In: Plants in the developments of modern medicine.
Ed. by: T. Swain.
Harvard University Press, Cambridge, Mass. 1972, pp.235-260.

Ergot–A Rich Source of Pharmacologically Active Substances

ALBERT HOFMANN

INTRODUCTION

Since the discovery of penicillin, research on the chemistry of fungi has intensified to an unforeseen extent. Ergot, the subject of this chapter, is a fungus with no antibiotic activity, but it has engaged the interest of doctors, pharmacologists, and chemists for centuries, long before the antibiotic era.

What is commonly known as ergot (*Secale cornutum*) is the sclerotium of the fungus *Claviceps purpurea* (Fries) Tulasne which commonly grows on rye. The grains which are infected with the fungus develop a purple-brown curved body as can be seen in Fig. 1. Cereals other than rye, as well as wild grasses, can be infected by *C. purpurea* and other species of *Claviceps*, as will be described later.

HISTORY OF ERGOT

Ergot has a fascinating history. Over the centuries its role and significance have undergone a complete metamorphosis. Once a dreaded poisonous contaminant, it has come to be regarded as a rich treasure house of drugs (1). Some of the most important dates are listed in Table 1.

Ergot began its history as a poisonous contaminant of edible grain. As early as 600 B.C., an Assyrian tablet alluded to a "noxious pustule in the ear of grain." In the Middle Ages, bizarre epidemics occurred in Europe which cost tens of thousands of people their lives, caused by bread made from rye contaminated with ergot. According to ancient records, 40,000 people died in the south of France during a severe epidemic in 994, and 12,000 died in the Cambrai region in 1129. This

Fig. 1 Ergot growing on rye.

Table 1. History of Ergot

	A poisonous contamination of edible grain:
600 B.C.	Assyrian tablet "noxious pustule in the ear of grain."
Middle Ages	Epidemics of Ergotismus Convulsivus and Ergotismus Gangraenosus described as "ignis sacer," "holy fire," "St. Antony's fire."
	A remedy for quickening childbirth:
1582	Adam Lonitzer ". . . a proved means of producing pains in the womb."
1808	John Stearns in the Medical Repository of New York "Account of the Pulvis Parturiens."
	A remedy to control post-partum hemorrhage:
1824	D. Hosack in "Observations on Ergot" recommended ergot to be used only to control post-partum hemorrhage.
	A source of pharmacologically useful alkaloids:
1906	G. Barger and F. H. Carr: Isolation of ergotoxine and discovery of its adrenolytic activity.
1918	A. Stoll: Isolation of ergotamine, the first pure pharmacologically active ergot alkaloid.
1935	H. W. Dudley and C. Moir and other groups: Isolation of ergonovine (ergometrine, ergobasine, ergotocine), the oxytocic principle of ergot.
1935 onward	Extensive investigations on the chemistry of ergot alkaloids by W. A. Jacobs and L. C. Craig (U.S.A.); S. Smith and G. M. Timmis (England); A. Stoll, A. Hofmann et al. (Switzerland), and other groups; extensive pharmacological and clinical investigations by E. Rothlin, A. Cerletti et al. (Switzerland), and other groups.

Fig. 2 St. Anthony, patron saint of the Order, caring for sufferers from ergotism.

scourge, in which gangrenous manifestations leading to mummification of the extremities were a prominent feature, was known as "ignis sacer," "holy fire," or "mal des ardents."

In 1093, a religious Order was founded in southern France for the purpose of caring for those afflicted by ergotism. The new Order chose St. Anthony as its patron saint (Fig. 2). Figure 2 shows St. Anthony surrounded by patients stricken with ergotism. From this time, "mal des ardents," or the "holy fire," came to be called also "St. Anthony's fire."

The cause of the epidemics was recognized in the seventeenth century, and since then there have been only sporadic outbreaks of ergot poisoning.

Ergot was first mentioned as a remedy used by midwives for quickening labor by the German physician Lonitzer in 1582. The first scientific report on the use of ergot as an oxytocic agent, "Account of the Pulvis Parturiens," was given by the American physician Stearns in 1808. But in 1824, Hosack, recognizing the dangers of using ergot for accelerating child-birth, recommended that the drug be used only to control postpartum hemorrhage. Since that time ergot has been used in obstetrics mainly for this purpose.

The last and most important chapter in the history of ergot, and one which is still not completed, concerns ergot as a source of pharmacologically useful alkaloids. It started with the isolation of ergotoxine in 1906 by Barger and Carr and the discovery of its adrenolytic activity. In 1918, Stoll isolated ergotamine, the first ergot alkaloid to find widespread therapeutic use in obstetrics and internal medicine. Another important step was the discovery in 1935 of the specific oxytocic principle of ergot by Dudley and Moir, which resulted in the isolation of the alkaloid ergonovine simultaneously in four separate laboratories.

Since 1935, extensive investigations on the chemistry of ergot alkaloids have been carried out mainly by Jacobs and Craig in the United States, Smith and Timmis in England, and Stoll, Hofmann et al., paralleled by pharmacological and clinical investigations by Rothlin, Cerletti et al., in Switzerland (2).

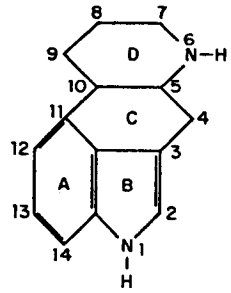
THE CHEMISTRY OF THE ERGOT ALKALOIDS

The ergot alkaloids belong to the large and important class of indole alkaloids. All ergot alkaloids contain a tetracyclic ring system, which has been named ergoline (I).

The most important ergot alkaloids are derivatives of lysergic acid, which is 6-methyl-ergolene-($\Delta^{9,10}$)-8β-carboxylic acid (II).

Lysergic acid (II) and its derivatives, the ergot alkaloids, epimerize very easily at position 8, giving rise to isolysergic acid (III) and its derivatives, respectively. The latter compounds are usually much less physiologically active than the genuine alkaloids, and great care must be taken to avoid such isomerization during extraction.

The structure of lysergic acid (II) was confirmed by total synthesis by Kornfeld and co-workers in the Lilly Laboratories in 1954 (3). This



I. Ergoline

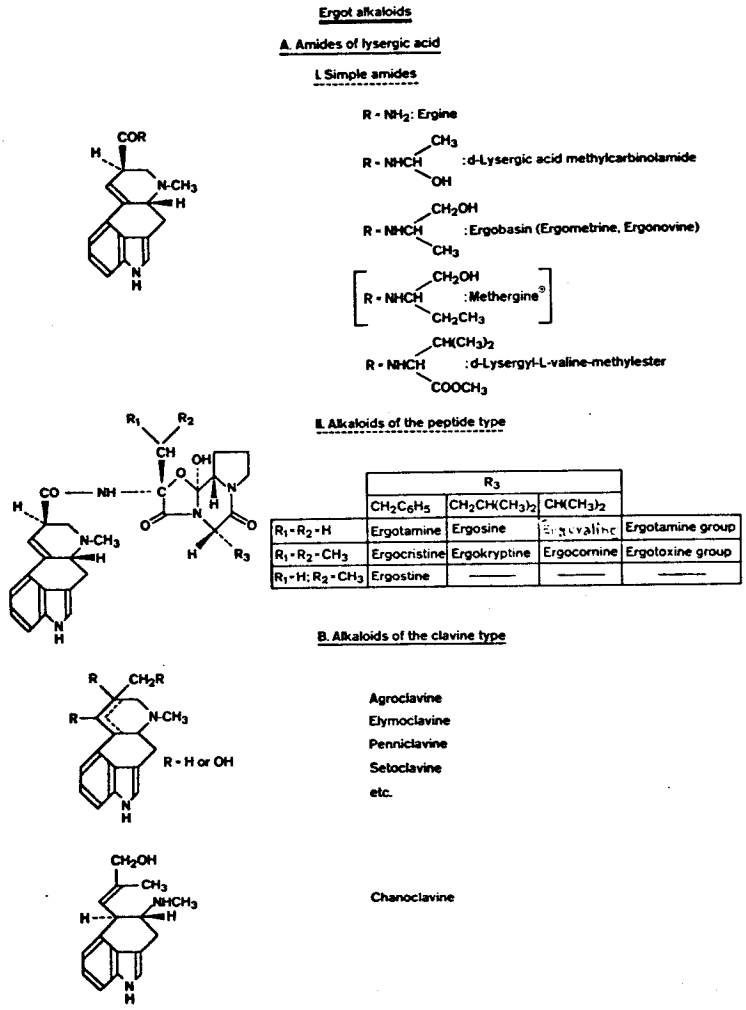
synthesis has not found industrial application because of the poor yield, and because, as will be described later, lysergic acid can be produced today by fermentation processes on an industrial scale.

Up to the present time, some two dozen alkaloids have been isolated from various species of ergot and their structures and stereochemistry have been completely elucidated (Fig. 3). They can be divided into two main groups, A and B. Group A comprises amides of lysergic acid: subgroup A I contains simple amides and subgroup A II, amides of the peptide type. In the first subgroup, the amide radical may be simply NH_2, as in ergine, or it may be an amino-alcohol such as 2-amino-propanol in ergometrine, the oxytocic principle of ergot. The therapeutically most important ergot alkaloids belong to subgroup A II, in which lysergic acid is combined with various cyclic tripeptide (Fig. 3). These tripeptides all contain a proline residue, joined to a second amino acid, which can be either L-phenylalanine, L-leucine, or L-valine, and an *a*-hydroxy-*a*-amino-acid, either *a*-hydroxy-alanine, *a*-hydroxy-valine, or *a*-hydroxy-*a*-amino-butyric acid.

In 1961, the first total synthesis of a peptide-type ergot alkaloid, namely of ergotamine, was accomplished in my laboratory (4). This synthesis, which will be discussed later, afforded confirmation of the special, cyclol structure of the peptide moiety.

The ergot alkaloids of the second main group (clavine type, Fig. 3) differ from those of Group A in that the carboxyl group of lysergic acid is replaced by a hydroxymethyl or a methyl group. The alkaloids of the clavine type occur mainly in ergot growing on wild grasses and are of no value in medicine.

Fig. 3 Ergot alkaloids.



PRODUCTION OF ERGOT ALKALOIDS BY FERMENTATION

When the medicinal importance of the ergot alkaloids was realized, many attempts were made to produce them by growing the *Claviceps* fungus *in vitro*, instead of on rye.

Abe, in Japan, discovered in 1951 a species of *Claviceps* growing on wild grasses which produced ergot alkaloids in good yield in submerged cultures (5). However, these alkaloids were of the clavine type, which,

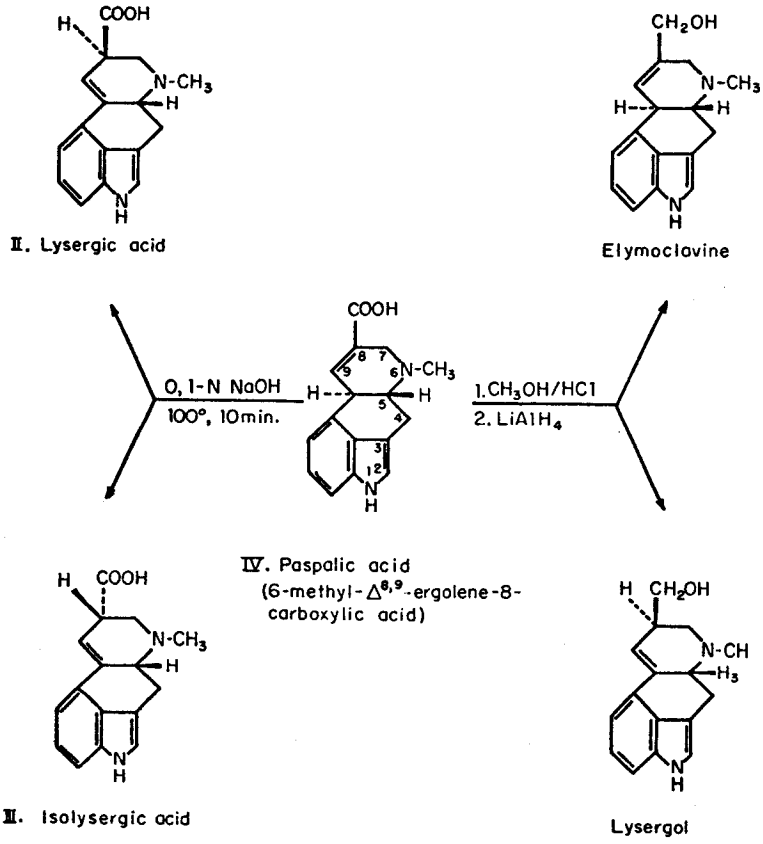
as I have already pointed out, are of no use in medicine. In 1953, Stoll Brack, Hofmann, and Kobel first succeeded in producing ergotamine by *in vitro* cultivation of *C. purpurea* (6). However, the yields were low, and the surface culture method they used was not suitable for industrial production. Recently, Tonolo (7), and somewhat later, Amici et al. (8) reported that they had isolated a strain of *C. purpurea* which produced ergotamine in appreciable yield in submerged culture. Unfortunately, this strain too cannot be used for the industrial production of ergotamine as the yield is too low.

A discovery of industrial importance was the observation in 1960 by Chain and his co-workers, at the Istituto Superiore di Sanità in Rome, that an Italian strain of *C. paspali* was able to produce lysergic acid amide and simple derivatives of lysergic acid amides in high yield in submerged culture (9). These lysergic acid amides can be readily hydrolyzed to lysergic acid, which can be used as starting material for the synthetic production of therapeutically useful pharmaceutical preparations.

More recently, after investigation of many hundreds of ergot samples from all over the world, Kobel, Schreier, and Rutschmann of the Sandoz Laboratories succeeded in isolating, from ergot found in Portugal on *Paspalum dilatatum,* a *Claviceps* strain capable of producing excellent yields of a mixture of free lysergic acid isomers in submerged cultures (10). This mixture consists of some 30 percent of lysergic acid (II) with a small amount of isolysergic acid (III) and of some 70 percent of a new isomer of lysergic acid. We have named this new acid from *Paspalum* ergot *paspalic acid* (IV). The structure and stereochemistry of paspalic acid and its relationship to lysergic and isolysergic acid is illustrated in Fig. 4.

The structure and configuration of the new acid were apparent from the fact that $LiAlH_4$-reduction of its methyl ester yielded a mixture of elymoclavine and lysergol, two ergot alkaloids of known structure. Paspalic acid is thus 6-methyl-($\Delta^{8,9}$) ergolene-8-carboxylic acid. The isolated double bond migrates very easily from the 8,9-position into the 9,10-position under alkaline conditions, producing a mixture of lysergic and isolysergic acid. Paspalic acid, which can be produced on an industrial scale, is therefore a very suitable starting material for the synthesis of lysergic acid which, in turn, can be used for the synthetic production of useful ergot alkaloids or their derivatives.

Fig. 4 Paspalic acid and its products of transformation.

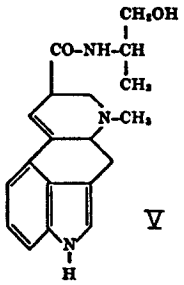


SYNTHESIS OF AMIDES OF LYSERGIC ACID

Today, all the naturally occurring ergot alkaloids can be synthesized. Within the scope of this review, the discussion will be limited to the synthesis of those ergot alkaloids which are of therapeutic interest, namely those of the lysergic acid amide type. As already mentioned, none of the alkaloids of the clavine type (Fig. 3) has been found to be of value in therapy.

Ergometrine and Other Simple Amides. The synthesis of simple amides of lysergic acid (Fig. 3, subgroup A I) was accomplished a number of decades ago. Lysergic acid being a labile, very sensitive compound, the problem was to prepare a suitable activated derivative of lysergic acid

which can be reacted with the appropriate amine. The first successful method of amidation was that using the Curtius reaction via lysergic acid hydrazide and azide (11). Later, other methods were used for the preparation of lysergic acid amides (12-15). By the first procedure, ergometrine (V, ergobasine, ergonovine = d-lysergic acid L-isopropanolamide), the oxytocic principle of ergot, and a large number of other lysergic acid amides were synthesized (11).



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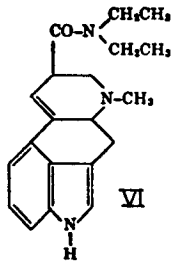

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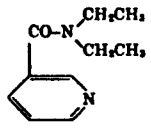
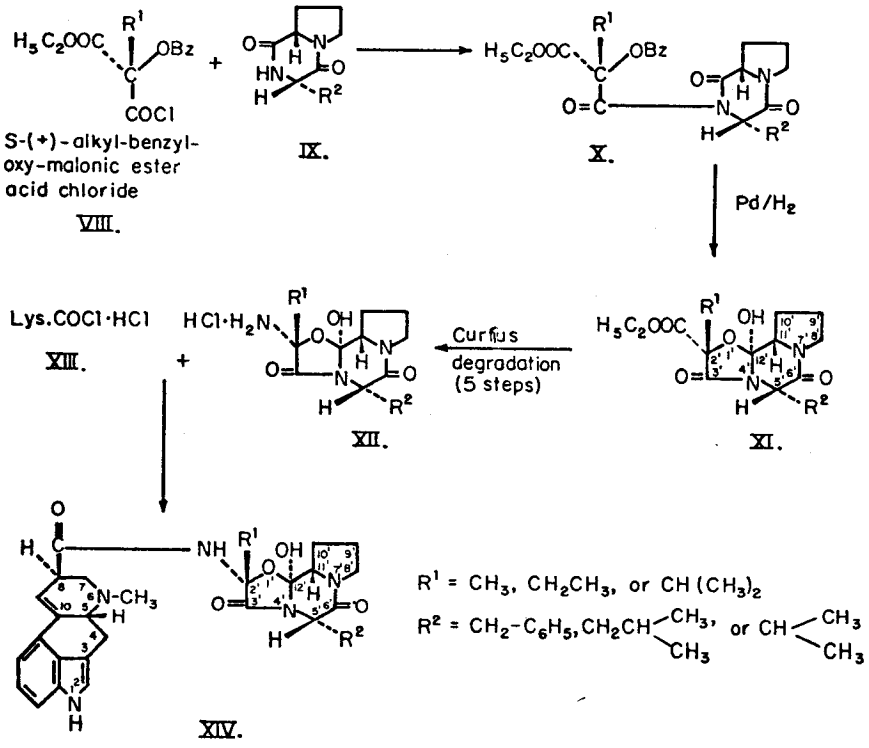


VII

It was during these investigations that I prepared the diethylamide of lysergic acid (VI) or LSD-25. The idea which urged me to synthesize this compound was a certain structural similarity with coramine (VII, nikethamide), a proven analeptic. Pharmacological analysis showed lysergic acid diethylamide to be a strong oxytocic agent with about 70 percent the activity of ergometrine.

Some years later, I prepared LSD a second time in order to provide our pharmacologists with substance for more profound pharmacological investigation. When I was purifying lysergic acid diethylamide (VI) in the form of its tartrate, I experienced a strange, dream-like state which wore off after some hours. The nature and course of this extraordinary disturbance aroused my suspicions that some exogenic intoxication might be involved and that the substance with which I had been working, lysergic acid diethylamide tartrate, could be responsible. In order to ascertain whether or not this was so, I decided to test the compound in question on myself. Being by nature a cautious man, I started my experiment with the lowest dose which presumably could have any effect, taking 0.25 mg LSD tartrate. This first planned experiment with LSD took a dramatic turn and led to the discovery of the extraordinarily high psychotomimetic activity of this compound. The fascinating psychic effects of the diethylamidemide of lysergic acid prompted the synthesis of a large number of analogues, homologues, and derivatives. None of them proved to be more active in its hallucinogenic psychotomimetic properties. But these investigations were successful in other

Fig. 5 Synthesis of peptide-type ergot alkaloids.



respects. Compounds with other valuable pharmacological properties were found among these derivatives, as will be described later.

Ergot Alkaloids of the Peptide Type. The most important recent developments in ergot research have been in the synthesis of new alkaloids of the peptide type (Fig. 3, subgroup A II). Since the first synthesis of a peptide-type ergot alkaloid, ergotamine, in our laboratory in 1961 (16), we have improved the various steps of the synthesis, achieving an appreciable increase in overall yield. In the meantime, the same scheme and sequence of reactions that we used for the synthesis of ergotamine has been applied for the synthesis of the other naturally occurring ergot alkaloids of the ergotamine and ergotoxine group. The general scheme used for these syntheses is shown in Fig. 5.

A suitable substituted alkyl-benzyloxy-malonic ester acid chloride is reacted with a dioxopiperazine (IX) consisting of the radical of L-proline and of a variable amino-acid, either L-phenylalanine, L-leucine, or L-valine. The preparation of the malonic acid derivatives (VIII), where R^1

stands for either methyl, ethyl, or isopropyl, and their separation into the optically active forms is almost a synthesis in its own right. The S-form possesses the stereochemistry corresponding to the configuration at the asymmetric center 2′ in the natural alkaloids. The acylated dioxopiperazine (X) (Fig. 5) is treated with hydrogen and Pd-catalyst in order to remove the benzyl group. The resulting compound with the free hydroxyl undergoes spontaneous cyclolization in a stereo-specific manner to yield the cyclol ester XI. The ethoxycarbonyl group of (XI) is replaced by an amino group following the steps of a Curtius degradation (i.e. via free acid, acid chloride, azide, carbobenzoxyamide) and removal of the benzyl group by catalytic hydrogenation in acidic solution to give the hydrochloride of the aminocyclol (XII). The free aminocyclol (XII), which represents the complete peptide part of the corresponding natural alkaloids, is an extremely labile compound, but it can be isolated in the form of relatively stable crystalline salts, e.g. in the form of the hydrochloride. Using special conditions, it is possible to acylate (XII) with lysergic acid chloride hydrochloride (XIII) to obtain the corresponding natural peptide alkaloid (XIV) in good yield. Starting with malonic ester and the free amino acids and with lysergic acid, this synthesis of a peptide-type ergot alkaloid comprises 22 steps. Using this procedure, the following naturally occurring alkaloids have already been synthesized: ergotamine, ergosine, and the missing link in the natural system of peptide ergot alkaloids with valine as the variable amino acid, which we have named ergovaline (Fig. 3) (17). Ergostine, an alkaloid which occurs only in traces in ergot, and which is characterized by an ethyl substituent at the position 2′ (18), and quite recently, the three alkaloids of the ergotoxine group, which are characterized by an isopropyl substituent at position 2′, i.e. ergocristine, ergokryptine, and ergocornine, have also been synthesized.

With this method developed for the synthesis of the natural ergot alkaloids, we are now in the position to synthesize a great variety of lysergic acid peptides with amino acids other than those occurring naturally, and to study the structure-activity relationship in pharmacological agents of this type. As an example of this line of our current research, suffice it to mention the synthetic analogue of ergotamine in which the L-phenylalanine residue is replaced by an α-methyl-alanine residue. This compound, the activity spectrum of which shows true differences from that of ergotamine, possesses valuable pharmacological properties, as is shown in the section on pharmacology.

CHEMICAL MODIFICATIONS OF THE LYSERGIC ACID MOIETY

Much work has been done and is still in progress to modify or replace the lysergic acid part in the natural ergot alkaloids and in synthetic lysergic acid derivatives. Only a few of the more important modifications which have led to derivatives with interesting pharmacological properties will be discussed.

Hydrogenation of the 9, 10 Double Bond. Catalytic hydrogenation of lysergic acid or of its derivatives yields the corresponding 9,10-dihydro derivatives, a new asymmetric center being formed at C 10. Whereas lysergic acid and its derivatives give only one of the two theoretically possible stereoisomers (XV, XVII) namely, the epimer (XV) with the hydrogen atom in α-position at C 10, isolysergic acid and its derivatives yield both epimers (XVI, XVIII) (19, 20). The stereochemistry of these dihydro derivatives is depicted on Fig. 6. The dihydro derivatives of the ergot alkaloids differ fundamentally in pharmacological activity from the natural compounds, as will be discussed later.

Saturation of the double bond in the 9,10 position can be achieved also by addition of the elements of water. This occurs when an acidic solution of the alkaloids is irradiated with u.v. light (21). These so-called lumi-derivatives are of no pharmacological interest.

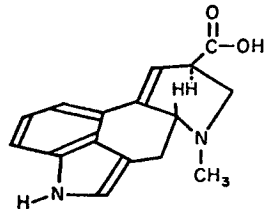
Substitution at Positions 1 and 2. Of the various substitutions which have been carried out at position 1 of lysergic acid and dihydrolysergic acid derivatives (Fig. 7) alkylation, principally methylation (22, 23) cause an interesting shift in pharmacological activity. Halogenation, especially bromination, in position 2 (24) (Fig. 7) can also produce fundamental changes in pharmacological and clinical properties, for example, of LSD.

PHARMACOLOGY AND THERAPEUTIC USE OF ERGOT PREPARATIONS

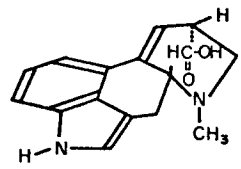
Before we deal with the changes in the pharmacological properties resulting from chemical modifications of the natural ergot alkaloids, let us first take a look at the main pharmacological activities of the natural alkaloids themselves. The ergot alkaloids have an astonishingly wide spectrum of action, a multiplicity of different pharmacological activities such as is rarely found in any other group of natural products.

The pharmacological effects of ergot alkaloids fall into six categories as listed in Fig. 8. They can be divided into three groups, depending on the

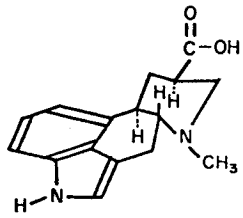
Fig. 6 Stereochemistry of the dihydro derivatives of d-lysergic and d-isolysergic acids.



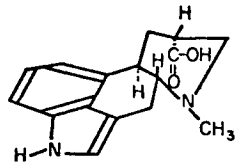
Ⅱ. d-lysergic acid



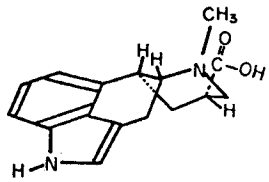
Ⅲ. d-isolysergic acid



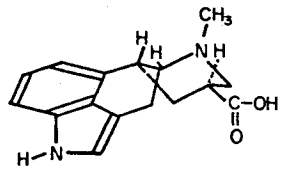
XV. dihydro-d-lysergic acid-(I)



XVI. dihydro-d-isolysergic acid-(I)

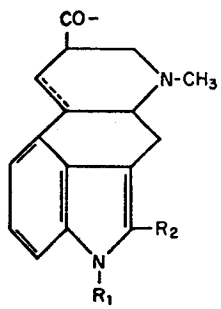


XVII. dihydro-d-lysergic acid-(II)



XVIII. dihydro-d-isolysergic acid-(II)

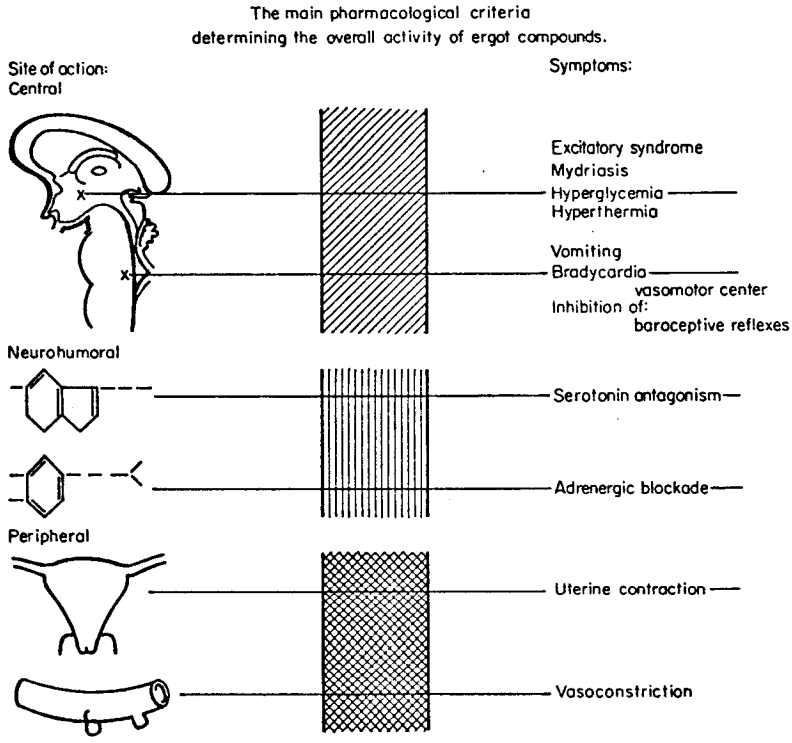
Fig. 7 Substitutions at positions 1 and 2 of lysergic acid and dihydrolysergic acid derivatives.



R_1 = $COCH_3$, $COCH_2COCH_3$
CH_2OH, CH_2OCOCH_3
$CH_2N(alkyl)_2$
CH_3, C_2H_5,
$CH_2CH=CH_2$, $CH_2C_6H_5$

R_2 = Cl, Br, J

Fig. 8 The main pharmacological effects of ergot alkaloids.



site of action, a distinction being made between central, neurohumoral and peripheral effects. The peripheral action on smooth muscle is manifest as vasoconstriction and uterine contraction. The classical indication for ergot alkaloids, i.e., their use in obstetrics to arrest hemorrhage and promote uterine contractions, is based on this effect.

Neurohumoral effects are antagonism to adrenaline and to serotonin. Antagonism to adrenaline and to the effects of postganglionic sympathetic nerve stimulation, i.e. adrenolytic and sympathicolytic activities, account for many of the uses of the ergot preparations in internal medicine. The other neurohumoral effect, antagonism to serotonin, has been selectively developed in certain ergot derivatives, as will be shown later.

Central effects occupy an important place in the activity spectrum of the ergot alkaloids. The site of action is in the medulla oblongata and in the midbrain. The ergot alkaloids reduce the activity of the vasomotor center in the medulla oblongata, and this reduced activity is responsible for the vasodilator, hypotensive and bradycardic effects of certain ergot

alkaloids. Many ergot alkaloids stimulate the vomiting center in the medulla oblongata. Sympathetic structures in the midbrain, particularly in the hypothalamus, are stimulated. This leads to a comprehensive excitation syndrome, with such signs as mydriasis, hyperglycaemia, hyperthermia, tachycardia, and so on. This excitation syndrome is connected with the psychotomimetic and hallucinogenic actions of certain ergot derivatives such as LSD.

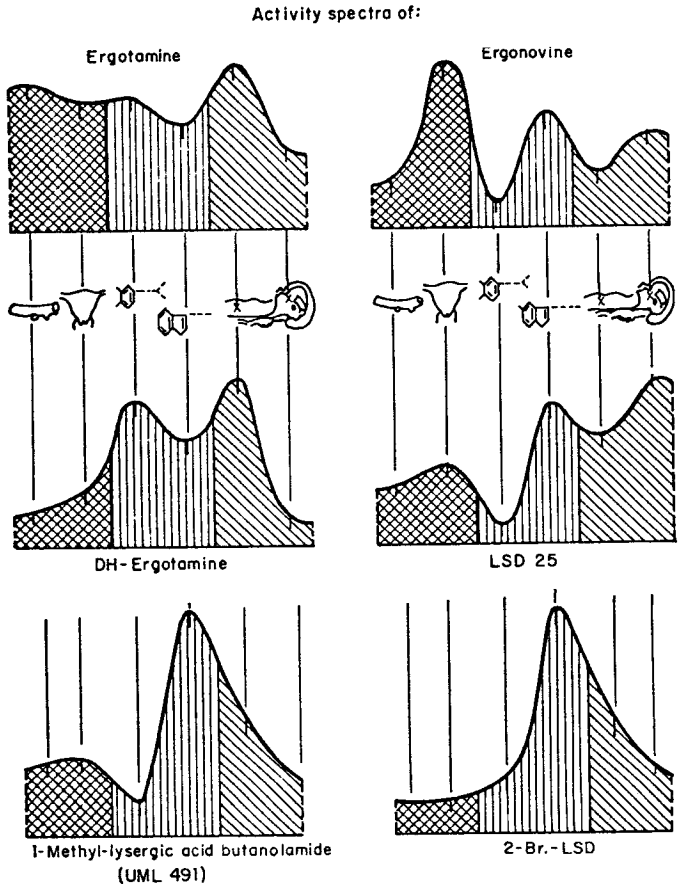
The various structural types of natural ergot alkaloids and their derivatives differ in biological activity in that the relative predominance of these six main effects varies from compound to compound. One or more of these activity components may be almost completely absent; other effects may remain unaltered or may even be enhanced. The goal of chemical modification is to arrive at compounds with a narrower range of activity, but with more selective specific effects.

Cerletti has delineated the activity spectra of the various types of ergot alkaloids with reference to the six main effects described (25). He depicted his findings graphically by selecting a relative scale for each compound, beginning with the smallest effective dose (top) and finishing with the 100 percent lethal dose (bottom). The maximum value indicates which of the six main effects is particularly prominent.

It will be seen that in the case of ergotamine (Fig. 9), the ratio between the various effects is rather well balanced. Thus, this alkaloid exerts the full effects of ergot, in that it causes the uterus to contract, reduces the activity of the adrenergic system, and elicits central effects by inhibiting the vasomotor center. This spectrum of actions accounts for the use of ergotamine in obstetrics as a hemostatic and in internal medicine and neurology as an agent blocking the sympathetic nervous system and as a cranial vasoconstrictor in migraine and related headache syndromes.

Saturation of the double bond at position 9,10 in the lysergic acid moiety has furnished a number of pharmacologically interesting derivatives. As can be seen from the spectrum of dihydroergotamine (Fig. 9), hydrogenation results in a fundamental change in pharmacological actions. The dihydro derivatives of the other peptide alkaloids possess similar spectra of activity. The vasoconstrictor and uterotonic actions, the classical effects of ergot, and the stimulation of central sympathetic structures are greatly attenuated, so that they are barely present within the therapeutic dose range. Instead, the dihydro derivatives of the peptide alkaloids exert a marked sympathicolytic-adrenolytic effect and reduce the activity of the vasomotor center. These effects of dihydroergotamine are exploited

Fig. 9 Activity spectra for various ergot alkaloids and synthetic analogs.



therapeutically, e.g. in the pharmaceutical preparation "Dihydergot" ®. The adrenolytic, vasodilator, and hypotensive effects are even more pronounced in the case of the dihydro derivatives of the alkaloids of the ergotoxin group. A combination of equal amounts of dihydroergocristine, dihydroergokryptine, and dihydroergocornine is used under the brand name "Hydergine" ® for the treatment of vascular disease in order to improve the peripheral and cerebral circulation, especially in geriatric patients.

As can be seen from Fig. 8, the activity spectrum of ergonovine is quite different from that of ergotamine and the other peptide alkaloids. It exerts practically no adrenolytic action. It retains considerable antiserotonin activity. The predominant effect is that on the uterus—the hemostatic and oxytocic action. For this reason, ergonovine is used almost exclusively in obstetrics. Methylergometrine, a synthetic compound

in which the L-2-aminopropanol side chain of ergonovine is replaced by a L-2-aminobutanol residue, possesses the same activity spectrum as ergonovine. This derivative, which is also known under the trade name "Methergine" ®, has a somewhat stronger and longer-lasting vasoconstrictor effect on the uterus than the natural alkaloid.

LSD, which differs from the natural alkaloid ergonovine only in having a diethylamide instead of an isopropanolamide side chain, shows an activity spectrum which is quite different from that of ergonovine. LSD exhibits marked antagonism to serotonin (Fig. 9). However, its curve attains its maximum for stimulation of central nervous structures in the hypothalamus. The syndrome of central excitation is elicited even by extremely minute doses and is characterized by mydriasis, hyperthermia, hyperglycaemia, etc. This central excitation syndrome seems to be related to the impressive psychic effects of LSD, which have rendered this substance of considerable importance in experimental psychiatry, neurophysiology, and many other areas. The LSD problem, of course, could be the subject of a chapter of its own.

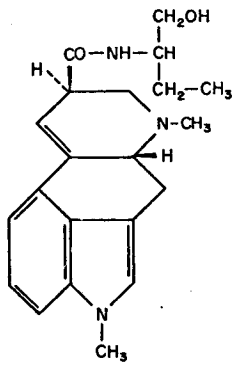
As examples of how chemical modifications in the lysergic acid radical can change pharmacological activity, let us now briefly discuss the effect of bromination at position 2, and methylation at position 1 (Fig. 7).

Bromination produces fundamental changes in the pharmacological effects of LSD, as can be seen from the activity spectrum of 2-bromo-LSD in Fig. 9. The high psychotomimetic activity of LSD has disappeared. The outstanding pharmacological property of 2-bromo-LSD is its specific antiserotonin activity.

A similar profile of activity, namely, predominance of the antiserotonin component, results when the hydrogen atom on the indole nitrogen is replaced by a methyl group. 1-Methyl ergot derivatives include the most potent serotonin antagonists yet discovered. Today, serotonin antagonists are playing an important role in pharmacological research, because it is with their aid that we are able to study the biological functions of serotonin which is an important neurohumoral factor with manifold effects on major structures and functions of the organism. Only a few of these effects can be mentioned here. The brain stem and the hypothalamus have a particularly high serotonin content, which suggests that the compound is important to the function of these structures. Serotonin increases permeability and elicits pain; it has been postulated that it may be the humoral pain factor in migraine. This will suffice to show that substances exhibiting a specific antagonism to serotonin are not merely

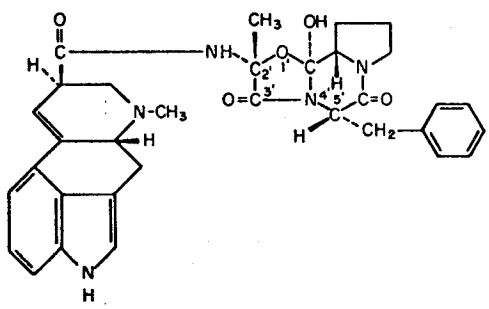
of academic interest; they may also be of great importance from the point of view of therapy.

From the large number of 1-methyl ergot derivatives which have been studied in our laboratories as serotonin antagonists, one compound with especially favorable pharmacological properties was selected for introduction into therapy, namely, 1-methyl lysergic acid L-butanolamide (XIX), which is also known as UML-491, and marketed under the brand name "Sansert" ® . Its activity spectrum is depicted in Fig. 9. It has found widespread use in the prophylactic treatment of migraine and other vascular headaches between attacks.

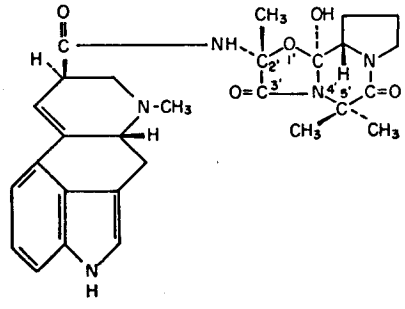


XIX

As a last example of how the pharmacological properties of the natural ergot alkaloids are changed by chemical modifications, I should like to say something about our recent investigations in the field of synthetic peptide-type ergot alkaloids. From the many synthetic analogues which we have lately prepared, only one modification will be mentioned here, i.e. the compound in which we have replaced the L-phenylalanine residue of ergotamine (XX) by an α-methylalanine residue and which was named 5'-methylergoalanine (XXI) (26). As may be seen from Table 2, the con-



XX Ergotamine



XXI 5'-Methylergoalanine

Table 2. Pharmacology of 5′-Methyl-ergoalanine

Substance	Vasoconstrictor effect: blood pressure increase in spinal cats i.v.(%) (A)	Uterotonic effect in non-pregnant oestrous rabbits i.v.(%) (B)	Emetic effect in conscious dogs i.v.(%) (C)	A/B	A/C
Ergotamine (XX)	100	100	100	1	1
Ergostine (Fig. 3)	100 ±15	42 ±11	41	2.4	2.4
5′-Methyl-ergoalanine (XXI)	155 ±29	5 ±1	32	31	4.8

tractile effect of ergotamine on smooth muscle, which is manifest on vascular smooth muscle and on extravascular smooth muscle, notably on the uterus, is modified in 5′-methylergoalanine. Whereas the vasoconstrictor effect is increased by 55 percent, the uterotonic effect is decreased by 95 percent (27). It is generally accepted that the therapeutic effect of ergotamine in the migraine attack is due mainly to its vasoconstrictor activity (28). Its uterotonic effect is not desired in the treatment of migraine attack. It can be concluded, therefore, that 5′-methylergoalanine, which is a more specific vasoconstrictor than ergotamine, might have been an improved medicament for the therapy of migraine attack. Furthermore, the emetic effect of 5′-methylergoalanine is less pronounced than that of ergotamine, which was another favorable feature in the activity profile of this chemical modification of the natural alkaloid. Recent clinical investigations, however, showed that this drug elicits certain undesirable side effects which has prevented its therapeutic use.

These few examples may suffice to illustrate how chemical modification of the natural ergot alkaloids, which are themselves useful therapeutic agents, can lead to a variety of compounds with more interesting pharmacological profiles. It will also have shown that ergot is indeed a treasure house of pharmacological active principles.

At this point, my thesis on ergot as a rich source of pharmacological constituents could be brought to a close. But there is another fascinating aspect of research in this field which I should like to report briefly.

OCCURRENCE OF ERGOT ALKALOIDS IN "OLOLIUQUI" AND OTHER CONVOLVULACEAE

The discovery of LSD in the course of our investigations on the alkaloids of ergot awoke our interest in psychotropic agents and in psychopharmacological research in general. This led us to examine the "magic" mushrooms of Mexico, which were reported to elicit psychic effects similar to those of LSD.

The survival of the ancient Indian mushroom cult in the remote mountains of southern Mexico was discovered by Schultes and Wasson. As far back as 1939, Schultes was the first to offer an identification of "teonanacatl," the Aztec hallucinogen, as a mushroom (29). And on several expeditions between 1953 and 1956, Gordon Wasson and his wife studied and described in a masterful manner the ancient and present-day ceremonial use of the hallucinogenic teonanacatl mushrooms. Through the help of Professor Roger Heim, who continued the work of Schultes in identifying and cultivating the "magic" mushrooms, my laboratory obtained samples, and we were able to isolate the active principles, psilocybin and psilocin, elucidate their structure, and synthesize them (30).

After the mushroom problem had been resolved, we decided to tackle the chemical investigation of another enigmatic magic plant of Mexico, namely "ololiuqui." Here again, I was able to rely on the basic research of Schultes, who had published an excellent review on the historical, botanical, and ethnological aspects of ololiuqui in 1941, entitled "A contribution to our knowledge of *Rivea corymbosa*, the narcotic ololiuqui of the Aztecs" (31). And Gordon Wasson again participated in the project. He provided me with original ololiuqui seeds collected in the Mexican state of Oaxaca, where the Indians of several tribes still use these seeds for divinatory purposes in their medical-mystical practices.

Ololiuqui is the Aztec name for the seeds of *Rivea corymbosa* (L.) Hall. f, which is shown in flower in Fig. 10; the seeds are shown in Fig. 12.

The Zapotec Indians use for the same purposes the seeds of another morning glory, *Ipomoea violacea* L., which has been spread all over the world as an ornamental plant. It is the Morning Glory of our gardens (Fig. 11 and 12).

We were surprised to find in ololiuqui seeds active principles familiar to us for a long time, that is, the ergot alkaloids (32, 33). From the phytochemical point of view this finding was quite unexpected and of particular chemotaxonomic interest, for lysergic acid alkaloids which had hither-

Fig. 10 *Rivea corymbosa* in flower.

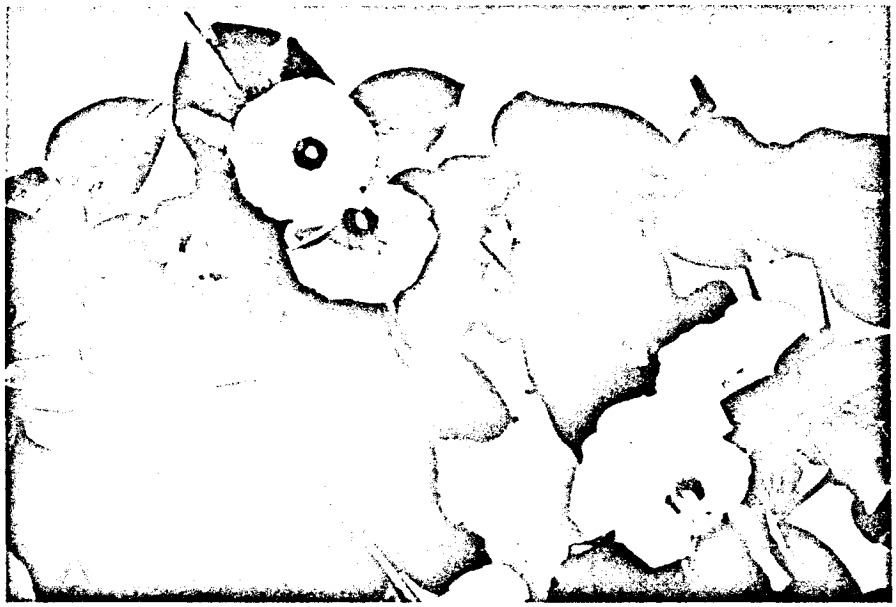


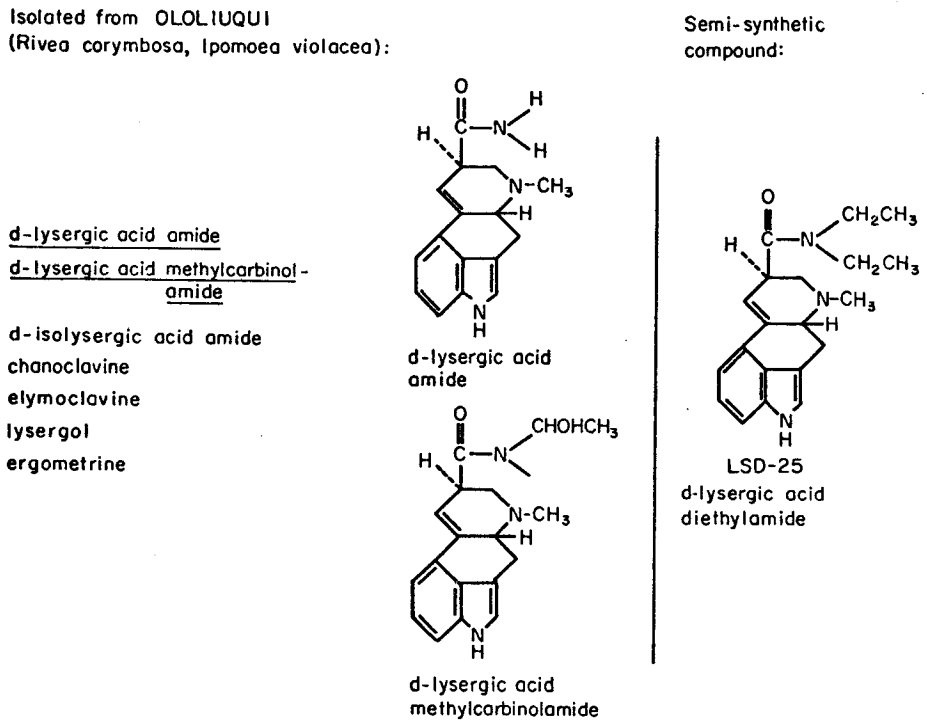
Fig. 11 *Ipomoea violacea* in flower.

Fig. 12 Seeds of Ololiuqui. Left: *Rivea corymbosa.* Right: *Ipomoea tricolor.*

Table 3. Plants of the Family Convolvulaceae Containing Ergot Alkaloids

Plants	Alkaloids	Authors
Rivea corymbosa (L.) HALL.f.	ergine, isoergine	A. Hofmann u. H. Tscherter (1960) (32). A. Hofmann (1961) (33). A. Hofmann and A. Cerletti (1961) (34).
Ipomoea violacea L. [Ololiuqui]	d-lysergic acid methylcarbinolamide, chanoclavine, elymoclavine, lysergol, ergometrine	
Ipomoea rubro-caerulea HOOK *Ipomoea coccinea* L.	same as above	D. Gröger (1963) (35).
Ipomoea and *Convolvulus* spec. (ornamental varieties)	same as above and penniclavine	W. A. Taber, L. C. Vining and R. A. Heacock (1963) (36).
Argyreia nervosa	same as above	J. W. Hylin and D. P. Watson (1965) (37).
Ipomoea argyrophylla VATKE	ergosine, ergosinine, agroclavine	D. Stauffacher, H. Tscherter and A. Hofmann (1965) (38).
Ipomoea hildebrandtii VATKE	Cycloclavine	D. Stauffacher, H. Tscherter and A. Hofmann (1966) (39).

Fig. 13 Structural relation between active principles of ololiuqui and LSD-25.



to been found only in lower fungi of the genus *Claviceps,* were now shown for the first time to be present in higher plants also (34).

The alkaloids isolated from ololiuqui are listed in Table 3. The main active principle of ololiuqui is d-lysergic acid amide, also named ergine, and lysergic acid methylcarbinolamide. Present as minor constituents were chanoclavine, elymoclavine, lysergol, and ergometrine. The occurrence of ergot alkaloids in *Ipomoea* species was later confirmed in other laboratories (35, 36, 37). In African species, we also found ergot alkaloids of the peptide type (38) and a new ergoline alkaloid, cycloclavine, which has so far not been discovered in ergot (39).

The main active principles of ololiuqui, i.e. d-lysergic acid amide and d-lysergic acid methylcarbinolamide (=d-lysergic acid α-hydroxy-ethylamide) are closely related to LSD, as can be seen from Fig. 13.

Nevertheless, this slight difference in structure is responsible for a pronounced qualitative and quantitative difference in activity between LSD and the ololiuqui alkaloids. The latter are about 20 times less active than LSD, and their action is more narcotic than hallucinogenic.

CONCLUSIONS

With the isolation of lysergic acid amides from ololiuqui, a series of researches in my laboratory had gone the full circle. The series began with the synthesis of lysergic acid diethylamide and the discovery of its hallucinogenic properties, proceeded via the investigation on the sacred Mexican mushroom teonanacatl, and then led us to investigate another magic Mexican plant, ololiuqui, which was found to contain lysergic acid amides closely related to lysergic acid diethylamide, LSD, the starting point in the series of researches.

This discovery of relatives of LSD in the magic plants of the New World in Mexico may have completed the fascinating picture presented by the ergot alkaloids, alkaloids which are playing an important role in the development of modern medicine.

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