abe and Yamatodani, 1954; Abe *et al.*, 1956
		Claviceps gigantea	parasitic, on maize	Agurell and Ramstad, 1965
Molliclavine-I	16	*Claviceps* sp. from *Elymus mollis*	saprophytic	Abe and Yamatodani, 1955a
Setoclavine	17	*Claviceps* sp. from *Elymus mollis*	saprophytic	Abe *et al.*, 1955b
		Claviceps sp. from *Pennisetum typhoideum*	saprophytic	Hofmann *et al.*, 1957
Isosetoclavine	18	*Claviceps* sp. from *Elymus mollis*	saprophytic	Abe *et al.*, 1955b
		Claviceps sp. from *Pennisetum typhoideum*	saprophytic	Hofmann *et al.*, 1957
Costaclavine	19	*Claviceps* sp. from *Agropyrum semicostatum*	saprophytic	Abe *et al.*, 1956
Pyroclavine	20	*Claviceps* sp. from *Agropyrum semicostatum*	saprophytic	Abe *et al.*, 1956
		Claviceps gigantea	parasitic, on maize	Agurell and Ramstad, 1965

Table 2 (*Continued*)

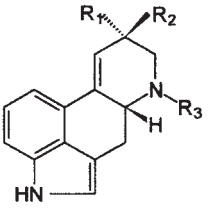
Alkaloid	*Structure*	*Source*	*Growing*	*References*
Isopenniclavine	21	*Claviceps* sp. from *Pennisetum typhoideum*	saprophytic	Hofmann *et al.*, 1957
Lysergene	22	*Claviceps* sp. from *Agropyrum semicostatum*	saprophytic	Yamatodani, 1960; Abe *et al.*, 1961
Lysergol	23	*Claviceps* sp. from *Agropyrum semicostatum*	saprophytic	Yamatodani, 1960; Abe *et al.*, 1961
Lysergine	24	*Claviceps* sp. from *Agropyrum semicostatum*	saprophytic	Yamatodani, 1960; Abe *et al.*, 1961
Dihydrolysergol	25	*Claviceps gigantea*	parasitic, on maize	Agurell and Ramstad, 1965
Isolysergol	26	*Claviceps* sp. from *Pennisetum typhoideum*	saprophytic	Agurell, 1966a,b
Norsetoclavine	27	*Claviceps* sp. from *Pennisetum typhoideum*	saprophytic	Ramstad *et al.*, 1967
Elymoclavine-monofructoside	28	*Claviceps purpurea*	saprophytic	Floss *et al.*, 1967b
Dihydroseto-clavine	29	*Claviceps paspali* from *Paspalum dilatatum*	saprophytic	Tscherter and Haut, 1974
Elymoclavine-difructoside	30	*Claviceps fusiformis*	saprophytic	Flieger *et al.*, 1989a

acid can be easily isomerised to isolysergic acid—Figure 8—and, therefore, most of its derivatives, both simple and peptidic ones, occur in two isomeric forms: lysergic acid derivative bearing the basic trivial name, e.g., ergometrine or ergine and isolysergic acid derivative bearing the suffix -inine, e.g., ergometrinine or erginine.

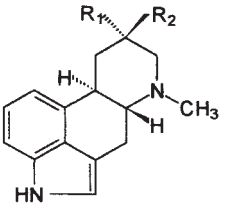
The first simple derivative of lysergic acid, ergometrine, was isolated by three groups of researchers and thus it has two other alternative names—ergobasine and ergonovine. Later free lysergic acid, paspalic acid and many of their derivatives were found in the nature. All of them are summarised in the Table 4

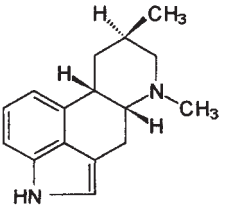


12 agroclavine, $R_1 = H$, $R_2 = CH_3$
13 elymoclavine, $R_1 = H$, $R_2 = CH_2OH$
16 molliclavine-I, $R_1 = OH$, $R_2 = CH_2OH$
28 elymoclavine *O*-β-D-fructofuranoside
30 elymoclavine *O*-β-D-fructofuranosyl-(2→1)-*O*-β-D-fructofuranoside



14 penniclavine, $R_1 = OH$, $R_2 = CH_2OH$, $R_3 = CH_3$
17 setoclavine, $R_1 = OH$, $R_2 = CH_3$, $R_3 = CH_3$
18 isosetoclavine, $R_1 = CH_3$, $R_2 = OH$, $R_3 = CH_3$
21 isopenniclavine, $R_1 = CH_2OH$, $R_2 = OH$, $R_3 = CH_3$
22 lysergene, $R_1 + R_2 = CH_2$, $R_3 = CH_3$
23 lysergol, $R_1 = H$, $R_2 = CH_2OH$, $R_3 = CH_3$
24 lysergine, $R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$
26 isolysergol, $R_1 = CH_2OH$, $R_2 = H$, $R_3 = CH_3$
27 norsetoclavine, $R_1 = OH$, $R_2 = CH_3$, $R_3 = H$





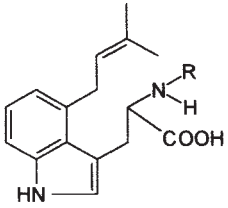
15 festuclavine, $R_1 = H$, $R_2 = CH_3$
20 pyroclavine, $R_1 = CH_3$, $R_2 = H$
25 dihydrolysergol, $R_1 = H$, $R_2 = CH_2OH$
29 dihydrosetoclavine, $R_1 = OH$, $R_2 = CH_3$

19 costaclavine

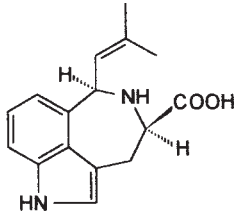
Figure 6 Clavine alkaloids: ergolines and ergolenes

Table 3 Alkaloids with modified ergoline skeleton

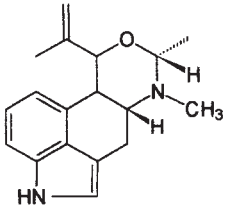
Alkaloid	*Structure*	*Source*	*Growing*	*References*
4-dimethylallyl-tryptophan	31	*Claviceps sp.* from *Pennisetum typhoideum*	saprophytic	Agurell and Lindgren, 1968
Clavicipitic acid	32	*Claviceps fusiformis*	saprophytic	King *et al.*, 1973
Paspaclavine	33	*Claviceps paspali* from *Paspalum dilatatum*	saprophytic	Tscherter and Haut, 1974
N-methyl-4-dimethyl-allyltryptophan	34	*Claviceps*	saprophytic	Agurell and Lindgren, 1968



31 4-dimethylallyltryptophan, R = H
34 *N*-methyl-4-dimethylallyltryptophan, R = CH_3



32 clavicipitic acid



33 paspaclavine

Figure 7 Clavine alkaloids with modified ergoline skeleton

and their structures are in the Figure 9. Ergosecaline, mentioned as the last one in this group of EA is a transition between the simple derivatives of lysergic acid and alkaloids of peptide type, which are tetrapeptides, while ergosecaline is a tripeptide.

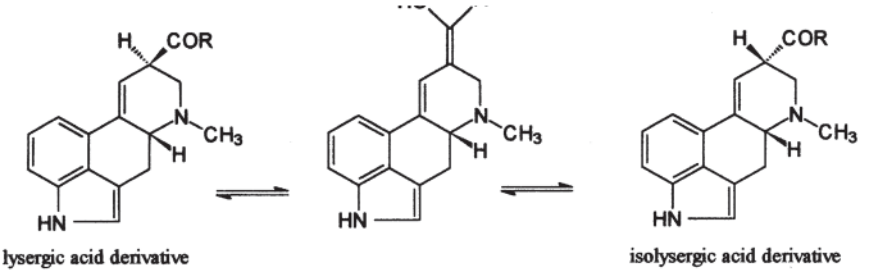


Figure 8 Epimerisation of lysergic acid derivatives

Table 4 Simple derivatives of lysergic and paspalic acids

Alkaloid	*Structure*	*Source*	*Growing*	*References*
Ergine	35	*Claviceps paspali* from *Paspalum distichum*	saprophytic	Arcamone *et al.*, 1961
Ergometrine	36	*Claviceps purpurea*	parasitic, on rye	Dudley and Moir, 1935; Kharash and Legaul, 1935a, b Thompson, 1935a, b, c; Stoll and Burckhard, 1935
Ergosecaline	37	*Claviceps purpurea*	saprophytic	Abe *et al.*, 1959
Lysergic acid α-hydroxy-ethylamide	38	*Claviceps paspali* from *Paspalum distichum*	saprophytic	Arcamone *et al.*, 1961
		Claviceps paspali	saprophytic	Flieger *et al.*, 1982
Lysergic acid	39	*Claviceps paspali* from *Paspalum dilatatum*,	saprophytic	Kobel *et al.*, 1964
		Claviceps purpurea from *Spartina townsendii*	saprophytic	Castagnoli and Mantle, 1966

Table 4 (*Continued*)

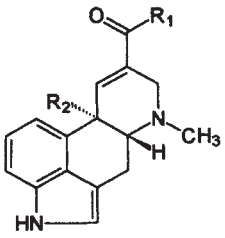
Alkaloid	*Structure*	*Source*	*Growing*	*References*
Paspalic acid	40	*Claviceps paspali* from *Paspalum dilatatum*, *Paspalum distichum*	saprophytic	Kobel *et al.*, 1964
		Claviceps purpurea from *Spartina townsendii*	saprophytic	Castagnoli and Mantle, 1966
8α-Hydroxyergine	41	*Claviceps paspali*	saprophytic	Flieger *et al.*, 1989
10-Hydroxy-*cis*-paspalamide	42	*Claviceps paspali*	saprophytic	Flieger *et al.*, 1993
10-Hydroxy-*trans*-paspalamide	43	*Claviceps paspali*	saprophytic	Flieger *et al.*, 1993

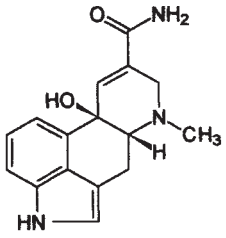
7.2.6. Peptidic Ergot Alkaloids

Ergopeptines

Ergopeptines are tetrapeptides formed by lysergic acid and a tripeptide moiety, a unique tricyclic structure called cyclol—**cyclol alkaloids**. Some years ago, ergopeptines seemed to be a closed group of natural product, containing only a limited number of L-amino acids: in position 2 hydroxylated alanine (alkaloids of **ergotamine group**), 2-aminobutyric acid (alkaloids of **ergoxine group**) or valine (alkaloids of **ergotoxine group**) as the first amino acid, phenylalanine, valine, leucine and isoleucine as the second and proline as the third amino acid of the peptidic moiety. This variability formed a basis for existence of 12 natural ergopeptines (three groups, each having four alkaloids), of course each of them with its isolysergic acid derivative called **ergopeptinine**. Only 10 of these ergopeptines were found in *Claviceps:*

ß-Ergosine was isolated from higher plant *Ipomoea argyrophylla* (Stauffacher *et al.*, 1965), *ß*-ergoptine was prepared synthetically only. Some novel ergopeptines, containing unusual amino acids as the second amino acid of the peptidic part were isolated recently from both parasitic and saprophytic cultivated ergot: ergogaline with L-homoisoleucine and ergoladine (only isolysergic acid derivative—ergoladinine—was described, it was later transfer to ergoladine—Cvak, personal communication) with L-methionine were isolated from parasitic ergot and ergobutine and ergobutyrine with L-2aminobutyric acid have been isolated from saprophytic culture of *Claviceps*. The last ergopeptine with L-2-aminobutyric acid in position 2 of peptidic part, ergobine, was prepared by directed biosynthesis only (Crespi-Perellino *et al.*, 1993), as

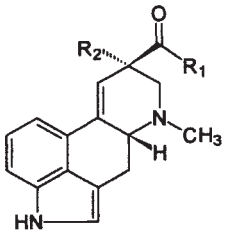


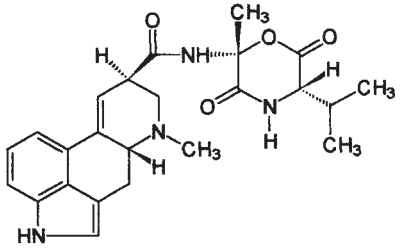


40 paspalic acid, R_1 = OH, R_2 = H

42 10β-hydroxy-*cis*-paspalamide

43 10α-hydroxy-*trans*-paspalamide, R_1 = NH_2, R_2 = OH





35 ergine, R_1 = NH_2, R_2 = H

37 ergosecaline

36 ergometrine, R_1 = NH-CH(CH_3)CH_2OH, R_2 = H

38 lysergic acid α-hydroxyethylamide, R_1 = NH-CH(OH)CH_3, R_2 = H

39 lysergic acid, R_1 = OH, R_2 = H

41 8α-hydroxyergine, R_1 = NH_2, R_2 = OH

Figure 9 Lysergic and paspalic acids and their simple derivatives

well as many other novel ergopeptines. Both, natural and synthetic amino acids were used as biosynthetic precursors for the directed biosynthesis producing ergopeptines with the modified second amino acid of the peptidic moiety: 2-aminobutyric acid, nor-valine, nor-leucine, *p*-chloro-phenylalanine, *p*-fluoro-phenylalanine, 5, 5, 5-trifluoro-leucine, 3-hydroxy-leucine and D-isoleucine (Cvak *et al.*, 1996). The incorporation of D-isoleucine into *epi-ß*-ergokryptine is very unusual (Flieger *et al.*, 1984). Many ergopeptine analogues were prepared by synthesis—these are not mentioned here. Finally a new alkaloid with hydroxylated isoleucine as the first amino acid was described by two groups of researchers. In accordance to the formerly accepted name *ß,* α-ergoannam for the ergopeptam alkaloid with the same amino acids (Flieger *et al.*, 1984), the name of this new ergopeptine is *ß*,α-ergoannine. This alkaloid is the first member of a new group of ergopeptines—***ß*-ergoainnine group,** having isoleucine as the first amino acid.

8α-Hydroxylated ergopeptines (8α-hydroxyergotamine and 8α-hydroxy-α-ergokryptine) are ergopeptine derivatives isolated from parasitic *Claviceps*

purpurea. The occurrence of other hydroxylated ergopeptines can be expected as well. Other ergopeptine derivatives isolated from saprophytic cultures are 12′-*O*-methyl ergopeptines (12′-methoxy ergopeptines).

Although many of the clavine alkaloids are ergolines without any double bond in the D cycle, dihydro-α-ergosine isolated from *Claviceps africana* (Mantle and Waight, 1968) is the only example of natural dihydrolysergic acid derivative.

Nearly all the new, recently described alkaloids were isolated by researchers from companies producing ergot alkaloids. The large quantities of processed material give them a chance to discover the minor alkaloids.

All the isolated natural ergopeptines and references about their occurrence are summarised in the Table 5 and their structures are in the Figures 10–12. Structures of some ergopeptines prepared by directed biosynthesis only are in the Figure 13.

Table 5 Ergopeptines

Alkaloid	*Structure*	*Source*	*Growing*	*References*
Ergotamine	44	*Claviceps purpurea*	parasitic	Stoll, 1945, 1952
α-Ergosine	45	*Claviceps purpurea*	parasitic	Smith and Timmis, 1936, 1937; Stoll, 1952
Ergocristine	46	*Claviceps purpurea*	parasitic	Stoll and Burckhard, 1937; Stoll, 1952
α-Ergokryptine	47	*Claviceps purpurea*	parasitic	Stoll and Hofmann, 1943; Stoll, 1952; Schlientz *et al.*, 1968
Ergocornine	48	*Claviceps purpurea*	parasitic	Stoll and Hofmann, 1943; Stoll, 1952
Ergostine	49	*Claviceps purpurea*	parasitic	Schlientz *et al.*, 1964
β-Ergokryptine	50	*Claviceps purpurea*	parasitic	Schlientz *et al.*, 1968
Dihydro-α-ergosine	51	*Claviceps africana*	parasitic, on *Sorghum vulgare*	Mantle and Waight, 1968
Ergonine	52	*Claviceps purpurea*	parasitic, on rye	Brunner *et al.*, 1979

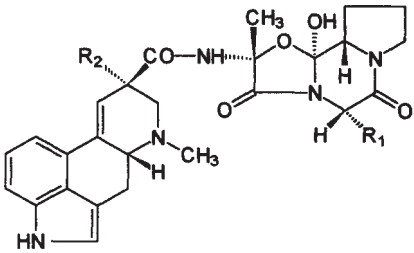
Table 5 (*Continued*)

Alkaloid	*Structure*	*Source*	*Growing*	*References*
α-Ergoptine	53	*Claviceps purpurea*	parasitic, on rye	Brunner *et al.*, 1979
Ergovaline	54	*Claviceps purpurea*	parasitic, on rye	Brunner *et al.*, 1979
8α-Hydroxy-ergotamine	55	*Claviceps purpurea*	parasitic, on rye	Krajíček *et al.*, 1979
Ergobutine	56	*Claviceps purpurea*	saprophytic	Bianchi *et al.*, 1982
Ergobutyrine	57	*Claviceps purpurea*	saprophytic	Bianchi *et al.*, 1982
12′-*O*-Methyl-ergocornine	58	*Claviceps purpurea*	saprophytic	Crespi-Perellino *et al.*, 1987
12′-*O*-Methyl-α-ergokryptine	59	*Claviceps purpurea*	saprophytic	Crespi-Perellino *et al.*, 1987
Ergogaline	60	*Claviceps purpurea*	parasitic, on rye	Cvak *et al.*, 1994a
β,α-Ergoannine	61	*Claviceps purpurea*	parasitic, on rye	Cvak *et al.*, 1994b; Szántay *et al.*, 1994
Ergoladinine	62	*Claviceps purpurea*	parasitic, on rye	Cvak *et al.*, 1996
8α-Hydroxy-α-ergokryptine	63	*Claviceps purpurea*	parasitic, on rye	Cvak *et al.*, 1997

Ergopeptams

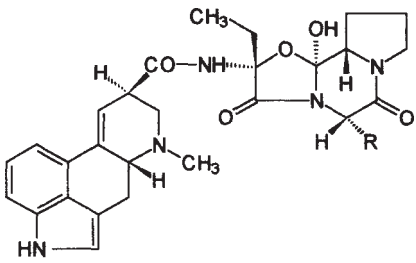
Ergopeptams (non-cyclol alkaloids, lactam alkaloids) are a relatively new group of peptidic EA. The first member of the group—ergocristam was described by Stütz *et al* (1973). Two other natural ergopeptams, ergocornam and α-ergokryptam were isolated from field ergot by Flieger *et al.* (1981). The last three known ergopeptams (*ß*-ergokryptam, α, *ß*-ergoannam and *ß*, *ß*-ergoannam) were isolated as the products of directed biosynthesis aimed at the saprophytic production of *ß*-ergokryptine by the feeding of isoleucine (Flieger *et al.*, 1984). The same authors suggested the new nomenclature of this new class of EA, using suffix -am to the name of ergopeptine containing the same amino acids.

Ergopeptams are minor products of the alkaloid biosynthesis. The probability of lactam formation decreases with the steric size of the side chain of the first amino acid. The lactam alkaloids originate as a result of easy racemisation of L-proline in *cis*-dioxopiperazines (biosynthetic precursors of ergopeptines—see Chapter 5) to the thermodynamically favoured *trans*-dioxopiperazines (Day *et al.*, 1985). The racemisation probably competes with hydroxylation of the



44 ergotamine, R_1 = benzyl, R_2 = H
45 α-ergosine, R_1 = isobutyl, R_2 = H
54 ergovaline, R_1 = isopropyl, R_2 = H
55 8α-hydroxyergotamine, R_1 = benzyl, R_2 = OH

Figure 10 Natural ergopeptines: ergotamine group



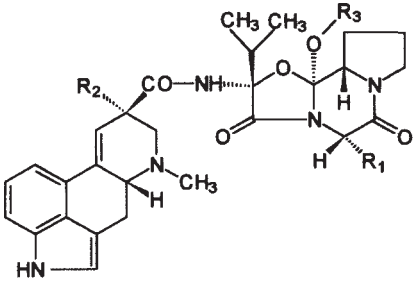
49 ergostine, R = benzyl
52 ergonine, R = isopropyl
53 α-ergoptine, R = isobutyl
56 ergobutine, R = ethyl

Figure 11 Natural ergopeptines: ergoxine group

amino acid attached to lysergic acid (Quigley and Floss, 1981). The probability of this process also decreases with increasing size of the first amino acid side chain. Consequently, only ergopeptams with valine, leucine or isoleucine in position 1 of the peptidic moiety have been isolated yet.

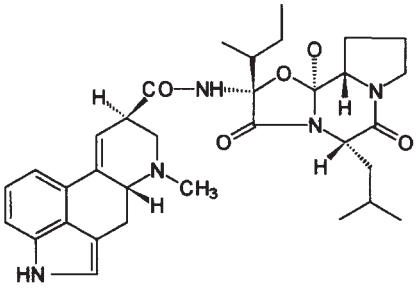
The amidic bond between the first amino acid and the dioxopiperazine part of ergopeptams can be easily cleaved by nucleophiles. Lysergyl-valinamide is formed by aminolysis and lysergyl-valine methyl ester by methanolysis of ergocristam. This fact is necessary to take into consideration when ergopeptams are isolated or analysed. Previously described new natural alkaloid, lysergylvalin methyl ester (Schlientz *et al.*, 1963), was the artefact of ergocristam decomposition.

References about the isolation of all the natural ergopeptams are summarised in the Table 6 and their structures are in the Figure 14.

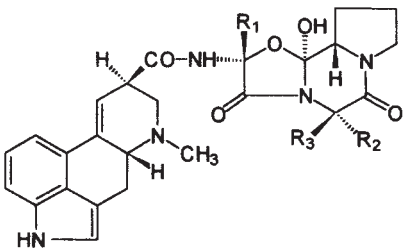


46 ergocristine, R_1 = benzyl, R_2 = R_3 = H
47 α-ergokryptine, R_1 = isobutyl, R_2 = R_3 = H
48 ergocornine, R_1 = isopropyl, R_2 = R_3 = H
50 β-ergokryptine, R_1 = *sec*-butyl, R_2 = R_3 = H
57 ergobutyrine, R_1 = ethyl, R_2 = R_3 = H
58 12'-*O*-methyl-ergocornine, R_1 = isopropyl, R_2 = H, R_3 = methyl
59 12'-*O*-methyl-α-ergpkryptine, R_1 = isobutyl, R_2 = H, R_3 = methyl
60 ergogaline, R_1 = 2-methyl-butyl, R_2 = R_3 = H
62 ergoladine, R_1 = methylthiomethyl, R_2 = R_3 = H
63 8α-hydroxy-α-ergokryptine, R_1 = isobutyl, R_2 = OH, R_3 = H

Figure 12 Natural ergopeptines: ergotoxine group



61 β,α-ergoannine



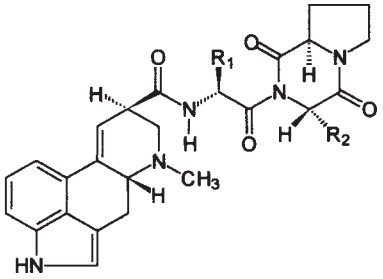
ergobine, R_1 = CH_3, R_2 = ethyl, R_3 = H
5'-*epi*-β-ergokryptine, R_1 = isopropyl, R_2 = H, R_3 = *sec*-butyl

Figure 13 *β*, α-Ergoannine and some ergopeptines prepared by directed biosynthesis

Table 6 Ergopeptams

Alkaloid	*Structure*	*Source*	*Growing*	*References*
Ergocristam	64	*Claviceps purpurea*	saprophytic parasitic, on rye	Stütz *et al.*, 1973 Černý *et al.*, 1976
α-Ergokryptam	65	*Claviceps purpurea*	parasitic, on rye	Flieger *et al.*, 1981 Stuchlík *et al.*, 1982
Ergocornam	66	*Claviceps purpurea*	parasitic, on rye	Flieger *et al.*, 1981 Stuchlík *et al.*, 1982
β-Ergokryptam	67	*Claviceps purpurea*	saprophytic*	Flieger *et al.*, 1984
β,β-Ergoannam	68	*Claviceps purpurea*	saprophytic*	Flieger *et al.*, 1984

*directed biosynthesis.



64 ergocristam, R_1 = isopropyl, R_2 = benzyl
65 α-ergokryptam, R_1 = isopropyl, R_2 = isobutyl
66 ergocornam, R_1 = isopropyl, R_2 = isopropyl
67 β-ergokryptam, R_1 = isopropyl, R_2 = *sec*-butyl
68 β,β-ergoannam, R_1 = *sec*-butyl, R_2 = *sec*-butyl

Figure 14 Ergopeptams (natural and prepared by directed biosynthesis)

7.3. OTHER SECONDARY METABOLITES

7.3.1. Pigments

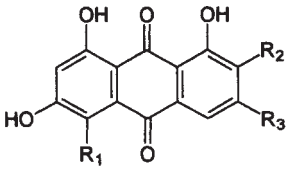
Ergot contains 1–2% of pigments (Lorenz, 1979; Schoch *et al.*, 1985). Violet, yellow-red and yellow pigments were isolated from various *Claviceps* species (ApSimon *et al.*, 1965; Franck *et al.*, 1965a; Kornhauser *et al.*, 1965; Perenyi *et*

al., 1966; Franck, 1980). These pigments belong to several structural groups: anthraquinones, biphenyls and organic iron complexes (Šmíd and Beran, 1965).

Three individual anthraquinone yellow-red pigments have been isolated from ergot: endokrocine, clavorubin and emodin-2-carboxylic acid—Figure 15—(Franck, 1960; Betina, 1988).

The yellow biphenyl pigments called ergochromes are dimers of tetrahydroxanthon units: four xanthon units, signed A, B, C and D were described by Franck *et al.,* (1965a, b)—Figure 16. Four particular dimers were described: ergoflavine (ergochrome CC 2, 2´), ergochrysine A (ergochrome AC 2, 2´), ergochrysin B (ergochrome BC 2, 2´) and secalonic acid A (ergochrome AA 4, 4´)—Figure 17. The secalonic acid A is the enantiomer of secalonic acid D the mutagenic and teratogenic metabolite produced by some species of *Penicillium* genus (Ciegler *et al.,* 1980; Betina, 1988).

Some species of *Claviceps* genus produce 2, 3-dihydroxybenzoic acid which forms violet complexes with Fe^{3+} (Kelleher *et al.,* 1971).



endocrocin, R_1 = H, R_2 = COOH, R_3 = CH_3
clavorubin, R_1 = OH, R_2 = COOH, R_3 = CH_3
emodin-2-carboxylic acid, R_1 = H, R_2 = H, R_3 = COOH

Figure 15 Anthraquinone pigments isolated from genus *Claviceps*

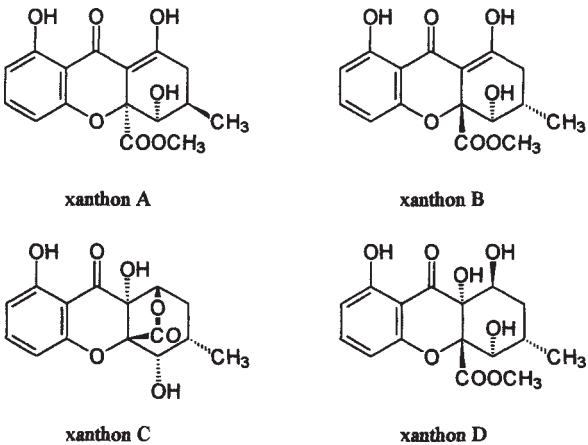
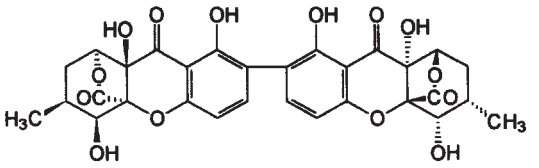
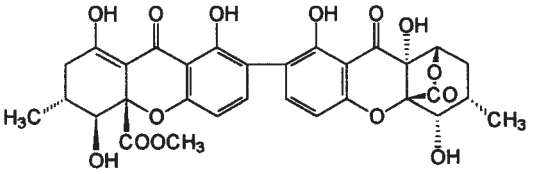


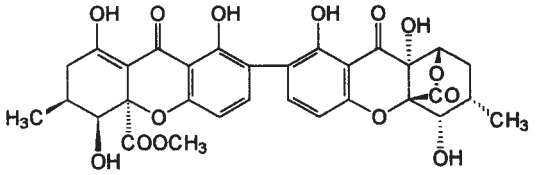
Figure 16 Tetrahydroxanthon units of biphenyl pigments



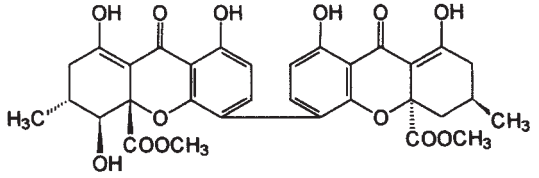
ergoflavin



ergochrysin A



ergochrysin B

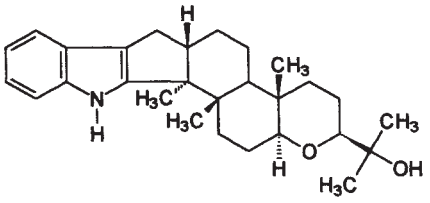


secalonic acid A

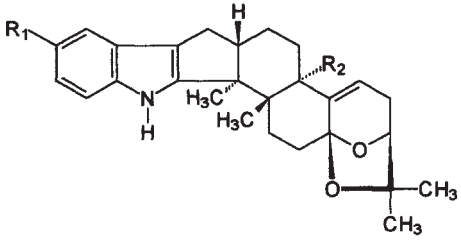
Figure 17 Biphenyl pigments (ergochromes) isolated from genus *Claviceps*

7.3.2. Mycotoxins

Five tremorgenic mycotoxins, containing indole condensed with a diterpenoid unit, have been isolated from *Claviceps paspali* paraziting on the grass *Paspalum dilatatum* (Acklin *et al.*, 1977; Cole *et al,* 1977; Scott, 1984). Their structures are in the Figure 18.



paspaline



paspalicine, R 1 = H, R2 = H
paspalinine, R 1 = H, R2 = OH
paspalitreme A, R 1 = $CH_2CH{=}C(CH_3)_2$, R2 = OH
paspalitreme B, R 1 = *trans*$CH{=}CHC(OH)(CH_3)_2$, R2 = OH

Figure 18 Mycotoxins isolated from genus *Claviceps*

7.4. PRIMARY METABOLITES

7.4.1. Lipids

Ergot contains usually 30–35% of oil, characterised by a high content of ricinoleic acid (12*(R)*-hydroxyoctadec-9*(Z)*-enoic acid)—up to 36%. Most of the oil is composed of triacylglycerols of estolide type in which, at least, one of the hydroxyl groups of glycerol is esterified by ricinoleic acid or its dimer or trimer (Morris and Hall, 1966; Mangold, 1967). The other hydroxyls of estolides are esterified by common higher fatty acids: palmitic, stearic, palmitoleic, oleic and linoleic (Batrakov and Tolkachev, 1997). Besides estolides the oil is created by common triacyl-, diacyl- and monoacyl-glycerols and free fatty acids. The cell membranes of ergot contain phospholipids (Anderson *et al.*, 1964).

Discovery of sterols began in 1889 when **ergosterol** was isolated from ergot (Tanret, 1889). Later, some other sterols and their precursors were isolated from ergot: fungisterol (Tanret, 1908), 7,22-ergostadienol (Heyl and Swoap, 1930; Heyl, 1932), squalene and cerevisterol (Wieland and Coutelle, 1941). Recently 15 sterols were identified in different *Claviceps* species, using GC-MS technique (Křen *et al,* 1986).

7.4.2. Other Primary Metabolites

Formation and storage of saccharides depends on the nutrient source, e.g., the glucose rich medium supports the extracellular accumulation of polysacharides (Perlin and Taber, 1963). The saccharide typical for *Claviceps* genus is trehalose (Taber and Wining, 1963; Taber, 1964; Vining and Taber, 1964). Besides saccharides, 10–17% of polyols, mainly mannitol, is accumulated in the mycelium of *Claviceps* genus (Lewis and Smith, 1967). Also stable viscous glucan is produced by genus *Claviceps,* one consists of *ß*-D-glucopyranosyl units, most of which constitute a (1→3)-linked main chain. Other units are attached as branches of the main chain by (1→6)-linkages and are distributed in a relatively uniform arrangement along the length of the polymer (Perlin and Taber, 1963; Buck *et al.,* 1968). This glucan could be autolysed by constitutive *ß*(1→3)-glucanase and *ß*-glucosidase to d-glucose (Dickerson *et al.,* 1970) or by exo type of laminarinase to D-glucose and gentobiose (Perlin and Taber, 1963). The content of polyphosphates in analysed saprophytic strains fluctuates between 0.1 and 2.0 in the dry basis of the mycelium (Taber and Wining, 1963; Kulaev, 1979).

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