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* A synthetic derivative, the tartrate of (*S*)-*N*-ethyl-*N*-methyl-3-[(dimethylamino)ethyl]-phenylcarbamate (rivastigmine, INN) was just marketed in France (1998) with the following indication: for the symptomatic treatment of mild to moderately severe forms of Alzheimer's disease.

Ergoline Alkaloids

1. GENERALITIES

All of the alkaloids in this group are derived from a tetracyclic, octahydroindoloquinoline nucleus, namely ergoline. Although these are commonly classified as clavines, simple lysergic acid derivatives, and ergopeptines, it is also possible, and less ambiguous, to classify the various known alkaloids as a function of their basic nucleus.

Thus the following are distinguished:

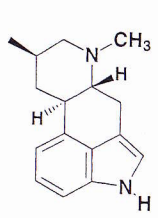
1. Ergoline alkaloids. Ergoline alkaloids can be substituted at C-8, most often by a methyl group (e.g., festuclavine), or a hydroxymethyl group (e.g., dihydrolysergol), at C-8 and C-9 in rare cases.

2. 8-Ergolene alkaloids. 8-Ergolene alkaloids can be substituted at C-8 by a methyl group (e.g., agroclavine), a hydroxymethyl group (e.g., elymoclavine), or a carboxyl group (e.g., paspalic acid).

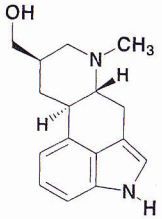
3. 9-Ergolene alkaloids. 9-Ergolene alkaloids include the chief alkaloids of the ergot of rye, whether they have an amino acid structure (e.g., ergometrine), a peptide structure with a cyclol moiety (ergopeptines), or a peptide structure without a cyclol moiety (ergopeptams).

4. Secoergoline alkaloids. Secoergoline alkaloids have an open D ring (e.g., chanoclavine I).

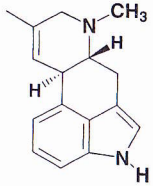
5. Related structures. Related structures, sometimes referred to as proergolines, include the precursor of all of these compounds, in other words dimethylallyltryptophan, and products such as the clavicipitic acids.



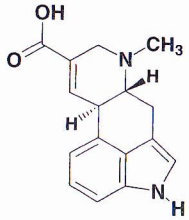
Festuclavine



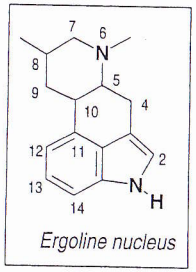
Dihydrolysergol



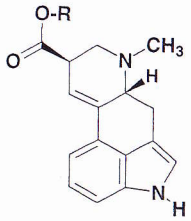
Agroclavine



Paspalic acid

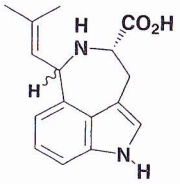


Ergoline nucleus



Lysergic acid and ergopeptines

Norchanoclavine I



Clavicipitic acids, I and II

2. DISTRIBUTION OF ALKALOIDS DERIVED FROM ERGOLINE

These alkaloids were initially characterized in the ergot of rye, *Claviceps purpurea*. The genus *Claviceps* comprises about fifty species, and several of them are capable of infesting Poaceae, including cereals and non-cereals, and particularly the Paniceae. Examples include *C. purpurea* on *Secale cereale*, *C. paspali* on *Paspalum* spp., and *C. fusiformis* on *Pennisetum*. *C. purpurea* and *C. paspali* elaborate mostly ergopeptines and simple lysergic acid derivatives, respectively, but most of the other *Claviceps* synthesize clavines.

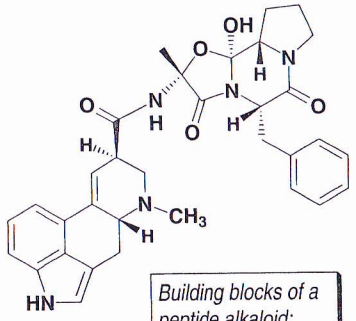
These clavines are also synthesized by other fungi (*Aspergillus*, *Balansia*, *Penicillium*, *Rhizopus*) which, in rare cases, elaborate more complex structures (dihydroergosine of *Sphacelia sorghi*, ergobalansine of *Balansia* spp.).

Curiously, certain higher plants are capable of producing clavines, simple amides (ergine, hydroxyethylamide), and even ergosine, for example several species in the family Convolvulaceae, more specifically in the genera *Argyreia*, *Ipomoea*, *Turbina*, and *Strictocardia*.

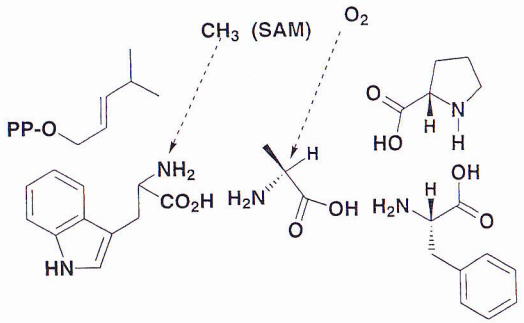
3. BIOSYNTHETIC ORIGIN

The feasibility of the saprophytic culture of ergot of rye has greatly facilitated the study of the biogenesis of these compounds, and, although several points remain to be clarified, the main steps which lead to the elaboration of these compounds in this fungus have now been described.

Labelling experiments show that the precursors of the ergoline nucleus are tryptophan, mevalonic acid, and methionine: tryptophan provides the indole nucleus, C-4, C-5, and N-6; mevalonic acid, *via* dimethylallyl pyrophosphate, is the origin of C-7, -8, -9, -10, and of the C-8 substituent; methionine (as *S*-adenosyl-methionine) methylates N-6.

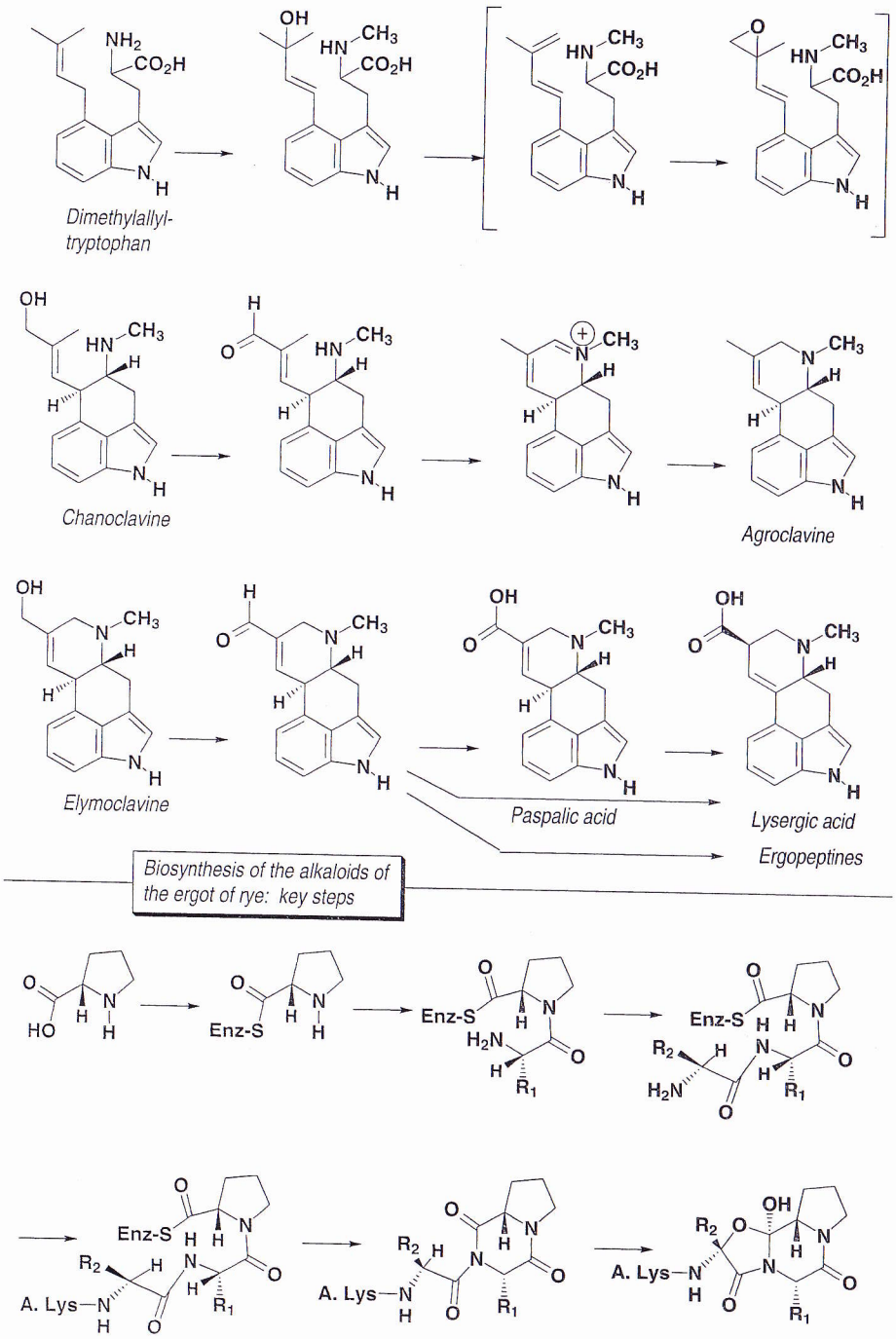


Building blocks of a peptide alkaloid: e. g. ergotamine



Even though several mechanistic details remain to be elucidated, the sequence which leads to the alkaloids in *Claviceps purpurea* is fairly well known.

Several mechanisms have been proposed to rationalize the first step in the elaboration of ergoline, in other words the formation of *dimethylallyltryptophan* (= DMAT): it involves the alkylation of tryptophan by dimethylallyl pyrophosphate, directly at C-4 (which is not the position most likely to get substituted), catalyzed by a specific enzyme, DMAT synthetase. The next step leads to chanoclavine: DMAT is *N*-methylated and decarboxylated, the methyl group (*Z*) oxidized to a hydroxy-methyl group (probably *via* an epoxide), and the double bond isomerized. During the next step, which is the formation of agroclavine upon closure of the D ring, the double bond is isomerized a second time: the *Z* methyl group becomes *E*, and the



hydroxymethyl group is oxidized to an aldehyde, which reacts with the secondary amine. Subsequently, a mono-oxygenase induces the hydroxylation of the C-8 methyl group (elymoclavine). A hypothesis, based on the use of ^{18}O, is that peptide alkaloids are formed from the aldehyde which arises from the oxidation of the hydroxymethyl group of elymoclavine, without going through an acid as an intermediate (lysergic or paspalic acid). Regarding the elaboration of the characteristic tripeptide of the ergot alkaloids, note that the isolation of ergopeptam (with no cyclol) proves that the hydroxylation at C-2', which is required for the formation of the cyclol, occurs late in the sequence.

4. ERGOT OF RYE, *Claviceps purpurea* (Fries) Tulasne

It was around 1000 A.D. that the first precise descriptions of "St. Anthony's fire" appeared; they referred to ergotism outbreaks, which ravaged western Europe for several centuries *. Ergotism, the consequence of the ingestion by humans of the cereals contaminated by the fungus, commonly occurred as one of two forms: in the gangrenous form ("St. Anthony's fire"), the disease began with a painful inflammation of the extremities, and resulted in numb, blackened, and dry extremities, sometimes ending with their spontaneous loss at a joint; in the convulsive form, the dominant symptoms were mental agitation, delirium, and sensory perturbations.

The prevalence of ergotism decreased rapidly as agriculture improved and as nutrition became more diversified; however, ergotism epidemics did take place in the north and the east of Europe until the nineteenth century *, and in the former Soviet Union until 1926. More recently (1977-78), 47 deaths linked to the ingestion of contaminated cereals were documented in Ethiopia **.

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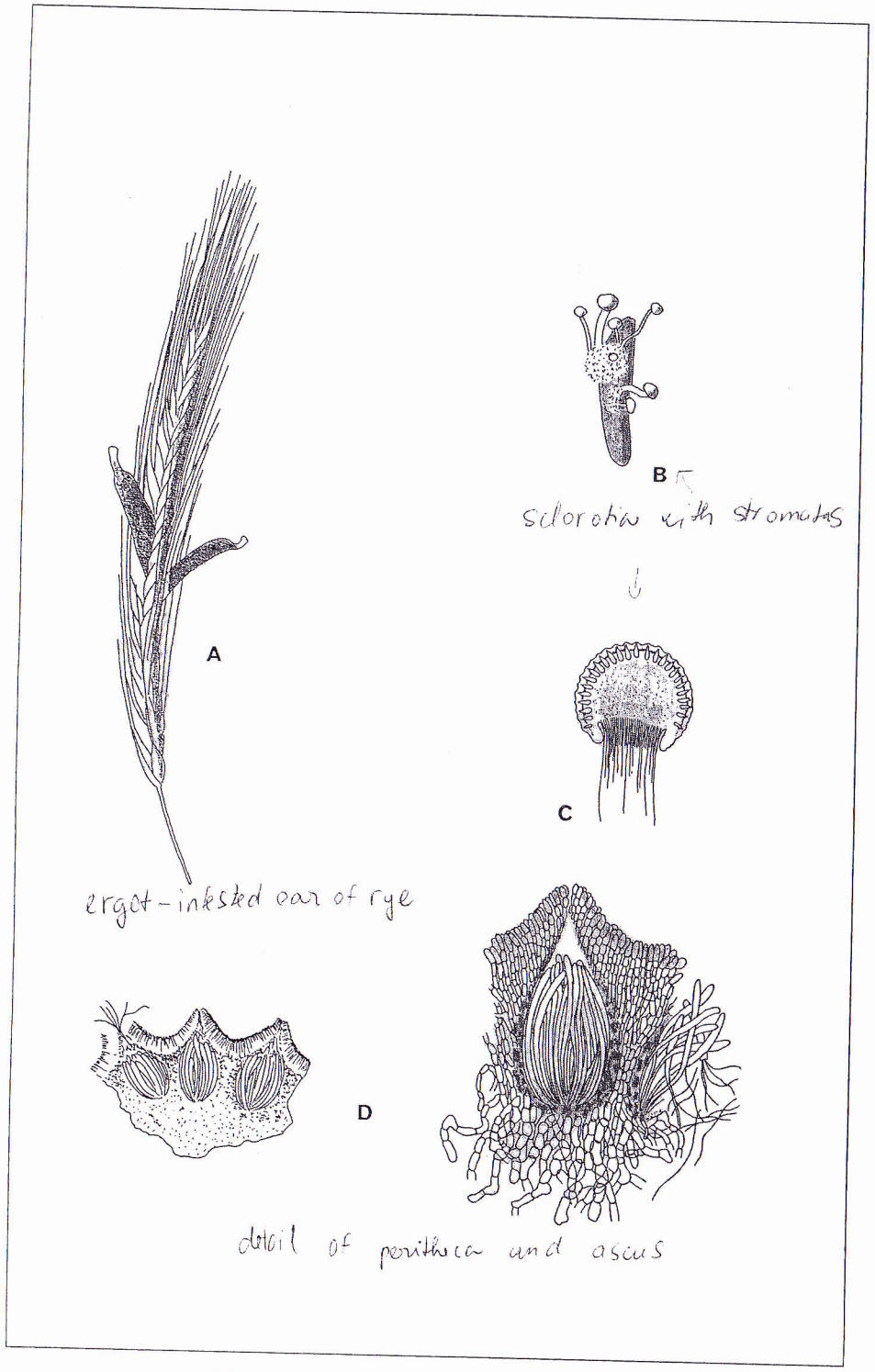
* Did the activity of the ergot alkaloids influence the evolution of European demography? A highly documented study postulates a correlation between the consumption of ergot-infested flours and a decrease in fertility in the population. See Matossian, M.K. (1989). Poisons of the Past. Molds, Epidemics and History. Yale University Press; New Haven (see also, in the same reference, the hypothesis that there was a relationship between the consumption of ergot-infested rye and the collective panic which took several French provinces by storm and led to uprisings in the summer of 1789).

** Demeke, T., Kidane, Y. et Wuhib, E. (1979). Ergotism – A Report on an Epidemic, 1977-78, *Ethiop. Med. J.*, **17**, 107-113. We must emphasize that farm animals are still periodically poisoned by ergot (*C. purpurea*) growing on various Poaceae. The resulting ergotism can be convulsive (especially in sheep) or, as is almost always the case in bovines, gangrenous. Abortions are observed in mares. Recently, in France, there have been reports of *C. paspali* developing on an imported Poaceae, namely *Paspalum distichum*. For reports on recent intoxications, see: (1) Coppock, R.W., Mostrom, M.S., Simon, J., McKenna, D.J., Jacobsen, B. and Szlachta, H.L. (1989). Cutaneous Ergotism in a Herd of Dairy Calves, *J. Am. Vet. Med. Assoc.*, **194**, 549-551; (2) Riet-Correa, F., Mendez, M.C., Schild, A.L., Bergamo, P.N. and Flores, W.N. (1988). Agalactica, Reproductive Problems and Neonatal Mortality in Horses Associated with the Ingestion of *Claviceps purpurea*. *Aust. Vet. J.*, **65**, 192-193.



Claviceps purpurea (Fries) Tulasne

The responsibility of bread made from infested rye was not suspected until the end of the seventeenth century, and it was not demonstrated in animals until one century later. The fungal nature of ergot was recognized in 1711, but the mystery of its development cycle was not elucidated until 1853. The twentieth century was to be that of the isolation of the alkaloids (ergotamine, Stoll, 1918), of the demonstration of their pharmacological properties, and later, of their mass production by fermentation. The oxytocic properties of ergot had long been known (Lonicer, 1582) and used (*pulvis parturiens*) before they became reserved for the control of post-partum hemorrhage (this led to a decrease in the number of still births!).

A. The Fungus, the Drug

At first glance, the fungus exists in two forms: the vegetative form which is a conidiospore-bearing stroma known as sphacelia, and the resting form or sclerotium. The sphacelia is formed by the mycelium, whose hyphae have invaded the ovary of the rye flower. It is at the end of some of the hyphae that the conidiospores develop as the organs of asexual reproduction. All of this is bathed in a sweet and viscous mass, referred to as "honeydew". The sclerotium is an elongated, arched, and purplish black mass, destined to spend the winter on the ground. These two forms alternate according to a complex cycle:

- the sexual cycle begins in the spring with the formation, on the sclerotium, of masses of stromata on stalks, each containing numerous perithecia, in other words follicles opening by an ostiole and containing the asci. The filamentous ascospores (60-70 x 2 µm) released and carried by the wind infect the flowers of other plants. At this point, the mycelium develops into a stroma, which produces the conidiospores;
- the conidiospores, transported by insects, ensure the asexual reproduction of the haploid mycelial gametophyte.

The drug, which was the subject of a monograph in the 8th edition of the French Pharmacopoeia, measures from 1 to 4 cm in length for a diameter of 3 to 8 mm; it is tapered at the ends. The surface is blackish and slightly cracked. It breaks with a clean whitish fracture. The odor is amine-like and gets stronger as the drug gets older.

B. Alkaloid Production

For a long time, the needs of the pharmaceutical industry were fulfilled exclusively by extraction from sclerotia obtained by artificially infesting rye. Later, it became possible to meet part of the international demand for active alkaloids by saprophytic culture of selected strains of various species of *Claviceps*. The alkaloids extracted from the culture media were used directly or after chemical transformation (semisynthesis). Which is the larger source? Information is scarce and sometimes contradictory: according to Magnier*, "today the *in vitro* production of alkaloids

[...] has finally completely disappeared"... but the author does not specify if this statement applies worldwide or only in France. In contrast, Rehacek and Sajdl (1990) note ** that: "...the parasitic culture of ergot in the western hemisphere (predominantly Switzerland) has almost stopped". In view of this, we shall examine the principle of both processes.

1. Field Cultivated Ergot

These ergots are obtained by artificial infestation of cereals with strains of the fungus selected for their virulence and their high concentration of alkaloids. This infestation was initially practiced on rye, and can now be applied to a hybrid of wheat and rye, known as triticale (x *Triticosecale* sp.): this hexaploid combines the susceptibility of rye to *Claviceps* and the productivity of wheat.

The traditional method includes several steps. First, the selected strain is cultured in a liquid medium with a composition appropriate for inducing the formation of conidiospores. At the time of infestation, an inoculum is prepared by suspending the spores in water (3,000-5,000 spores per mm3). Next, the inoculum is used to inoculate the young ears (at the latest at the very beginning of the floration). The injection is accomplished using systems resembling hypodermic syringes connected to a reservoir containing the conidiospore suspension; a specially designed mechanical device brings the ears in contact with the needles. The harvest may begin six to seven weeks after inoculation. The yield of sclerotia is very variable and can reach 300 kg/hectare (= 300 kg/2.47 acres).

Apparently, more complex methods have been developed: progress with the technique, increased virulence, the abandonment of the traditional inoculation technique, and the move to a new support may have multiplied the yields by a factor of 8 to 10* (up to 4 metric tons/hectare or 2.47 acres for some trials in progress).

2. Industrial Fermentation ***

The knowledge of how to develop *Claviceps* on synthetic media is about one hundred years old, but multiple difficulties, particularly the degeneracy of the *C. purpurea* strains, had precluded the optimization of a profitable commercial

* Magnier, G. (1992). Ces plantes dont on ne parle pas–Comment acquérir et préserver une position de leader mondial dans la culture des plantes médicinales, *in* "3e rencontres techniques et économiques plantes aromatiques et médicinales". (Verlet, N., Ed.), pp. 206-215, Nyons. (These plants about which no one speaks–How to attain and conserve a position of world leader in the culture of medicinal plants. Third technical and economic symposium on aromatic and medicinal plants.)

** Rehacek, Z. and Sajdl, P. (1990), see bibliography, p. 56; the same authors contradict themselves a few pages later [p. 97: "ergopeptines are still mostly produced by agricultural exploitation" (?)]

*** For an overview of this type of process, and of fermentation procedures, see, among others, Scriban, R. (Ed.) (1993). Biotechnologie, 4th edition. Tec & Doc, Paris.

process until the 1960s and 1970s. The different *Claviceps* can be cultured at pHs near 5.5, which are best adjusted with ammonium salts of the acids of Krebs' cycle (succinate, citrate). Frequently, the alkaloid production is dependent on the phosphate concentration of the medium, and for many strains, on the precise concentrations of minerals (iron, zinc, copper, boron) which directly influence the productivity. The oxygenation of the culture medium must be intense. Cell differentiation and alkaloid production are controlled by the addition of nutrients: a rich medium causes the formation of abundant hyphal mycelium and no alkaloid production. The latter is triggered when the medium becomes poor in certain nutrients. For many strains, it is the phosphate concentration that conditions the passage from the mycelium proliferation phase to the biochemical differentiation phase. Tryptophan, added at the beginning of the fermentation, acts as an enzymatic inducer, and therefore it increases the quantity of alkaloids formed.

Alkaloids produced

Two approaches are possible. The first one consists of producing simple ergolenes, namely paspalic acid or the hydroxyethylamide of lysergic acid. These two compounds are biosynthesized by *Claviceps paspali* Stevens & Hall with yields largely exceeding 2 g/L. Other *Claviceps* could potentially produce clavines with much higher yields.

Once isolated from the culture medium, the two ergolene derivatives are transformed—the first by isomerization, the second by hydrolysis—into lysergic acid, the starting material for the synthesis of non-peptidic alkaloids used in therapeutics (ergometrine and others). Some clavines can also be the starting materials for the synthesis of more complex products.

The second approach, which is more recent, leads to the direct production of ergopeptines, particularly ergocryptine, from strains of *C. purpurea* and possibly from other species. The fermentation is lengthy, and the ergopeptines are obtained in a yield on the order of g/L. The culture can be directed by adding to the medium the amino acids that are the precursors of the desired tricyclic peptide.

Since the specificity of the synthetic system is low, it is possible to introduce in the medium abiogenetic amino acids, in order to obtain alkaloidal compounds that do not occur naturally and are novel for pharmacological experimentation.

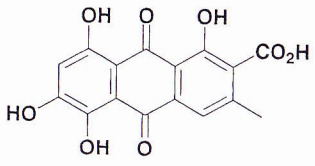
In any event, the products must be extracted, keeping in mind that a fraction remains inside the cells (ion-exchange resins).

C. Chemical Composition

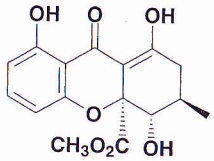
The ergot of rye is a drug of complex composition. Besides the sugars and a large number of amino acids, the drug contains a high proportion of lipids: 20 to 40% of its mass consists of an oil which readily turns rancid, hence its degradation in storage. Note also the presence of sterols (ergosterol and related compounds),

minor and anthraquinone-like (clavorubin, endocrocin), the others are dominant and are mostly xanthone dimers or ergochromes.

The concentration of active substances, in other words of ergoline alkaloids, varies greatly: it might reach 1% in strains intended for the artificial infestation of cereals.



Clavorubin



Monomeric xanthone (constitutive of ergochromes)

Alkaloids of *Claviceps purpurea*

Alongside traces of clavines, two main groups of alkaloids are distinguished:

1. *The simple amides of lysergic acid.* The simple amides of lysergic acid represent about 20% of the total alkaloids. The chief alkaloid in the group is ergonovine (ergobasine, ergometrine), the amide of lysergic acid and of 2-amino-propanol. Ergot also contains a small amount of ergine (lysergic acid amide), perhaps arising from the spontaneous decomposition of the 2-hydroxyethylamide of lysergic acid;

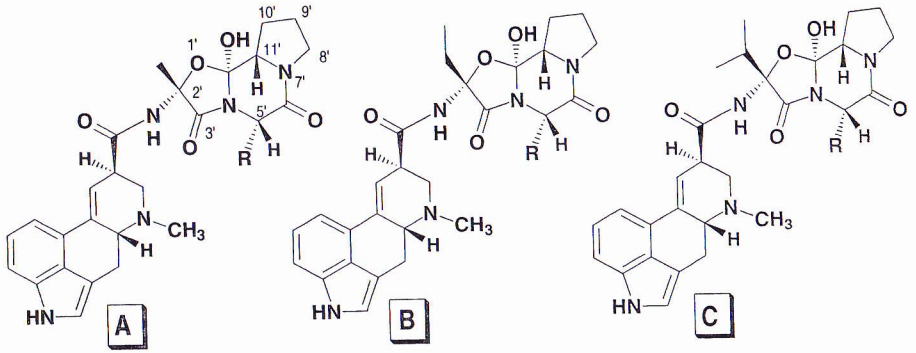
2. *The ergopeptines.* The ergopeptines are insoluble in water, are by far the principal alkaloid constituents (80% of the total alkaloids), and their hydrolysis affords lysergic acid, proline, ammonia, an amino acid which may be phenylalanine, leucine, isoleucine, or valine, and an α-ketoacid (pyruvic acid, dimethylpyruvic acid, α-ketobutyric acid). The characteristic structural element of these ergopeptines is the cyclol formed by the reaction of the hydroxyl group on the α-carbon of an amino acid (that which, by hydrolysis of the peptide, leads to the α-ketoacid), and the carboxyl group of proline. To simplify the nomenclature of such an edifice, the term ergopeptine is used for the basic skeleton, and in current practice, the common denominations that are most widely accepted are being used.

The principal alkaloids in this group are ergotamine and "ergotoxine", a mixture of ergocornine, ergocryptine (α + β), and ergocristine. The other alkaloids (see the table on the next page) are not abundant and are of no therapeutic interest.

Comment: instability of lysergic acid derivatives.

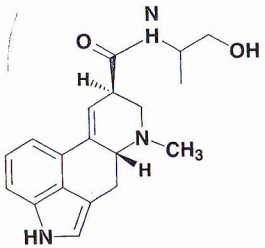
The derivatives of lysergic acid readily epimerize at C-8 to form derivatives of isolysergic acid. This epimerization is enhanced in polar solvents and goes through an enol intermediate. The nomenclature of the two series differs by the ending of the name of the alkaloid, which is *-ine* for lysergic acid derivatives, and *-inine* for the corresponding C-8 epimers or isolysergic acid derivatives (e.g., ergonovine and ergonovinine, ergosine and ergosinine). The [illegible]

Principal alkaloids of the ergot of rye, Claviceps purpurea

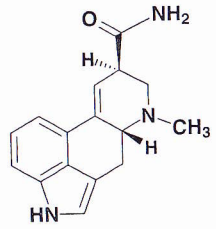


	A : Ergotamines	B : Ergoxines	C : Ergotoxines
R = CH_2 Ph	*Ergotamine*	*Ergostine*	*Ergocristine*
R = CH_2 $CH(CH_3)_2$	*α-Ergosine*	*α-Ergoptine*	*α-Ergocryptine*
R = $CH(CH_3)CH_2CH_3$	*β-Ergosine*	*	*β-Ergocryptine*
R = $CH(CH_3)_2$	*Ergovaline*	*Ergonine*	*Ergocornine*
R = CH_2CH_3	*Ergobine*	*Ergobutine*	*Ergobutyrine*

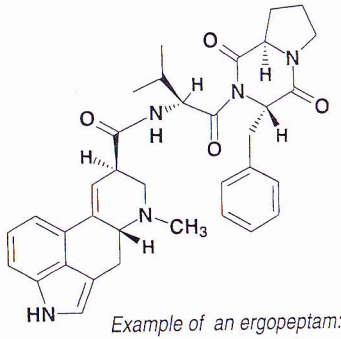
* not known



Ergonovine (= ergometrine)



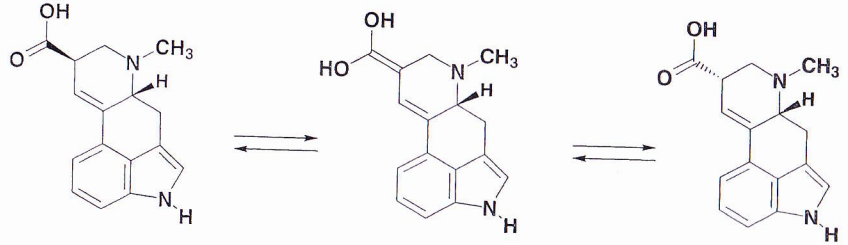
Ergine



Example of an ergopeptam: ergocristam

a pharmacological nature: the derivatives of isolysergic acid are devoid of activity. Fortunately, these derivatives are alteration products: they are practically absent from the extraction residue when the extraction has been carried out under good conditions.

The aqueous solutions of alkaloids derived from lysergic acid are sensitive to UV radiation: the photoaddition of a molecule of water across the 8,9-double bond yields stereoisomers.



Lysergic acid *Isolysergic acid*

D. Tests

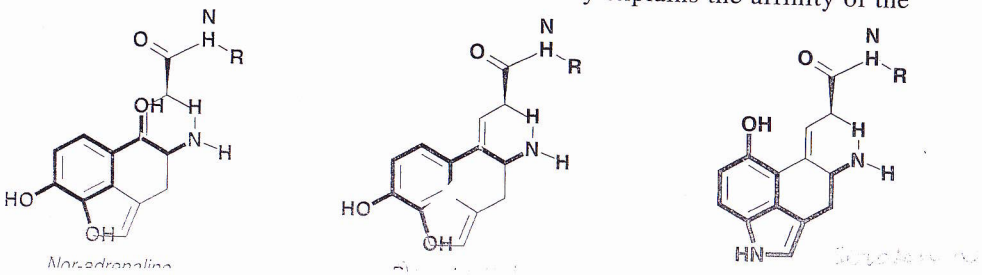
The alkaloids can be detected by color reactions. The ergot alkaloids react with 4-dimethylaminobenzaldehyde under acidic conditions to give a blue color (van Urk reaction). This color reaction can be used for quantitation, for example the quantitation described in the 9th edition of the French Pharmacopoeia, following extraction of the total alkaloids as tartrates from the defatted drug.

The analysis of complex alkaloid mixtures (total alkaloids, fermentation media, pharmaceutical formulations) can be performed efficiently by HPLC (UV detection).

The detection of ergot metabolites in agricultural products can be achieved by chromatographic techniques (TLC, HPLC), and also by mass spectrometry and immunological techniques.

E. Pharmacological Activity

The pharmacological activity of the ergot of rye alkaloids is particularly complex and is due to their structural analogy with endogenous amines: noradrenaline, dopamine, and serotonin. This structural similarity explains the affinity of the



Nor-adrenaline

alkaloids and their derivatives for the endogenous amine receptors and their ability to exert agonistic or antagonistic effects on those receptors. It also explains how, even though these alkaloids may develop a preferred activity on one specific type of receptor (α-adrenergic, dopaminergic, or serotonergic), they also have at least some partial activity on the other types of receptors: this helps to resolve the complexity of their actions.

- **Ergonovine**

This alkaloid is a potent oxytocic: it increases basal tone, and the frequency and strength of uterine contractions; the more advanced the pregnancy, the stronger the effect is. This activity is thought to be linked to the stimulation of the α-adrenergic receptors in the myometrium. Uterine hypertonicity is at the origin of the antihemorrhagic effects of ergonovine. In practice, methylergonovine is the preferred medication: this is the amide of lysergic acid and of 2-aminobutanol, a semisynthetic derivative which is more active on the uterus; it also has a vaso-constrictive activity on arteries (at high doses).

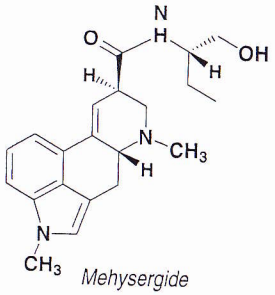
- **Ergotamine**

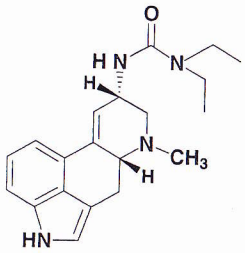
At low doses, ergotamine is a potent vasoconstrictor acting by stimulation of the α-adrenergic receptors (or of the serotonergic receptors in the case of the cranial blood vessels). The change in vascular tone is particularly marked peripherally and in the branches of the external carotid; this reaction is accompanied by the closure of the arterio-venous shunts. At higher doses, an adrenergic antagonist activity appears, which is weak, and illustrates the duality in the activities of this compound. In addition, ergotamine is an oxytocic.

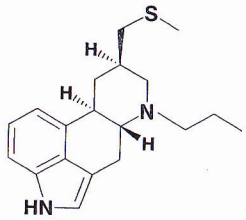
- **Hydrogenated Derivatives of Naturally-occurring Alkaloids**

- **9,10-Dihydroergotamine.** 9,10-Dihydroergotamine results from the hydrogenation of the 9,10-double bond, which greatly decreases the agonist activity at the α-adrenergic receptors (the intensity of the activity is thought to be dependent on the preexisting vascular tone) and reinforces the potency of the adrenergic and serotonergic antagonist activity. 9,10-Dihydroergotamine is more active on veins than arteries; it is a vasoregulator which "stabilizes vascular tone".

- **9,10-Dihydroergotoxine.** 9,10-Dihydroergotoxine has a complex pharmacology (stimulation of central receptors, peripheral vasodilation, regulating activity on the neuronal metabolism) which might explain its beneficial effects on what are commonly thought of as behavioral problems due to senile cerebral insufficiency.


Mehysergide


Lisuride


Pergolide

• Other Semisynthetic or Synthetic Derivatives

• **Methysergide** (INN). Methysergide results from the methylation of the indole nitrogen atom of methylergonovine. This is a potent serotonergic antagonist, devoid of intrinsic vasoconstricting effect. All of its activities (inhibition of the increase in permeability caused by serotonin, decrease of the release of histamine by mastocytes, and more) contribute to making it a basic treatment of migraine headaches.

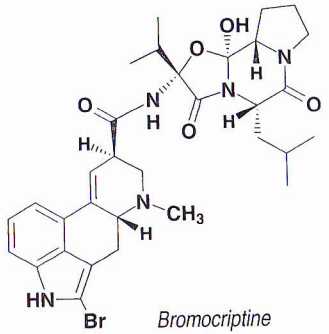
• **Nicergoline** (INN). Nicergoline is a synthetic derivative, more specifically an ester of 10α-methoxylysergol in which the ergoline nucleus is hydroxymethylated at C-8. An almost pure α-1-adrenergic antagonist, nicergoline is a "cerebral vasodilator": it increases the arterial blood flow to the brain and enhances glucose and oxygen utilization by brain cells; it also decreases platelet aggregation.

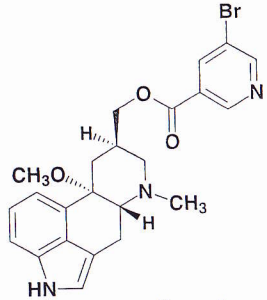
• **2-Bromo-α-ergocryptine** (= bromocriptine, INN). Bromocriptine results from the introduction of a bromine atom on the carbon atom which is α to the indole nitrogen atom, and its postsynaptic dopaminergic agonist properties are exacerbated: it inhibits the secretion of prolactin by the hypothalamus-pituitary axis; in the central grey area, it compensates the dopamine depletion due to the degeneracy of the pathway between the substantia nigra and the corpus striatum in parkinsonism. Other dopaminergic effects are worth noting: hypotensive activity, emetic effect, and at high doses, induction of psychic symptoms by stimulation of the dopaminergic receptors of the limbic system.

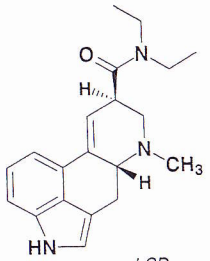
• **Lisuride**. Lisuride is a synthetic derivative of the 8α-aminoergoline type. Like bromocriptine, it is a dopaminergic agonist with predominant central activity, decreasing prolactin secretion, and compensating dopamine depletion at the substantia nigra-corpus striatum level. It is also active at serotonergic receptors

• *Lysergic acid diethylamide* = LSD (i.e., *Lysergsäurediethylamid*, in German). LSD is a semisynthetic derivative, of no use in therapeutics, and it is a potent psychedelic: it is thought to act by interfering with normal serotonergic transmission. Its psychic effects are very marked, and manifest themselves by perceptual changes (shapes, colors, sounds), subjective time alt...

disintegration of the self, an increase in suggestibility, the resurgence of forgotten memories, and more. Physiologically, mydriasis, tachycardia, and tremors are observed, as well as a desynchronization of the electroencephalogram. The environment and the state of mind of the subject (previous experiences, expectations) are determining factors in the onset of undesirable effects: propensity to panic, anxiety, fear of death and insanity, changes in personality, persistence of a psychotic syndrome, and spontaneous recurrence, sometimes for long periods of time, of the psychedelic experience in the absence of further ingestion of the product. LSD induces tolerance, but no physical dependence (no withdrawal symptoms).


Bromocriptine


Nicergoline


LSD

F. Uses of Ergot Alkaloids

(natural, modified, semisynthetic, synthetic analogs)

Methylergometrine (INN). Methylergometrine maleate (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) is indicated (injectable solution) for obstetric emergencies: afterbirth delivery and post-partum hemorrhages, after cesarean sections, after curettage, after abortion by suction or curettage, and for uterine atony after giving birth. For these indications, it is administered by IM injection (0.2 mg). It is contraindicated during pregnancy; during labor until the posterior shoulder of the newborn is free; in case of abnormal presentation, until the whole newborn is free; in case of severe arterial hypertension, occlusive vascular disease, or severe infectious disease. Except for specific indications and for a short time only (< 3 days), the compound must not be used in breast-feeding women. The blood pressure of patients taking it must be monitored, and side effects are rare (hypertension attacks).

In specialized hospital wards, this alkaloid is used for diagnostic purposes or to evaluate certain treatments (methylergometrine test).

When it is used by the oral route (solution, tablets), ergometrine is indicated: 1. for afterbirth delivery and post-partum hemorrhages (following oxytocics administered parenterally); 2. for metrorrhagia of various origins (after giving birth, therapeutic abortion, spontaneous abortion); 3. for the adjunctive treatment of ...orrhagia in the absence of pregnancy after attempts have been made to

determine the cause of the disorder (but for this indication, some feel that the benefit-to-risk ratio is unfavorable).

Ergotamine. Ergotamine tartrate (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed; a prescription drug in the United States) is used orally or rectally, in combination with caffeine, which accelerates and reinforces its digestive resorption by about 45%. This compound provides a specific treatment of the acute attack of migraine headache and related vascular headaches; it must not be considered a basic treatment of the patient with migraines. Its mode of action (vasoconstriction) explains why its efficacy is maximal at the beginning of the attack, when it is administered as soon as the prodromal symptoms of the acute attack of migraine headache are felt *. In the majority of cases, the administration of 2 mg is sufficient (in adults). If the symptoms persist or reappear, it is possible to take another dose; it is recommended, however, not to exceed 6 mg per day, and in case of multiple doses per week, 10 mg per week. If ischemic symptoms appear (vasoconstriction of the extremities, tingling) the treatment must be discontinued immediately. Although the risk of ergotism is low, a certain number of pathological conditions increase it, and therefore there are contraindications: occlusive vascular disease, arterial hypertension, coronary insufficiency, and severe hepatic or renal insufficiency. The concomitant use of ergotamine and macrolide-type antibiotics (except for spiramycine) must be proscribed (risk of ergotism ** with necrosis of the extremities); the combination with sumatriptan is also formally contraindicated (risk of arterial hypertension and coronary arterial vasoconstriction). Its use is discouraged in pregnant and breast-feeding women, as well as in children under the age of 10. The simultaneous use of β-blockers requires close medical supervision.

Dihydroergotamine. Dihydroergotamine has the following indications: for the treatment of migraines and vascular headaches; to improve the symptoms of venous and lymphatic vessel insufficiency. It is also proposed for the treatment of orthostatic hypotension. It is used orally (mesylate, tablets, capsules, or solution, a controlled substance on French *liste II*, i.e., a prescription drug, 3 x 3 mg/day; 2 x 5 mg/day). It is well tolerated, and must not be given concomitantly with macrolide antibiotics (except for spiramycine). The administration on an empty stomach is to be avoided (risk of nausea). It is best to avoid giving it to pregnant or breast-feeding women.

In France, an injectable form and a nasal spray (the bioavailability is better than *per os*) are currently available and used to treat the acute attack of migraine headache, with the same indications, contraindications, and precautions as ergotamine. In the United States, dihydroergotamine mesylate is a prescription drug available in injectable solution.

* It is generally accepted that the acute attack of migraine headache consists of two phases: a first vasoconstrictive phase due to the release of serotonin (scintillating scotoma, tingling, psychic symptoms) and a second phase—the headache—due to vasodilation (decrease in serotonin levels, passive relaxation of the blood vessels).

** Vera[illegible]

Dihydroergotoxine - dihydroergocristine. Dihydroergotoxine mesylate (a controlled substance on French *liste II*, i.e., a prescription drug) is available under various forms designed for oral administration (solution, tablets or single dose lyophilisate, capsules containing microgranules for slow release) and as an injectable solution.

Also used as a mesylate, dihydroergocristine (a controlled substance on French *liste II*, i.e., a prescription drug) is commonly combined with an adrenergic antagonist like raubasine (= ajmalicine) or to a substance that will enhance its intestinal absorption (lomifilline).

These two alkaloids have similar indications: they are proposed for oral administration (2-5 mg/day) as a corrective treatment of senile cerebral insufficiency (lack of attention, memory loss), to treat the sequelae of cerebrovascular accidents, dizziness in the elderly,and retinal disorders of vascular origin. If administration on an empty stomach is avoided, side effects are rare (nausea). IV administration (infusion) is reserved for the relief of the painful symptoms of arterial disease during the attack of ischemia and for the treatment of the sequelae of cerebrovascular accidents. As emphasized by the French regulatory phrase "proposed for", the efficacy of this alkaloid and its combinations—and ANDEM points out that this is true for all of the "vasodilators and anti-ischemics"—for the prophylaxis or the treatment of acute cerebrovascular accidents of ischemic origin, has not been proved. Its benefit in the treatment of chronic symptoms thought to be of ischemic origin or else ill-defined is not proved either, as for most of the compounds in this class (yet short term use is acceptable after the desired benefits and potential risks have been evaluated).

Methysergide (INN). Methysergide maleate (a controlled substance on French *liste II*, i.e., a prescription drug; a prescription drug in the United States) is used orally, only in adults (1 mg/day with gradual increase to 4-6 mg/day in France; 2-mg tablets for a usual adult dose of 4-8 mg/day in the United States) for the following principal indications: basic treatment of migraines and facial pain of vascular origin. It is not a treatment for permanent migraine. It is contraindicated in cases of severe hypertension, coronary insufficiency, peripheral vascular symptoms, serious hepatic or renal insufficiency, pregnancy, and breast-feeding. Continuous administration must not exceed 6 months, and successive courses of treatment must be separated by 1 month. Possible side effects, especially at the beginning of treatment, include digestive and nervous symptoms (nausea, dizziness, insomnia, or drowsiness). Continuous treatment can induce retroperitoneal fibrosis leading to dysuria or oliguria, but in most cases, disappearing upon discontinuation of the treatment (such symptoms are rare when treatment is limited and not continuous).

Nicergoline (INN). Nicergoline (a controlled substance on French *liste II*, i.e., a prescription drug), given its α-blocking properties, is indicated for the adjunctive treatment of the intermittent claudication due to chronic occlusive arterial disease of the lower limbs. It is proposed orally or parenterally to improve some of the

dizziness in the elderly. It is proposed by the parenteral route for acute cerebrovascular accidents of ischemic origin and for the acute manifestations of arteritis of the lower limbs (see above).

2-Bromo-α-ergocryptine (= bromocriptine, INN). There are three main groups of indications for this substance (on French *liste I*, i.e., a prescription drug which may not be renewed; a prescription drug in the United States).

1. • Prolactin-secreting adenomas: basic treatment; in preparation for surgical procedures in case of macroadenoma; in case of early or late failure following surgery: for the clinical consequences of recurring hyperprolactinemia. The average posology is, after beginning with small doses and increasing them slowly, 5 mg/day. After 6 weeks, if the gonads are still not functional, the dose can be doubled.

• Clinical consequences of hyperprolactinemia: severe disturbances of the menstrual cycle, sterility, galactorrhea, and in men, gynecomastia and impotence.

2. Inhibition of lactation: prevention and inhibition of physiological lactation for medical reasons immediately after delivery (ablactation) or a long time after delivery (weaning). (2 x 2.5 mg/day). The average posology is, after beginning with small doses and increasing them slowly, 5 mg/day for 14 days.

3. Treatment of parkinsonism alone (patients over 65 years of age) or in combination with levodopa (to decrease the doses of each drug and delay the onset of fluctuations in efficacy and abnormal movements). The average efficacious posology is between 10 and 40 mg/day.

The side effects (nausea, vomiting, orthostatic hypotension) generally disappear fairly rapidly; at high doses and in case of preexisting mental deterioration, psychic symptoms may appear (visual hallucinations, confusion): if they are observed, the posology must be decreased, or the treatment must be discontinued. There are various precautions, including verifying the absence of pituitary adenoma, and discontinuing the treatment in case of pregnancy, which must then be monitored closely.

Reports of serious accidents (hypertension, convulsions, cerebrovascular accidents, infarction) have led some countries (United States, Canada) to delete the inhibition of lactation from the indications for bromocriptine.

Lisuride. Lisuride maleate (a controlled substance on French *liste I*, i.e., a prescription drug which may not be renewed) has as a chief indication the treatment of parkinsonism, either in combination with levodopa early in the treatment, which allows a decrease in the doses of each drug and delays the onset of fluctuations in efficacy and abnormal movements, or else later in the treatment, when the efficacy of levodopa decreases or becomes inconsistent. The gynecological indications of lisuride are the same as those of bromocriptine (clinical consequences of hyperprolactinemia). The side effects are similar to those induced by bromocriptine (nausea, vomiting, orthostatic hypotension, mental confusion, hallucinations, risk of vascular accidents). The doses must be increased very gradually, precautions must be taken, and warnings must be heeded. One of the medicines available on the market may claim the following indication: prolactin inhibition.

Lysergide or LSD 25. The production, marketing, and use of this compound are prohibited in France (French decree of September 10, 1992, *J. O. Rép. fr.*, September 20, 1992, p. 10 039 *sq.*).

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