13. INDUSTRIAL PRODUCTION OF ERGOT ALKALOIDS

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13.1. INTRODUCTION

This chapter contains information about all the therapeutically used ergot alkaloids and their manufacture. Not all such information can be found in the literature and supported by references. The technology used for manufacture can be traced in the patent literature but not all the patented processes are actually used in the production and, on the other hand, not all the technologies used have been patented. So at least a part of this information is based on personal communication only or is deduced from some indirect cues—for instance the profile of impurities. Further information, not usually published is the amount of individual manufactured products. These estimations are based on a long-term experience in ergot alkaloid business. Even if all such estimations can be inaccurate, I believe that in a book published in a series "Industrial profiles" they cannot be omitted.

The history of industrial production of ergot alkaloids began in 1918, when Arthur Stoll patented the isolation of ergotamine tartrate (Stoll, 1918), which the Sandoz company introduced on the market in 1921. Until the end of World War II, Sandoz remained virtually the only real industrial ergot alkaloid producer. The first competitors appeared in the fifties. Sandoz is still the world leading ergot alkaloid producer (lately under the name Novartis). The company sells the whole production in its own pharmaceutical products. Other major producers sell most of their products as "bulk pharmaceutical chemicals": Boehringer Ingelheim (Germany), Galena (Czech Republic), Gedeon Richter (Hungary), Lek (Slovenia), Poli (Italy). Besides these producers manufacturing a broad spectrum of ergot alkaloids, two other companies influenced ergot research, manufacture and business—see Chapter 1. History of ergot research. Farmitalia (Italy, now a part of Pharmacia-Upjohn) developed and produces nicergoline (Sermion) and cabergoline (Dostinex), and Eli Lilly developed and produces pergolide mesylate (Permax). Some others, usually locally active producers, exist in India, Finland and Poland and other companies produce some products from purchased intermediates: Rhone Poulenc (France), Indena and Linea Nuova (both Italy) producing nicergoline and Sanofi and Piere Fabre (both France) manufacturing dihydroergotamine and dihydroergocristine. Schering AG (Germany) and Maruko Seiyaku (Japan) were, or are, active in ergot alkaloid research.

A distinct trend can be seen in the use of ergot alkaloids in the last few decades. While the therapeutic use of classical ergot alkaloids (ergotamine,

dihydroergotamine, dihydroergotoxine) has been stable for many years and their production has been increasing only a little, the therapeutic use and consumption of new, semisynthetic derivatives is growing quickly (nicergoline, pergolide). The annual world production of ergot alkaloids can be estimated at 5000–8000 kg of all ergopeptines and 10000–15000 kg of lysergic acid, used for the manufacture of semisynthetic derivatives, mainly nicergoline. The larger part of this production comes from fermentations (about 60%), the rest comes from the field ergot. The estimation of individual product volumes is given in part 4 of this chapter.

13.2. SOURCES OF ERGOT ALKALOIDS

13.2.1. Field Ergot

Collected wild ergot was the only source of ergot alkaloids throughout the history, and ergot from artificial cultivation has remained an important source for alkaloid production. Two world leading alkaloid manufacturers, Boehringer Ingelheim and Galena, are the main producers of ergot.

Wild ergot was poorly suited for the isolation of alkaloids because of its great variability in alkaloid content and spectrum. In fact, it was the success of the artificial cultivation of ergot which created a basis for large-scale production of ergot alkaloids (Well, 1910; Hecke, 1922, 1923). Enormous effort was devoted to the selection of strains producing a defined spectrum of alkaloids. Later, similar effort was aimed at the economical parameters: yield of ergot and alkaloid content. While in the forties the average yield of ergot was 400 kg/ha (Stoll and Brack, 1944), today the yields of leading producers are over 1000 kg/ha. Similar development has taken place in the content of ergot alkaloids. Producer strains used by the leading manufacturers produce above 1% of alkaloids. In regard of the alkaloids produced, there are strains producing all the desired ergopeptines as separate single alkaloids, or producing an optimal mixture of alkaloids (e.g. a mixture of ergotoxine alkaloids for manufacture of dihydroergotoxine).

A special problem is the content of undesirable minor ergopeptines—potential impurities in the final products. In spite of all the effort devoted to minimising their formation, they always persist in the ergot and the purification processes used by individual producers can remove them to a different extend. This can be demonstrated by the isolation of many novel alkaloids in the laboratories of leading ergot alkaloid manufacturers (Krajíček *et al.,* 1979; Szantay *et al.,* 1994; Cvak *et al.,* 1994, 1996, 1997). Besides ergopeptines, each ergot contains some simple lysergic acid derivatives, mainly ergine (lysergic acid amide) and ergometrine. These are not usually taken as undesirable because they can be easily removed during ergopeptine purification and, moreover, can be used for lysergic acid manufacture. Ergometrine, when present in a higher concentration (sometimes up to 0.1% of the total alkaloid content of about 1%), can be isolated as a by-product.

All the aspects of parasitic ergot production are described in detail in Chapter 11—Parasitic production of ergot.

Ergot Extraction

Extraction of ergot is described mainly in older literature devoted to first isolations of new alkaloids (for example Stoll, 1945), or in the patent literature. When analysing the patent literature, one has to be careful. Many patented procedures are so complicated that they can hardly be used for industrial production. While a two-stage process is usually used in lab-scale extraction of alkaloids—defatting by a nonpolar solvent being followed by alkaloid extraction by a more polar solvent, a one-stage direct extraction is used on industrial scale.

Patented procedures use both organic solvent and water extraction. Although the solubility of ergopeptines in diluted aqueous acids is satisfactory, ergot swells in such solvents and the problems connected with this fact have never been overcome. Only organic solvents are therefore used for industrial-scale extraction. Methylenechloride, trichloroethylene, ethyl acetate, acetone, methylisobutyl ketone and mixtures of toluene with methanol or ethanol and ether with ethanol are or were used. Percolation technology is used to reach satisfactory yield, using a battery of percolators or some type of a continual extractor (usually carousel-type extractor). Extraction of at least 95% of alkaloids present in the ergot is usually accepted as economically satisfactory.

Primarily obtained extracts are usually subjected to liquid-liquid extraction using aqueous diluted acids. Alkaloids are transferred into the water phase, whereas fats remain in the organic reffinate. Further processing of aqueous extracts depends on the experience of individual producers. In any case, the product of ergot extraction is a crude concentrate of alkaloids containing all the alkaloids present in ergot (sometimes excluding the water-soluble ergometrine) and only a low amount of other ballast components. A very important factor which is necessary to take into account is the epimerisation of lysergic acid derivatives—ergopeptines into isolysergic acid derivatives—ergopeptinines—see Figure 1. Individual processes differ in the rate of

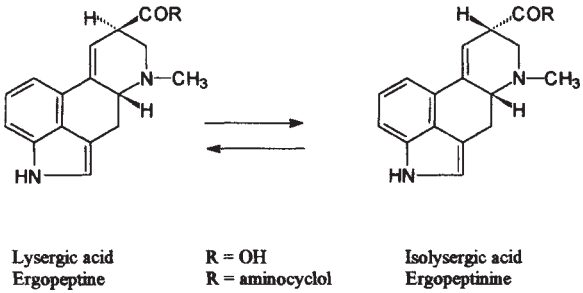

Figure 1 Epimerisation of lysergic acid derivatives

epimerisation and each crude alkaloid concentrate contains higher or lower amounts of ergopeptinines or the sole product of extraction is the respective ergopeptinine.

Purification of Ergot Alkaloids

The processes used for purification of individual alkaloids depend on the quality of the starting crude concentrate and the required quality of the product. There are so many processes developed by individual producers that only their general features can be mentioned here.

The goal of the purification process is the complete removal of both ballast components and minor undesirable ergopeptines or other alkaloids. While the complete elimination of ballast components is not so difficult, the complete elimination of minor alkaloids was successful only in some cases and practically each purified product (ergopeptine or dihydroergopeptine) contains some minor ergopeptines. In the past, many processes for separation of individual ergopeptines were developed using crystallisation, liquid-liquid extraction (the Craig process) or preparative-scale chromatography. Such processes are usually no longer used, because better strains producing individual alkaloids were developed.

Two main separation operations are used for ergopeptine purification: 1. Crystallisation of alkaloids, both bases and their salts, from different solvents. 2. Preparative-scale chromatography on silica or alumina. Also epimerisation of ergopeptinine into ergopeptine is always a part of the purification process. The basic procedure for epimerisation of ergotaminine was described by Stoll (1945). The procedure was later developed for the epimerisation of all the ergopeptinines and it was repeatedly improved to reach higher yield and better quality of the product (for example Terdy *et al.*, 1981; Schinutschke *et al.*, 1979).

13.2.2. Fermentation

Fermentation of ergot alkaloids is the subject of Chapter 12 and so only *the state of the art* in the industrial-scale production of ergot alkaloids will be mentioned here.

Only submerged (deep) fermentation is used for ergot alkaloid production. The fermenter size depends on the quantity of the product required: ergot alkaloids are medium-size products and medium size fermenters are therefore used for their production—10 to 50 m^3. Inoculation of such fermenters must be done in multiple stages—3 or 4. The duration of the production stage is 12 to 21 days. Fermentation is used for the production of both ergopeptines and simple ergoline compounds used for partial synthesis of therapeutically used derivatives. Because these two cases differ in downstream processing, they will be discussed separately.

Ergopeptines

Processes for ergopeptine fermentation were developed by Sandoz (e.g., Kobel and Sanglier, 1976, 1978), Farmitalia (Amici *et al.,* 1966, 1969), Gedeon Richter (Udvardy *et al.,* 1982), Lek and Poli. The production of ergopeptines presented in the literature is below 1 g/1 but the top production is now between 1 and 2 grams per liter of fermentation broth. The solubility of all ergopeptines in water at a pH value suitable for the fermentation process is low and this is the reason why most of produced alkaloids remain in the biomass (mycelium)—the liquid phase usually contains less than 5% of all the alkaloids of the fermentation broth.

Two types of downstream processes are used for alkaloid extraction. In a two-stage process the mycelium is filtered off and the alkaloids are isolated from the mycelium only. The filtrate is usually processed in a waste-water-treatment plant. The extraction of alkaloids from the mycelium is a process similar to ergot extraction, water-miscible organic solvents being usually used for this operation. In a one stage-process (direct extraction) the whole fermentation broth is subjected to extraction with a water-immiscible solvent (ethyl acetate, butyl acetate). The two-stage process is less effective but it does not require a special centrifugal extractor which is used for the direct extraction.

The processes for purification of ergopeptines are the same as those used for the isolation of crude alkaloid concentrates from ergot and they are therefore not discussed here.

Simple Ergolines

The need for simple ergoline derivatives was initiated by the progress in synthetic chemistry which enabled both the synthesis of natural alkaloids from their ergoline precursors (ergometrine, ergopeptines) and the synthesis of new semisynthetic derivatives providing pharmacological and therapeutical benefits (methylergometrine, methysergide, nicergoline). A cheap source of lysergic acid or some other ergoline precursor was a prerequisite for such syntheses. The first suitable product available by fermentation was elymoclavine—Figure 7 (Abe *et al.,* 1952), to be followed by lysergic acid hydroxyethylamide—Figure 6 (Arcamone *et al.,* 1961) and by paspalic acid—Figure 5 (Kobel *et al.,* 1964). Also ergometrine—Figure 11—is now available by submerged fermentation (Rutschmann and Kobel, 1963). Lysergic acid hydroxyethylamide and paspalic acid are now the most important simple ergoline products obtained by fermentation. They are converted into lysergic acid which is the starting material for chemical syntheses. Fermentation processes used for their production can produce broth containing up to 5 grams of alkaloids per litter.

All the above mentioned simple ergoline products are relatively well soluble in water and are therefore present mostly in the liquid phase of the fermentation broth. The mycelium is usually discharged after filtration and only the filtrate

is used for alkaloid isolation. Two different processes can be used for this purpose: liquid-liquid extraction into an organic solvent (with the exception of paspalic acid which cannot be extracted into any organic solvent) and sorption on an ion exchanger. The latter is the preferable method of isolation of simple ergoline products from fermentation broths.

13.2.3. Higher Plants

The occurrence of ergot alkaloids in higher plants is discussed in Chapter 18. Of practical importance is the industrial isolation of lysergol from the Kaladana seeds. Kaladana is the aboriginal name for a plant, botanically classified as *Ipomoea (Ipomoea hederacea, Ipomoea parasitica, Caloniction Ipomoea)* and growing wildly in the for-Himalaya area of India. Its seeds contain up to 0.5% of lysergol and only a low amount of other alkaloids. Patents belonging to the Italian company Simes (later Farmex) describe the isolation of lysergol from these seeds and the process for nicergoline manufacture from lysergol (Simes, 1971; Mora, 1979; Bernardelli, 1987). Production of nicergoline from this source is not very important and its competitivity is questionable. It depends on the crop of wildly growing Kaladana seeds and the reliability of such a source is low.

13.2.4. Organic Synthesis

Considerable effort was devoted to the total synthesis of ergoline compounds. Information about this area can be found in a review (Ninomyia and Kiguchi, 1988). Although many interesting approaches were developed, a process producing ergot alkaloids more effectively than is their isolation from natural material was never found.

Partial synthesis of more complex alkaloids from simple ergoline precursors brought more success. The first total synthesis of the peptidic part of ergopeptines (the cyclol part) was achieved by Sandoz researchers (Hofmann *et al.,* 1961). This synthesis (Figure 2) was extended to all the natural ergopeptines, their dihydroderivatives and other non-natural analogues and derivatives—(i.e. Stadler *et al.,* 1963, 1969; Stadler and Hofmann, 1969; Hofmann *et al.,* 1963; Stütz *et al.,* 1969; Guttmann and Huguenin, 1970). Alternative syntheses of the cyclol moiety were described by Stadler (1978 and 1980) and Losse (1982). The synthesis of the cyclol part of natural ergopeptines was developed by Sandoz up to the industrial scale and it is used for the manufacture of ergopeptines and dihydroergopeptines. The source of the ergoline part is a mixture of lysergic, isolysergic and paspalic acids of fermentation origin.

Chemical modification of the ergoline skeleton is described in Chapter 8—"Chemical modification of ergot alkaloids". From the point of view of industrial production, the first such modification was hydrogenation of ergopeptines to dihydroergopeptines, first described by Stoll and Hofmann (1943a). Later, many modifications of hydrogenation were patented using

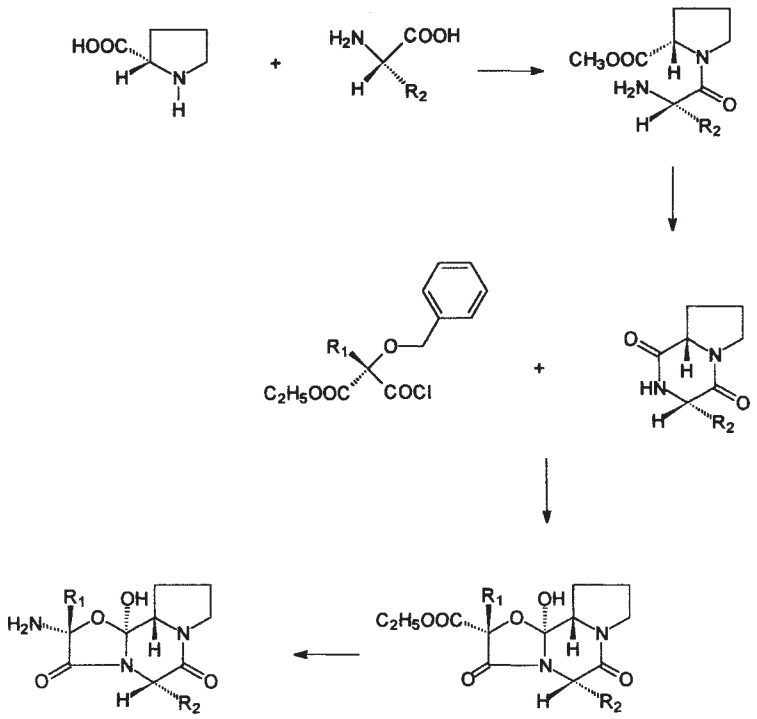

Figure 2 Synthesis of cyclol moiety of natural ergopeptines: R_1=methyl, ethyl or isopropyl; R_2=benzyl, isopropyl, isobutyl or *sec*-butyl

different catalysts (PtO_2, palladium, Raney-nickel) and claiming some special conditions. Lysergic acid derivatives are hydrogenated easily (at atmospheric pressure) and stereoselectively, forming dihydroderivatives with *trans* connection of C and D rings. Isolysergic acid derivatives have to be hydrogenated at a higher pressure and a mixture of *trans* (ergoline-I) and *cis* (ergoline-II) dihydroderivatives is obtained. The ratio of ergoline-I to ergoline-II can be modified by reaction conditions (Sauer *et al.,* 1986).

Successful therapeutic use of some semisynthetic ergolines initiated the search for new synthetic methods giving higher yield and better product quality. Looking for new, patentable processes was another goal. Many procedures for bromination of ergoline compounds were developed aiming at the synthesis of bromokryptine (Troxler and Hofmann, 1957; Ručinan *et al.,* 1977; Stanovnik *et al.,* 1981; Börner *et al.,* 1983; Megyeri *et al.,* 1986; Cvak *et al.,* 1988). Investigation of a new process for the manufacture of nicergoline brought new procedures for indole nitrogen alkylation (Troxler and Hofmann, 1957a; Ručman, 1978; Šmidrkal and Semonský, 1982; Cvak *et al.,* 1983; Gervais, 1986; Marzoni and Garbrecht, 1987).

Very interesting is the photochemically initiated addition of methanol to the ergolene skeleton (methyl lysergate or lysergol), which is the key step in

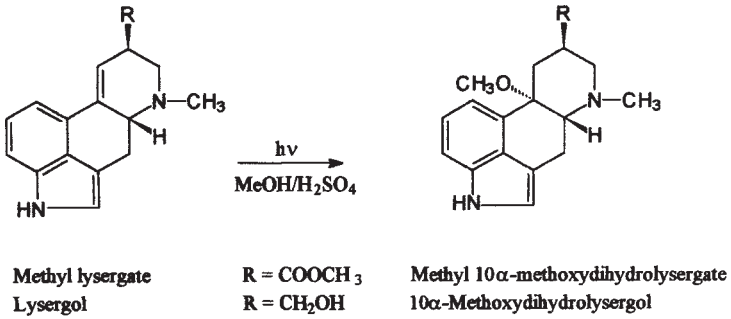

Figure 3 Photochemical methoxylation of methyl lysergate and lysergol

nicergoline synthesis (Figure 3). The original work of Hellberg (1957) on the water addition to ergopeptines, in which their acidic aqueous solutions were irradiated by UV light (10-hydroxy derivatives called lumi-derivatives were produced), was extended to an industrial-scale method. The photomethoxylation is a stereoselective process (more than 90% of 10α-methoxy derivative) giving a quantum yield of 0.48 (Cvak, 1985). It is one of the rare industrial applications of photochemistry (Bernardi *et al.,* 1966; Stres and Ručman, 1981; Bombardelli and Mustich, 1985).

Another frequently used industrial synthesis is the coupling of lysergic or dihydrolysergic acids with amines, which is the key step of the syntheses of ergometrine and methylergometrine and ergopeptines and dihydroergopeptines. Many coupling reagents were suggested for this purpose (Pioch, 1956; Garbrecht, 1959; Frey, 1961; Hofmann and Troxler, 1962; Černý and Semonský, 1962; Patelli and Bernardi, 1964; Stuchlík *et al.,* 1985), but only a few are really used on the industrial scale.

Some other chemical modifications of ergot alkaloids are used for production of particular semisynthetic, therapeutically used derivatives. They are mentioned in part 4 of this chapter.

13.3. INTERMEDIATES FOR INDUSTRIAL PARTIAL SYNTHESES OF ERGOT ALKALOIDS

13.3.1. Lysergic Acid

Lysergic acid is the basic and universal intermediate for the syntheses of all the therapeutically used ergot alkaloids. It is produced in the chiral form with configuration *5R* and *8R* (designations d-lysergic acid or D-lysergic acid are also used). The annual world production of lysergic acid can be estimated at 10–15 tons. Most of this quantity is used for nicergoline manufacture, the rest for ergometrine, methylergometrine and methysergide. Novartis company uses lysergic acid for the syntheses of ergopeptines.

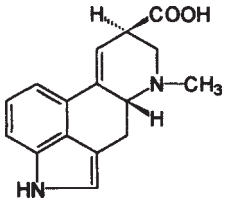

Figure 4 d-Lysergic acid

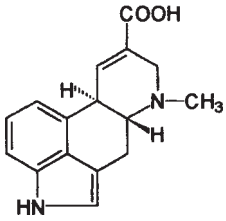

Figure 5 Paspalic acid

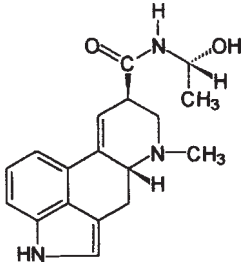

Figure 6 Lysergic acid hydroxyethylamide

There are two methods for lysergic acid manufacture. The first one is hydrolysis of ergopeptines isolated from ergot or of fermentation origin, the second one is the direct fermentation of one of its simple precursor—paspalic acid (Figure 5) or lysergic acid hydroxyethylamide (Figure 6). The former process is based on works of Jacobs and Craig (1934, 1934a, 1935, 1935a, 1936) on alkaline hydrolysis of ergopeptines. Many patents appeared later, specifying reaction conditions or isolation and purification of the product (i.e. Ručman, 1976; Cvak *et al.*, 1978).

The majority of lysergic acid is produced fermentatively. Because there exists no strain producing lysergic acid as the main secondary metabolite, it is manufactured indirectly *via* its available precursors. While paspalic acid is converted into lysergic acid very easily (Troxler, 1968), the lysergic acid hydroxyethylamide is easily hydrolysed only to ergine and erginine, which

must be hydrolysed to lysergic acid by alkaline hydrolysis similarly as ergopeptines.

13.3.2. Dihydrolysergic Acid

Dihydrolysergic acid can be used only for the manufacture of dihyhroergopeptines, metergoline, pergolide, terguride and cabergoline. Its world production is very limited. It can be obtained by the hydrolysis of dihydroergopeptines (often wastes from their purification) or by hydrogenation of lysergic or paspalic acids.

13.3.3. Lysergol

As mentioned above, lysergol (Figure 8), isolated from the Kaladana seeds is used for the manufacture of nicergoline. There are two other processes for lysergol production. Methyl lysergate can be reduced to lysergol by lithium aluminium hydride (Stoll *et al.*, 1949) or sodium borohydride (Beran *et al.*, 1969). The latter process uses elymoclavine (Figure 7) available by fermentation. Eich (1975) described the isomerisation of elymoclavine to lysergol.

13.3.4. Dihydrolysergol

Dihydrolysergol (Figure 9) is the intermediate for the production of pergolide. It is produced by the hydrogenation of lysergol or elymoclavine. Production from dihydrolysergic acid *via* reduction of its methyl ester is also possible.

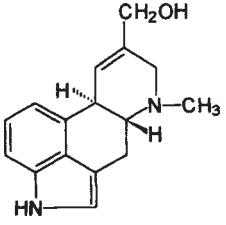

Figure 7 Elymoclavine

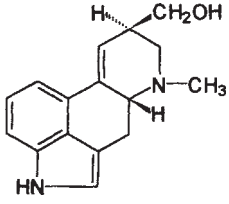

Figure 8 Lysergol

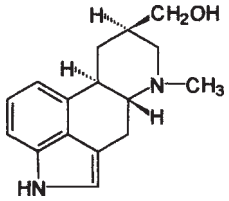

Figure 9 Dihydrolysergol

13.3.5. Other Intermediates

There are some other intermediates used for the manufacture of other therapeutically used alkaloids. Lisuride can be prepared from erginine (Sauer and Haffer, 1981; Bulej *et al.*, 1990), which is obtained by partial hydrolysis of ergopeptines or lysergic acid hydroxyethylamide. Dihydroergine, produced by partial hydrolysis of dihydroergopeptines, can be used for the manufacture of metergoline.

13.4. THERAPEUTICALLY USED ERGOT ALKALOIDS AND THEIR PRODUCTION

All the therapeutically used ergot alkaloids and their derivatives are described in the following part of the chapter. The main qualitative requirements of actual world leading pharmacopoeias (Eur. Ph. 1997, USP 23 and JP XIII), in which the substances have been incorporated and the names of pharmaceutical specialities with ergot alkaloids (Negwer, 1994) are presented here.

Ergot alkaloids are rather complicated molecules. As a consequence, many chemical names of ergot alkaloids, both correct and faulty, can be found in the literature. Only some examples of different types of nomenclature are presented here, namely the nomenclature according to Chemical Abstracts, where the trivial names ergoline for the tetra-cyclic system and ergotaman for the seven-cyclic ergopeptine system are used, and the nomenclature according to the IUPAC rules for heterocyclic compounds.

Pharmacology, toxicology and metabolism of therapeutically used ergot alkaloids were reviewed in monograph of Berde and Schild (1978) and therefore only references to newly developed products or to some new findings and reviews of older products are presented here.

13.4.1 Ergotamine

Chemical names: 2′-Methyl-5′-benzyl-ergopeptine;
12′-hydroxy-2′-methyl-5′-(phenylmethyl)-ergotaman-3′, 6′, 18-trione;
(6a*R*, 9*R*)-*N*-[(2*R*, 5*S*, 10a*S*, 10b*S*)-5-benzyl-10b-hydroxy-2-methyl-3, 6-dioxo-octahydro-8H-oxazolo [3, 2-a] pyrolo[2, 1-c]-pyrazin-2-yl]-7-methyl-4, 6, 6a, 7, 8, 9-hexahydroindolo-[4, 3-fg]quinoline-9-carboxamide

Structural formula:	See Figure 10	
Empirical formula:	base	$C_{33}H_{35}N_5O_5$
	tartrate	$(C_{33}H_{35}N_5O_5)_2 \cdot C_4H_6O_6$
Molecular weight:	base	581.7
	tartrate	1313.4
CAS No.	base	113–15–5
	tartrate	379–79–3

Specifications and their requirements:

Eur. Ph. 1997	Ergotamine tartrate	assay (titration): 98.0–101.0% in dry substance total impurities: not more than 1.5% (TLC) only one impurity more than 0.5% (TLC)
USP 23	Ergotamine tartrate	assay (titration): 97.0–100.5% in dry substance total impurities: not more than 2.0% (TLC) only one impurity more than 1.0% (TLC)
JP XIII	Ergotamine tartrate	assay (titration): not less than 98.0% in dry substance total impurities: not more than 2.0% (TLC)

Typical impurities: ergotaminine
aci-ergotamine
material isolated from both field ergot and fermentation broths contains usually some minor ergopeptines (ergosine, ergostine, ergocristine, α-ergokryptine or 8-hydroxyergotamine)

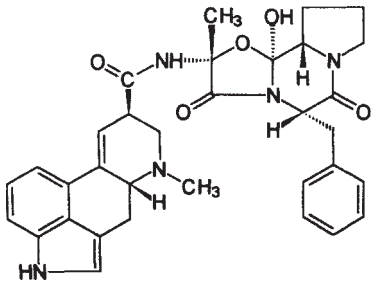

Figure 10 Ergotamine

Dosage forms:	Avetol, Bedergot, Cornutamin, Enxak, Ercal, Ergam, Ergane, Ergate, Ergocito, Ergofeina, Ergogene, Ergogyn, Ergo-Kranit mono, Ergomar "Fisons", Ergomigrin, Ergomine-S, Ergosanol SL, Ergostat, Ergostin, Ergota "Kanto", Ergotan, Ergotartrat, Ergoton-A, Ergotrat AWD), Etin, Exmigra, Exmigrex, Femergin, Fermergin, Gynecorn, Gynergen, Gynofort, Ingagen, Lagen, Lingrän, Lingraine, Lingrene, Masekal, Migretamine, Migrexa, Migtamin, Neo-Ergotin, Neo-Secopan, Pannon, Rigeta-min, Ryegostin, Secagyn, Secanorm, Secotamin, Secupan, Synergan, Vigrame, Wigrettes
Therapeutic use:	uterotonic, antimigrenic, vasoconstrictor, hemostatic
Introduction:	1921
World production:	1000–1500 kg per year
Bulk substance manufactures:	Boehringer Ingelheim (Germany)—isolation from ergot Galena (Czech Rep.)—isolation from ergot Lek (Slovenia)—fermentation Novartis (Switzerland)—synthesis Poli (Italy)—fermentation
Manufacture:	1. Isolation from field ergot 2. Isolation from fermentation broth 3. Synthesis from d-lysergic acid and synthetic peptidic moiety
References:	Kreilgard 1976 (anal.), Holger 1994 (therap.use)

13.4.2. Ergometrine

Other names:	Ergobasine Ergonovine	
Chemical names:	d-Lysergic acid-L-(+)-1-(hydroxymethyl)ethylamide; 9, 10-Didehydro-*N*-[*(S)*-2-hydroxy-1-methylethyl]-6-methylergoline-8*ß(S)*-carboxamide; (6a*R*, 9*R*)-*N*-[*(S)*-2-hydroxy-1-methylethyl]-7-methyl-4, 6, 6a, 7, 8, 9-hexahydroindolo [4, 3-fg]quinoline-9-carboxamide	
Structural formula:	See Figure 11	
Empirical formula:	base	$C_{19}H_{23}N_3O_2$
	maleate	$C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$
	tartrate	$(C_{19}H_{23}N_3O_2)_2 \cdot C_4H_6O_6$
Molecular weight:	base	325.4
	maleate	441.5
	tartrate	800.8
CAS No.:	base	60–79–7
	maleate	129–51–1
	tartrate	129–50–0

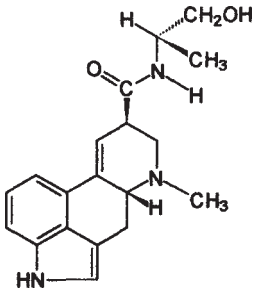

Figure 11 Ergometrine

Specifications and their requirements:

Eur. Ph. 1997	Ergometrine maleate	assay (titration): 98.0–101.0% in dry substance no impurity above 1.0% (TLC) only one impurity above 0.5% (TLC)
USP 23	Ergonovine maleate	assay (spectrophotometric): 97.0–103.0% total impurities: not more than 2.0% (TLC)
JP XIII	Ergometrine maleate	assay (spectrophotometric): not less than 98.0% total impurities: not more than 2.0% (TLC)

Typical impurities: ergometrinine
other impurities are specific for individual producers and depend on their manufacturing process

Dosage forms: Arconovina, Basergin, Cornocentin, Cryovinal, Ergofar, Ergomal, Ergomar Nordson, Ergomed "Promed", Ergomet, Ergometine, Ergometron, Ergomine, Ergostabil, Ergoton-B, Ergotrate Maleate, Ermalate, Ermeton, Ermetrin, Hemogen, Margonovine, Metriclavin, Metrisanol, Neofemergen, Novergo, Panergal, Secalysat-EM, Secometrin, Takimetrin, Uteron

Therapeutic use: uterotonic, oxytocic

Introduction: 1936

World production: 100–200 kg per year

Bulk substance manufactures: Boehringer Ingelheim (Germany)
Galena (Czech Rep.)
Lek (Slovenia)
Lonza (Switzerland)
Novartis (Switzerland)

Manufacture: 1. Isolation from field ergot as a minor by-product
2. Isolation from fermentation broth
3. Synthesis from d-lysergic acid and L-(+)-2-aminopropanol using different coupling reagents

References: Rutschmann and Kobel 1967 (fermentation), Stoll and Hofmann 1948 (synth.)
Reif 1982 (anal.)

13.4.3. Dihydroergotamine

Chemical names: 2´-Methyl-5´-benzyl-dihydroergopeptine;
9, 10-Dihydro-12´-hydroxy-2´-methyl-5´-(phenylmethyl)-ergotaman-3´, 6´, 18-trion;
(6a*R*, 9*R*, 10a*R*)-*N*-[(2*R*, 5*S*, 10a*S*)-5-benzyl-10b-hydroxy-2-methyl-3, 6-dioxo-octahydro-8H-oxazolo[3, 2-a]-pyrolo[2, 1-c] pyrazin-2-yl]-7-methyl-4, 6, 6a, 7, 8, 9, 10, 10aoctahydro-indolo [4, 3-fg]quinoline-9-carboxamide

Structural formula: See Figure 12

Empirical formula: base $C_{33}H_{37}N_5O5$
mesylate $C_{33}H_{37}N_5O_5{\cdot}CH_4O_3S$
tartrate $(C_{33}H_{37}N_5O_5)_2{\cdot}C_4H_6O_6$

Molecular weight: base 583.7
mesylate 679.8
tartrate 1317.5

CAS No.: base 511–12–6
mesylate 6190–39–2
tartrate 5989–77–5

Specifications and their requirements:

Eur. Ph. 1997	Dihydroergotamine mesilate	assay (spectrophotometric): 97.0–97.0–103.0% in dry substance no impurity above 0.5% and only two impurities above 0.2% (TLC)

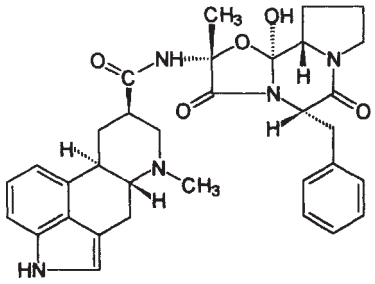

Figure 12 Dihydroergotamine

	Dihydroergotamine tartrate	assay (spectrophotometric): 97.0–103.0% in dry substance no impurity above 0.5% and only two impurities above 0.2% (TLC)
USP23	Dihydroergotamine mesylate	assay (spectrophotometric): 97.0–103.0% in dry substance total impurities: not more than 2.0% (TLC)
JP XIII	Dihydroergotamine mesilate	assay (titration): not less than 97.0% in dry substance no impurity above 0.5% and only two impurities above 0.2% (TLC)

Main impurities: ergotamine, egotaminine, aci-dihydroergotamine material produced *via* extraction from ergot or fermentation broth usually contains some minor dihydroergopeptines (dihydroergosine, dihydroergostine, dihydroergocristine, dihydro-α-ergokryptine, dihydro-8-hydroxy-ergotamine)

Dosage forms: Adhaegon, Agit, Angionorm, Biosupren, Bobinium, Clavigrenin, Cornhidral, Cozetamin, Dergiflux, Dergolyoc, Dergot, Dergotamine, Detemes, DETMS, DHE 45, DHE-MS, DHE-Puren, DHE-Ratiopharm, DE-Ergotamin, DHE-Tablinen, DHE-Tamin, Diaperos "Materia", Diergo-Spray, Di-ergotan, Di-got, Digotamin, Dihydergot, Dihydroergotamin-Sandoz, Dihy-ergot, Dihytam, Dihytamin, Diidergot, Dirgotarl, Disecotamin, Ditamin, Divegal, D-Tamin, Eldoral Dumex, Elmarine Genepharm, Endophleban, Ergomimet, Ergont, Ergospaon, Ergotex, Ergotonin, Ergott, Ergovasan, Esikmin, For You, Hidergot, Hidrotate, Hydro-Tamin, Hyporal, Ikaran, Itomet, Kidira, Kodamaine, Kouflem, Migergon D, Migretil, Migrifen, Mitagot, Morena, Neomigran, Orsta-norm, Ortanorm, Panergot, Pefanicol, Pervone "Sanofi-Greece", Phlebit, Rayosu, Rebriden, Restal Tokyo "Tanabe", Seglor, Tamik, Tariyonal, Tonopres, Vasogin, Verladyn, Verteblan, Youdergot, Yougovasin

Therapeutic use: antimigrenic, sympatholytic, vasoconstric

Introduction: 1946

World production: 1500–2000 kg per year

Bulk substance manufactures:
Boehringer Ingelheim (Germany)
Galena (Czech Rep.)
Lek (Slovenia)
Novartis (Switzerland)
Piere Fabre (France)

Poli (Italy)
Sanofi (France)

Manufacture: 1. Hydrogenation of ergotamine isolated from field ergot or fermentation broth
2. Synhesis from dihydrolysergic acid and synthetic peptidic part

References: Marttin 1997 (pharmacokinetics)

13.4.4. Dihydroergotoxine

Other names: Ergoloid
Codergocrine

Chemical name: Dihydroergotoxine is a mixture of Dihydroergocristine, Dihydoergocornine, Dihydro-α-ergokryptine and Dihydro-ß-ergokryptine

Structural formula: See Figure 13

Empirical formula: and Molecular weight			
	Dihydroergocristine base	$C_{35}H_{41}N_5O_5$	611.7
	Dihydroergocristine mesylate	$C_{35}H_{41}N_50_5{\cdot}CH_4O_3S$	707.9
	Dihydroergocornine base	$C_{31}H_{41}N_5O_5$	563.7
	Dihydroergocornine mesylate	$C_{31}H_{41}N_5O_5{\cdot}CH_4O_3S$	659.8
	Dihydro-α-ergokryptine base	$C_{32}H_{43}N_5O_5$	577.7
	Dihydro-α-ergokryptine mesylate	$C_{32}H_{43}N_5O_5{\cdot}CH_4O_3S$	673.8
	Dihydro-ß-ergokryptine base	$C_{32}H_{43}N_5O5$	577.7
	Dihydro-ß-ergokryptine mesylate	$C_{32}H_{43}N_5O_5{\cdot}CH_4O_3S$	673.8

CAS No.: Dihydroergotoxine mesylate 8067–24–1

Specifications and their requirements:

Eur. Ph. 1997	Not implemented	
BP93	Co-dergocrine mesylate	Assay (HPLC): 97.0–103.0% in dry substance 30.0–36.5% of dihydroergocristine mesylate

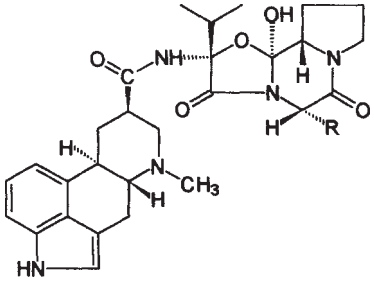

Figure 13 Dihydroergotoxine: R=benzyl for dihydroergocristine, isopropyl for dihydroergocornine, isobutyl for dihydro-α-ergokryptine and *sec*-butyl for dihydro-ß-ergokryptine

		30.0–36.5% of dihydroergocornine mesylate 30.0–36.5% of dihydroergokryptine mesylate ratio of α and β dihydroergokryptine is not less than 1.5:1.0 and not more than 2.5:1.0 (HPLC)
USP23	Ergoloid mesylates	Assay (HPLC): 97.0–103.0% in dry substance 30.3–36.3% of dihydroergocristine mesylate 30.3–36.3% of dihydroergocornine mesylate 30.3–36.3% of dihydroergokryptine mesylate ratio of α and β dihydroergokryptine is not less than 1.5:1.0 and not more than 2.5:1.0 (HPLC)
JP XIII	Not implemented, draft presented in JP Forum Vol. 5 No. 3 (1996)	
Dosage forms:	Alizon, Alkergot, Apolamin, Aramexe, Artedil, Artergin, Astergina, Baroxin "Toa Eiyo", Bordesin, Brentol, Capergyl, Carlom, CCK 179, Cervitonic, Circanol, Clavor, Coax, *Co-dergocrine mesylate,* Coplexina, Coristin, Cortagon, Cursif, Dacoren, DCCK, Deapril-ST, Defluina N, Demanda, Derginal, D-Ergotox, DH-Ergotoxin, DH-Tox-Tablinen, Dihydren, Dilaten, Doctergin, Dorehydrin, Dulcion, Ecuor, Elmesatt, Enirant "Gepepharm", Epos, Ercalon, Erginemin, Ergoceps, Ergocomb, Ergodesit, Ergodilat, Ergodina, Ergodose, Ergogine, Ergohydrin, Ergokod, Ergokrinol, *Ergoloid mesylates,* Ergomax, Ergomed Kwizda, Ergomolt, Ergoplex, Ergoplus, Ergotox v. ct, Ergoxyl, Erlagine, Fermaxin, Fluzal, Geroplus, H.E.A., Hidergo, Hidrosan, HY 71, Hyderan, Hyderaparl, Hydergin(e), Hydervek, Hydro-Cebral, Hydro-Ergot, Hydrolid G, Hydro-Toxin, Hydroxina, Hydroxium, Hynestim, Hyperloid, Ibergal, Indolysin, Inorter, Iresolamin, Iristan, Ischelium Kerasex, Kylistop, Larvin, Latergal, Lysergin, Medixepin, Memoxy, Milepsin, Minerizine, Necabiol, Nehydrin N, Niloric, Nor-madergin, Normanomin, Novofluën, Nulin Velka, Optamine, Orphol, Pallotrinate, Pérénan, Phenyramon, Primarocin, Progeril Midy-Milano; Sanofi-Basel, Redergin, Redergot, Redicor, Regotand, Relark, Samyrel, Santamin, Scamin, Secamin Lab, Secatoxin, Segol, Senart, Simactil, Siokarex,	

Sponsin, Stofilan, Theo-Nar, Theragrin-S, Toterjin, Tredilat Tri-Ergone, Trifargina, Trigot, Trihydrogen Goldline, Tusedon, TY-0032, Ulatil, Vasergot, Vasolax, Vimotadine, Youginin, Zenium, Zidrol, Zinvalon, Zodalin

Therapeutic use: cerebral and peripheral vasodilator

World production: 1000–1500 kg per year

Bulk substance manufacturers: Boehringer Ingelheim (Germany)
Galena (Czech Rep.)
Gedeon Richter (Hungary)
Lek (Slovenia)
Novartis (Switzerland)
Poli (Italy)

Manufacture:
1. Isolation of individual alkaloids or their mixtures from field ergot or fermentation broths, their hydrogenation, preparation of salts with methane sulphonic acid and adjustment to required ratio of individual components.
2. Synthesis of individual dihydroergotoxines from dihydrolysergic acid and coresponding synthetic peptidic parts, preparation of salts with methane sulphonic acid and adjustment to required ratio of individual components.

References: Schoenleber *et al.,* 1978 (anal.), Baer and Jenike, 1991 (therap. use), Wadworth and Chrisp, 1992 (pharmacology and use in geriatry), Ammon *et al.,* 1995 (clin.)

13.4.5. Dihydroergocristine

Chemical names: 2´-Isopropyl-5´-benzyl-dihydroergopeptine;
9, 10-Dihydro-12´-hydroxy-2´-(1-methylethyl)-5´-(phenyl methyl)ergotamane-3´, 6´, 18-trione;
(6a*R*, 9*R*, 10a*R*)-*N*-[(2*R*, 5*S*, 10a*R*, 10b*S*)-5-benzyl-10b-hydroxy-2-(1-methyl-ethyl)-3, 6-dioxo-octahydro-8H-oxazolo-[3, 2-a]pyrolo[2, 1-c]pyrazin-2-yl]-7-methyl-4, 6, 6a, 7, 8, 9, 10, 10a-octahydroindolo [4, 3-fg]quinoline-9-carboxamide

Structural formula: See Figure 14

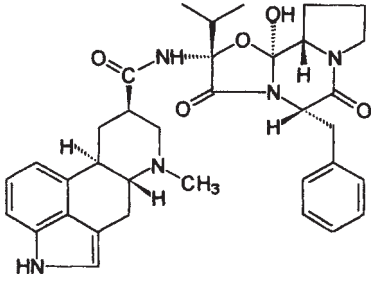

Figure 14 Dihydroergocristine

Empirical formula:	base	$C_{35}H_{41}N_5O_5$
	mesylate	$C_{35}H_{41}N_5O_5 \cdot CH_4O_3S$
Molecular weight:	base	611.7
	mesylate	707.9
CAS No.:	base	17479–19–5
	mesylate	24730–10–7
Specifications and their requirements:	Substance is included only in Czechoslovak pharmacopoeia.	
	Producers declare its quality by HPLC analysis.	
Typical impurities:	Ergocristine, ergocristinine, aci-dihydroergocristine, dihydroergine	
	Material manufactured from isolated ergocristine (from ergot or fermentation broths) usually contains some other dihydroergopeptines (dihydroergotamine, dihydroergocornine, dihydro-α-ergokryptine and others), dihydroergocristam or dihydroergometrine	
Dosage forms:	Angiodil, DCS 90, Decme Italmex; Spitzner; Zyma, Decril, Defluina Simes, Diertina, Diertine, Diertix, Difluid, Dirac, Enirant, Ergo Foletti, Ergocris, Ergodavur, Fluiben, Gral, Hydrofungin, Insibrin, Iskemil, Iskevert, Nehydrin, Normosedon, Unergol, Vigoton	
Therapeutic use:	sympatholytic, peripheric vasodilator	
World production:	1000–1500 kg per year	
Bulk substance manufacturers:	Boehringer Ingelheim (Germany) Galeana (Czech Rep.) Gedeon Richter (Hungary) Lek (Slovenia) Piere Fabre (France) Poli (Italy)	
Manufacture:	1. Isolation ergocristine from ergot or fermentation broth, its hydrogenation and salt formation with methane sulphonic acid 2. Synthesis from dihydrolysergic acid and synthetic pepetidic part	
References:	Mailand, 1992 (pharm. and clin. review), Malacco and Di Cesare, 1992 (therap. use), Franciosi and Zavattini, 1994 (use in geriatry)	

13.4.6. Dihydro-α-ergokryptine

Chemical names:	2´-Isopropyl-5´-isobutyl-dihydroergopeptine; 9, 10-Dihydro-12´-hydroxy-2´-(1-methylethyl)-5´-(2-methyl propyl)ergotamane- 3´, 6´, 18-trione;

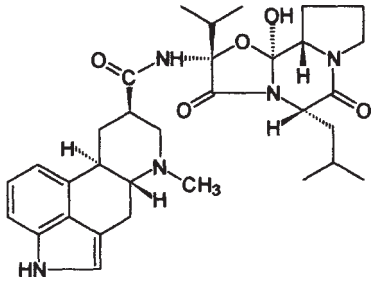

Figure 15 Dihydro-α-ergokryptine

(6a*R*, 9*R*, 10a*R*)-*N*-[(2*R*, 5*S*, 10a*S*, 10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3, 6-dioxo-octahydro-8H-oxazolo[3, 2-a]pyrrolo[2, 1-c]pyrazin-2-yl]-7-methyl-4, 6,-6a, 7, 8, 9, 10, 10a-octahydro-indolo[4, 3-fg]quinoline-9-carboxamide

Structural formula: See Figure 15

Empirical formula: base $C_{32}H_{43}N_5O_5$
mesylate $C_{32}H_{43}N_5O_5 \cdot CH_4O_3S$

Molecular weight: base 577.7
mesylate 673.9

CAS No.: base 25447–66–9
mesylate 29261–93–6

Specifications and their requirements: The substance is not monographed in any pharmacopoeia.

Producers declare its purity by HPLC analysis.

Dosage forms: Daverium, Myrol, Vasobral

Therapeutic use: antiparkinsonian, prolactine inhibitor, cerebral vasodilator

Introduction: 1989

World production: 400–600 kg per year

Bulk substance manufacturers: Galena (Czech Rep.), Poli (Italy)

Manufacture: Hydrogenation of α-ergokryptine isolated from ergot or fermentation broth and salt formation with methane sulphonic acid.

References: Poli, 1990; Coppi, 1991; Scarzela *et al.*, 1992 (all pharmacol. and therap.)

13.4.7. Bromokryptine

Chemical names: 2-Bromo-α-ergokryptine;
2-Bromo-2´-isopropyl-5´-isobutyl-ergopeptine;
2-Bromo-12´-hydroxy-2´-(1-methylethyl)-5´-(2-methylpropyl)-ergotamane-3´, 6´, 18-trione;

(6a*R*, 9*R*)-*N*-[(2*R*, 5*S*, 10a*S*, 10b*S*)-10b-hydroxy-2-(1-methylethyl)-5-(2-methylpropyl)-3, 6-dioxo-octahydro-8H-oxazolo[3, 2-a]pyrolo[2, 1-c]pyrazin-2-yl]-5-bromo-7-methyl-4, 6, 6a, 7, 8, 9-hexahydro-indolo[4, 3-fg]quinoline-9-carboxamide

Structural formula: See Figure 16

Empirical formula: base $C_{32}H_{40}BrN_5O_5$
mesylate $C_{32}H_{40}BrN_5O_5.CH_4O_3S$

Molecular weight: base 656.6
mesylate 750.7

CAS No.: base 25614–03–3
mesylate 22260–51–1

Specifications and their requirements:

Eur. Ph. 1997	Bromocriptine mesilate	Assay (titration): 98.0–101.0% in dry substance No impurity above 0.4% (TLC) One impurity above 0.2% (TLC)
USP23	Bromocriptine mesylate	Assay (titration): 98.0–102.0% in dry substance Total impurities (TLC): not more than 1.0% No impurity above 0.5% (TLC)
JP XIII	Bromocriptine mesilate	Assay (titration): Not less than 98.0% in dry substance No impurity above 0.5% (TLC) One impurity above 0.25% (TLC)

Typical impurities: Bromokryptinine, α-ergokryptine, 2-chloro-α-ergokryptine
Material manufactured from α-ergokryptine isolated from ergot or fermentation broth usually contains 2-bromoderivatives of some other ergopeptines (2-bromo-β-ergokryptine, 2-bromoergocristine, 2-bromo-ergogaline or others)

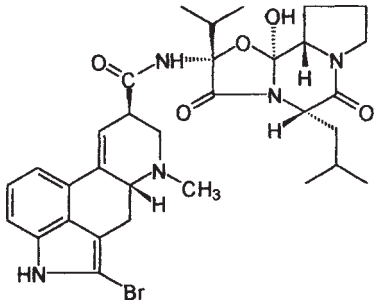

Figure 16 Bromokryptine

Material of some producers can contain dibromoderivatives (2, 12-dibromo-α-ergokryptine and/or 2, 13-dibromo-α-ergokryptine)

Dosage forms: Antipark, Atlodel, Axialit, Bagren, Bromed, Bromergon, Bromocorn, Bromopar, CB 154, Criten, Deparo, Elkrip, Erenant, Ergolactin, Grifocriptina, Kirim, Lactismine, Maylaktin, Morolack, NSC-169774, Padoparine, Palolactin, Antipark, Atlodel, Axialit, Bagren, Bromed, Bromergon, Parilac, Parlodel, Parlomin, Parodel, Parukizone, Practin, Pravidel, Prigost, Proctinal, Prospeline, Serocryptin, Serono-Bagren, Sintiacrin, Sulpac, Syntocriptine, Umprel, Upnol B

Therapeutical use: dopamine agonist, antiparkinsonian, prolactine inhibitor, treatment of acromegaly

Introduction: 1975

World production: 1000 kg per year

Bulk substance manufacturers:

Galena (Czech Rep.)
Gedeon Richter (Hungary)
Lek (Slovenia)
Novartis (Switzerland)
Poli (Italy)

Manufacture: Bromination of α-ergokryptine by different brominating agents (N-bromo-succinimide, pyrolidone hydrotribromide, N-bromosacharine and other N-bromo-derivatives, trimethylsilylbromide/dimethylsulphoxide, bromine/hydrobromide, bromine/bortrifluoride etherate and others)

Starting material, α-ergokryptine is isolated from ergot or fermentation broth or is synthetised from lysergic acid.

References: Flückiger and Troxler, 1973; Ručman *et at.,* 1977; Stanovnik *et al.,* 1981; Börner *et al.,* 1983; Megyeri *et al.,* 1986; Cvak *et al.,* 1988 (all manufacture), Giron-Forest and Schoenleber 1979 (anal.), Vigouret *et al.,* 1978, Lieberman and Goldstein 1985, Weil 1986 (all pharmacol. and therap.)

13.4.8. Nicergoline

Chemical names: 10α-Methoxy-1, 6-dimethylergoline-8β-methanol 5-bromonicotinate(ester);

10α-Methoxy-1-methyl-dihydrolysergol 5-bromonicotinate;

5-Bromopyridine-3-carboxylate of [(6a*R*, 9*R*, 10a*S*)-10a-methoxy-4, 7-dimethyl-4, 6, 6a, 7, 8, 9, 10, 10a-octahydro-indolo-[4, 3-fg]quinoline-9-yl]methyl

Structural formula: See Figure 17
Empirical formula: $C_{24}H_{26}BrN_3O_3$
Molecular weight: 484.4
CAS No.: 27848–84–6
Specification and their requirements: Substance is monographed only in French Pharmacopoeia, 10th edition, January 1995
Assay (titration): 98.0–101.0% in dry substance
Purity (HPLC): No impurity above 1.0%
Not more than 2 impurities above 0.5%
Not more than 4 impurities above 0.2%
Typical impurities: chloronicergoline
1-demethylnicergoline
10α-methoxy-1-methyl-dihydrolysergol
5-bromonicotinic acid
Dosage forms: Adavin, Cergodum, Circo-Maren, Dasovas, Dilasenil, Dospan, Duracebrol, Ergobel, Ergotop, F.I.6714, Fisifax, Mariol, Memoq, Nardil Gödecke, Nargoline, Nicergolent, Nicergolyn, Nicerhexal, Nicerium, 19561 R.P., Sermion, Sincleron, Specia, 287; Varson, Vasospan Exa, Vetergol
Therapeutic use: cerebral vasodilator
Introduction: 1978
World production: 7000–10000 kg per year
Manufacturers: Farmitalia (Pharmacia-Upjohn)
Galena (Czech Rep.)
Indena , Linea Nuova (both Italy)
Rhone Poulenc (France)
Manufacture: 1. From lysergic acid
2. From lysergol
References: Bernardi *et al.,* 1966; Arcari *et al.,* 1972; Ručman and Jurgec, 1977; Ručman, 1978; Stres and Ručman, 1981; Černý *et al.,* 1983; Cvak *et al.,* 1983, 1985; Bombardeli and Mustich 1985 and 1985a; Gervais 1986 (all manufacture);

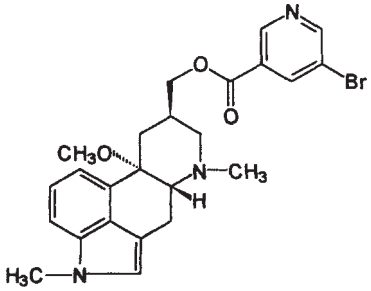

Figure 17 Nicergoline

Bernardi, 1979 (pharmacol. review); Banno, 1989 (analytics and stability)

13.4.9. Metergoline

Chemical names:	1-Methyl-*N*-carbonybenzyloxy-dihydrolysergamine; [(1, 6-Dimethylergolin-8β-yl)-methyl]-carbamic acid phenylmethyl ester;
Structural formula:	See Figure 18
Empirical formula:	$C_{25}H_{29}N_3O_2$
Molecular weight:	403.5
CAS No.:	17692–51–2
Specifications:	Substance is not monographed in any pharmacopeia; manufacturers have their own specifications
Dosage forms:	Al-Migren, Contralac, Liserdol
Therapeutic use:	serotonine antagonist, antimigrenic, prolactine inhibitor
Introduction:	1987
World production:	20–50 kg per year
Manufacturers:	Farmitalia (Pharmacia-Upjohn), Galena (Czech Rep.), Poli (Italy)
Manufacture:	1. From 1-methyl-dihydroergine *via* reduction with lithium aluminiumhydride to 1-methyldihydrolysergamine and its reaction with benzylchloroformate. 1-Methyl-dihydroergine is available from dihydroergotamine or another dihydroergopeptine. 2. From dihydrolysergole
References:	Bernardi *et al.*, 1964; Camerino *et al.*, 1966 (manufacture)

13.4.10. Methylergometrine

Other names:	Methylergobrevine Methylergobasine Methylergonovine
Chemical names:	d-Lysergic acid L-(+)-1-(hydroxymethyl) propylamide;

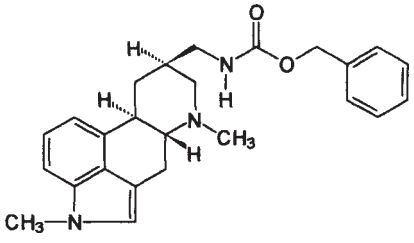

Figure 18 Metergoline

9, 10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methyl-ergoline-8ß*(R)*-carboxamide;
(6a*R*, 9*R*)-*N*-[*(S)*-1-(hydroxymethyl)propyl]-7-methyl-4, 6, 6a7, 8, 9-hexahydro-indolo[4, 3-fg]quinoline-9-carboxamide

Structural formula: See Figure 19

Empirical formula: base $C_{20}H_{25}N_3O_2$
maleate $C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$
tartrate $(C_{20}H_{25}N_3O_2)_2 \cdot C_4H_6O_6$

Molecular weight: base 339.4
maleate 455.5
tartrate 828.9

CAS No.: base 113–42–8
maleate 7432–61–8
tartrate 6209–37–6

Specifications:

USP23	Methylergonovine Maleate	Assay (spectrophotometric): 97.0–103.0% in dry substance Total impurities (TLC): not more than 2.0%
JP XIII	Methylergometrine Maleate	Assay (spectrophotometric): 95.0–105.0% in dry substance Purity (TLC): No impurity above 1.0%

Typical impurities: methylergometrinine
d-Lysergic acid D-(–)-1-(hydroxymethyl)propylamide other impurities are specific for individual producers and depends on their manufacturing processes

Dosage forms: Basofortina, Demergin, Derganin, Elamidon, Elpan S, Emifarol, Enovine, Erezin, Ergobacin, Ergopartin, Ergotyl, Ergovit-Amp., Levospan, Mergot, Metenarin, Methecrine, Methergen, Methergin, Metiler, Mitrabagin-C, Mitrosystal, Mitrotan, Myomergin, NSC-186067, Obstet, Partergin,

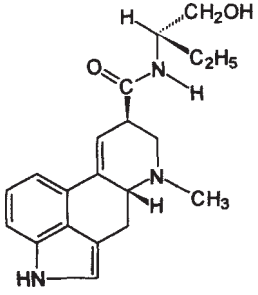

Figure 19 Methylergometrine

	Ryegonovin, Santargot, Secotyl, Spametrin-M, Takimetrin-M, Telpalin, Unidergin, Utergine, Uterin
Therapeutic use:	uterotonic, oxytocic
Introduction:	1946
World production:	80–150 kg per year
Bulk substance manufacturers:	Galena (Czech Rep.), Lek (Slovenia), Novartis (Switzerland)
Manufacture:	Synthesis from d-lysergic acid and L-(+)-2-aminobutanol using diffrent coupling reagents
References:	Stoll and Hofmann, 1941 and 1943 (manuf.)

13.4.11. Methysergide

Chemical names:	1-Methyl-d-lysergic acid-L-(+)-1-(hydroxymethyl)propylamide; 9, 10-Didehydro-*N*-[*(S)*-1-(hydroxymethyl)propyl]-1, 6-dimethylergoline-8*ß(R)*-carboxamide; (6a*R*, 9*R*)-*N*-[(*S*)-1-(hydroxymethyl)propyl]-4, 7-dimethyl-4, 6, 6a, 7, 8, 9-hexahydroindolo[4, 3-fg]quinoline-9-carboxamide
Structural formula:	See Figure 20
Empirical formula:	base $C_{21}H_{27}N_3O_2$ maleate $C_{21}H_{27}N_3O_2 \cdot C_4H_4O_4$
Molecular weight:	base 353.4 maleate 469.5
CAS No.:	base 361–37–5 maleate 129–49–7
Specifications:	USP23
Typical impurities:	methylergometrine (1-demethyl-methysergide) iso-methysergide
Dosage form:	Deseril, Sansert
Therapeutic use:	serotonine antagonist, antimigrenic

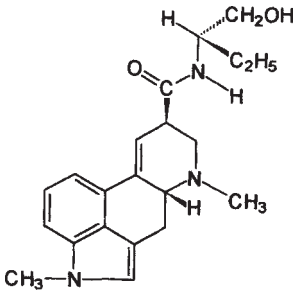

Figure 20 Methysergide

Introduction:	1960
World production:	30–50 kg per year
Bulk substance manufacturers:	Novartis (Switzerland)
Manufacture:	1. Synthesis from lysergic acid *via* 1-methyl lysergic acid 2. Methylation of methylergometrine
References:	No new reference

13.4.12. Lisuride

Chemical names:	3-(9, 10-Didehydro-6-methylergolin-8α-yl)-1, 1-diethylurea; *N*-(6-methyl-8-isoergolenyl)-*N′, N′*-diethylurea;	
Structural formula:	See Figure 21	
Empirical formula:	base	$C_{20}H_{26}N_4O$
	maleate	$C_{20}H_{26}N_4O \cdot C_4H_4O_4$
Molecular weight:	base	338.4
	maleate	454.5
CAS No.:	base	18016–80–3
	maleate	19875–60–6
Specification:	Substance is monographed only in Czechoslovak Pharmacopoeia	
Dosage forms:	Apodel, Cuvalit, Dispergol, Dopergin, Eunal, Lisenil, Lysenyl, Prolactam, Revanil	
Therapeutic use:	serotonine antagonist, antimigrenic, prolactine inhibitor, antiparkinsonic	
Introduction:	1971 (Czechoslovakia), 1987 other countries	
World production:	20–30 kg per year	
Bulk substance manufacturers:	Galena (Czech Rep.)	
Manufacture:	1. Synthesis from lysergic acid 2. Synthesis from erginine	
References:	Zikán and Semonský, 1960; Sauer and Haffer, 1981; Bulej *et al.,* 1990 (all manufacture); Calve *et al.,* 1983 (pharmacol. and therap.)	

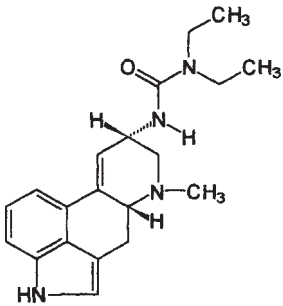

Figure 21 Lisuride

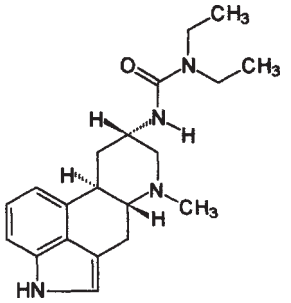

Figure 22 Terguride

13.4.13. Terguride

Other name:	Transdihydrolisuride	
Chemical names:	3-(6-Methylergolin-8α-yl)-1, 1-diethylurea; *N*-(6-Methyl-8-isoergolinyl)*N′*, *N′*-diethylurea;	
Structural formula:	See Figure 22	
Empirical formula:	base	$C_{20}H_{28}N_4O$
	maleate	$C_{20}H_{28}N_4O{\cdot}C_4H_4O_4$
Molecular weight:	base	340.4
	maleate	456.5
CAS No.:	base	37686–84–3
	maleate	
Specification:	Substance is not monographed in any pharmacopeia	
Dosage forms:	Mysalfon	
Therapeutic use:	dopamine agonist, prolactine inhibitor, antiparkinsonian	
Introduction:	1986 (Czechoslovakia), clinical trials in other countries	
World production:	10kg per year	
Bulk substance manufacturers: Galena (Czech Rep.)		
Manufacture:	1. Hydrogenation of lisuride 2. Reduction of lisuride by lithium in liquid ammonia	
References:	Zikán *et al.*, 1972; Sauer, 1980; Sauer *et al.*, 1986 (all manufacture); Kratochvíl *et al.*, 1993 (properties), Calve *et al.*, 1983; Golda and Cvak, 1994 (both pharmacol. and therap.)	

13.4.14. Pergolide

Chemical names:	8*ß*-[(Methylthio)methyl)-6-propylergoline; Methyl](6a*R*, 9*R*, 10a*R*)-7-propyl-4, 6, 6a, 7, 8, 9, 10, 10a-octahydroindolo[4, 3-fg]quinoline]-9-methylsulphide	
Structural formula:	See Figure 23	
Empirical formula:	base	$C_{19}H_{26}N_2S$
	mesylate	$C_{19}H_{26}N_2S{\cdot}CH_4O_3S$

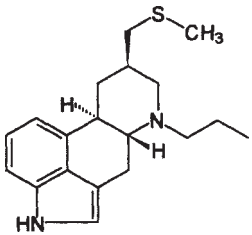

Figure 23 Pergolide

Molecular weight:	base	314.5
	mesylate	410.6
CAS No.:	base	66104–22–1
	mesylate	66104–23–2
Specification:	Substance is not monographed in any pharmacopoeia	
Dosage forms:	Celance, Parkotil, Permax, Pharken	
Therapeutic use:	dopamine agonist, prolactine inhibitor, antiparkinsoniac	
Introduction:	1989	
World production:	50 kg per year	
Bulk substance manufacturers:	Eli Lilly (USA) and Galena (Czech Rep.)	
Manufacture:	Synthesis from dihydrolysergol	
References:	Kornfeld and Bach, 1979; Misner, 1993; Misner *et al.,* 1996, 1997; Kennedy, 1997 (all manufacture); Sprankle and Jensen, 1992; Kerr *et al.,* 1981; Bowsher *et al.,* 1992 (all anal.); Owen, 1981 (pharmacol.)	

13.4.15. Cabergoline

Chemical name: 1-[(6-Allylergolin-8*β*-yl)carbonyl)-1-[3-(dimethylamino)-propyl]-3-ethylurea;

Structural formula: See Figure 24

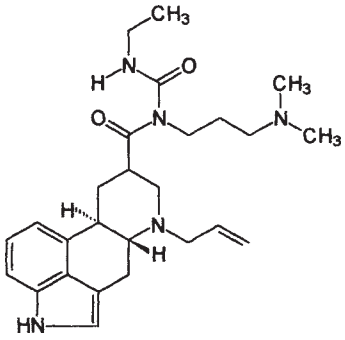

Figure 24 Cabergoline

Empirical formula:	base	$C_{26}H_{37}N_5O_2$
	phosphate	$C_{26}H_{37}N_5O_2.(H_3PO_4)_2$
Molecular weight:	base	451.6
	phosphate	647.7
CAS No.:	base	81409–90–7
	phosphate	85329–89–1
Specification:	Substance is not monographed in any pharmacopoeia	
Dosage forms:	Dostinex, Galastop, Cabaser	
Therapeutic use:	dopamine agonist, prolactine inhibitor, antiparkinsonian	
Introduction:	1993	
World production:	20–30 kg per year	
Bulk substance manufacturer:	Pharmacia-Upjohn	
Manufacture:	Synthesis from dihydrolysergic acid	
References:	Bernardi *et al.,* 1982; Salvati *et al.,* 1985; Brambilla *et al.,* 1989 (all manufacture); Lera *et al.,*1993; Rabey *et al.,* 1994 (both therap. use)	

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