Acta Physiol. Pharmacol. Neerlandica 8 (1959) 240–258;
North-Holland Publishing Co., Amsterdam

Sandoz Research Laboratories, Basle, Switzerland

615.711.71 LSD 25–092

PSYCHOTOMIMETIC DRUGS

CHEMICAL AND PHARMACOLOGICAL ASPECTS

BY

A. HOFMANN

When Professor VELDSTRA invited me to speak about hallucinogens at this Symposium he added that he would like to hear something about this subject first hand. I understood by this that he wished me to deal mainly with the hallucinogens which were discovered during our own investigations and which came into our hands first, namely d-lysergic acid diethylamide (LSD 25) and psilocybin, the active principle of certain Mexican mushrooms.

The hallucinogens belong to that large and important class of substances known as the psychotropic drugs, but they form a special sub-group by virtue of a characteristic pattern of effects.

The psychotropic drugs may be subdivided into the following groups on the basis of their main actions:

PSYCHOTROPIC DRUGS

1. *Analgesics, Euphorics:* Opium (morphine, heroine, etc.), pethidine, polamidone, etc., (alcohol?).
2. *Sedatives, Tranquillizers:* Rauwolfia (reserpine), chlorpromazine, meprobamate, etc., bromine salts.
3. *Stimulants:* Amphetamine, etc., caffeine, cocaine.
4. *Hypnotics:* Barbiturates, hydantoins, etc.
5. *Hallucinogens, Psychotomimetics:* Peyotl (mescaline), hashish, LSD, etc.

The pharmacological psychotropic actions of these substances show considerable overlapping, so that a further, somewhat different, classification could be made.

The following pattern of action justifies our distinction of the substances in the 5th group from the other psychotropic drugs:

They differ in their effects from the 4 other subgroups of psychotropic drugs in that the latter for the most part modify only the mood; they either calm or stimulate it. In contrast with this, the so-called hallucinogens or psychotomimetics produce profound and acute changes in the sphere of experience, in the perception of reality, changes even of space and time and in consciousness of self. Phenomena of depersonalisation may also occur. Retaining full consciousness, the subject experiences a kind of dream-world, which in many respects seems to be more real than the customary normal world. Objects and colours, which generally become more brillant, lose their symbolic character, they stand detached and assume an increased significance, having, as it were, their own more intense existence.

That is the general pattern of the main symptoms which these substances produce. True hallucinations by no means always occur, and if they occur, only with higher doses and depending upon the individual and the environment. It would therefore be more correct to call these drugs psychotomimetics and not hallucinogens. They mimic a psychotic state.

A number of drugs which may be classified as psychotomimetics on the basis of the foregoing criteria are listed in the following table.

PSYCHOTOMIMETIC DRUGS

A. Natural

Anhalonium lewinii (Lophora Williamsii), peyotl: mescaline

Cannabis indica, hashish, marihuana: cannabinol, cannabidiol, tetrahydro-cannabinole, etc.

Peganum harmala:
Banisteria caapi } harmine (banisterine, yageine)

Piptadenia peregrina: bufotenine, dimethyl-tryptamine

Piper methysticum, kawa-kawa: active principle unknown

Rivea corymbosa, ololiuqui: active principle unknown
Amanita muscaria: active principle unknown
Psilocybe mexicana: } psilocybin
Stropharia cubensis: }

B. SYNTHETIC

D-lysergic acid diethylamide (LSD 25)
N-methyl-3-piperidyl-benzylate

Nearly all the psychotomimetics known to us at the present time are produced by plants. Lysergic acid diethylamide is itself only a semi-synthetic, for the larger part of its molecule is a product of the ergot fungus. In the case of mescaline, the active principle of a Mexican cactus species, so much has been published that only a few remarks may be made here in order to show how this substance differs from LSD and psilocybin. A noteworthy feature of mescaline is the larger dose which is necessary to produce intoxication. It is usually given in doses of 0.3 to 0.5 g and soon after the drug has been taken, some very unpleasant vegetative symptoms are experienced: the hangover comes first, while the true state of intoxication only makes its onset 1 to 2 hours after the unpleasant side-effects have worn off. ALDOUS HUXLEY has recently given a masterly description of his experiences of mescaline intoxication in his two books "The Door of Perception" and "Heaven and Hell". He enters rather deeply into its implications.

Hashish has been known for thousands of years as a psychotropic drug and has also found some fame in the literature. BAUDELAIRE describes experiences with it in his book "Les Paradis Artificiels". Among the various substances which have been isolated from hashish, compounds of the tetrahydro cannabinole type seem mainly responsible for the psychotomimetic effect.

It has been possible to isolate the same active principle, the alkaloid harmine or banisterine, from two plants. These, peganum harmala, an indigenous Asian plant, and the South American creeper banisteria caapi, are both used as intoxicants in two quite different geographical regions. The reports in the literature,

however, do not prove conclusively that the hallucinogenic action of these two plants can be attributed solely to the harmine content.

The seeds of the mimosacee piptadenia peregrina are processed by certain Indian tribes in South America to give a snuff which the men take before going into battle. It is claimed that it makes them fearless and renders them impervious to pain. A number of substances, including bufotenine and dimethyl tryptamine, have been isolated from these seeds.

The active principles of the two hallucinogenic plants, piper methysticum, used in the South Sea Islands and the Mexican creeper rivea corymbosa, have not been adequately studied and the data in the literature on the potency of these plants are contradictory.

Certain Siberian tribes eat a special variety of the mushroom amanita muscaria for its intoxicating effect. The active principle is unknown. The muscarine and small amounts of bufotenine found in this mushroom cannot account for its psychotomimetic properties.

The last substance to be mentioned here is N-methyl-3-piperidyl benzylate. L. G. ABOOD, A. M. OSTFELD and J. BIEL (Proc. Soc. Exper. Biol. Med. 97, 483 (1958)) found this compound to have a particularly marked psychotomimetic activity. Oral doses of 5 to 15 mg. would appear to produce symptoms in man similar to that produced by LSD and mescaline.

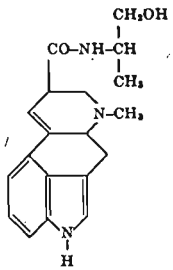
After this introductory review on the known psychotomimetic substances, LSD and the intoxicant Mexican mushrooms will be discussed in more detail.

D-lysergic acid diethylamide has been the subject of over 500 original pharmacological and clinical publications. This report is restricted to the personal experiences of the author with LSD, to a survey of its pharmacological properties and to the relationship between chemical structure and psychotropic activity.

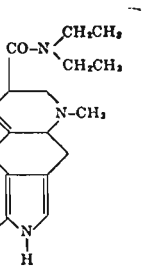
I shall begin with the history of the discovery of LSD. Such quite fantastic versions are current, even in professional circles, that I feel justified in now giving the true story.

15 years ago, in spring of 1943, I was occupied with the

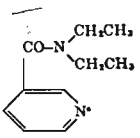
preparation of various amidic derivatives of lysergic acid in the Sandoz Laboratories, which were that time directed by Prof. STOLL. Lysergic acid is the characteristic nucleus of all the alkaloids of ergot and can be obtained by alkaline hydrolysis of these alkaloids. We had succeeded in synthesizing ergobasine, also called ergometrine or ergonovine, the well known oxytocic, which is d-lysergic acid L-isopropanolamide.



d-lysergic acid L-isopropanolamide ergobasine (ergometrine, ergonovine)



d-lysergic acid diethylamide LSD



nicotinic acid diethylamide coramine

This was the first synthesis of a natural ergot alkaloid (STOLL and HOFMANN, 1943). Afterwards we studied the way in which a change of pharmacological action would occur following an alteration in the amine residue which is linked to the lysergic acid. Among many other derivatives, I prepared d-lysergic acid diethylamide (STOLL and HOFMANN, 1943) with the hope of getting an analeptic. That could be expected because lysergic acid diethylamide has many structural features in common with coramine, which is nicotinic acid diethylamide, the well known analeptic.

In the afternoon of 16 April 1943, when I was working on this problem, I was seized by a peculiar sensation of vertigo and restlessness. Objects, as well as the shape of my associates in the laboratory, appeared to undergo optical changes. I was unable to concentrate on my work. In a dreamlike state I left for home, where an irresistible urge to lie down overcame me. I drew the curtains and immediately fell into a peculiar state

similar to drunkenness, characterized by an exaggerated imagination. With my eyes closed, fantastic pictures of extraordinary plasticity and intensive colour seemed to surge towards me. After two hours this state gradually wore off.

The nature and course of this extraordinary disturbance immediately raised my suspicions that some exogenic intoxication may have been involved, and that the lysergic acid diethylamide, with which I had been working that afternoon, was responsible. However, I could not imagine in which way I could have absorbed a sufficient quantity of this compound to produce such phenomena. Moreover, the nature of the symptoms did not coincide with those previously associated with ergot poisoning. However, I decided to get to the root of the matter by taking a definite quantity of the compound in question. Being a cautious man, I started my experiment by taking 0.25 mg of d-lysergic acid diethylamide tartrate, thinking that such an extremely small dose would surely be harmless, and bearing in mind that the natural ergot alkaloids produce toxic symptoms in man only with doses exceeding several milligrams.

After 40 minutes I noted the following symptoms in my laboratory journal: slight giddiness, restlessness, difficulty in concentration, visual disturbances, laughing.

At this point the laboratory protocol ends. The last words are hardly legible and were written only with greatest difficulty. It was now obvious that LSD was responsible for the earlier intoxication. I requested my laboratory technician to accompany me home. Since it was war time and no car available, we went by bicycle. This journey is about 4 miles and I had the feeling of not getting ahead, whereas my escort stated that we were rolling along at a good speed. I lost all count of time. I noticed with dismay that my environment was undergoing progressive changes. My visual field wavered and everything appeared deformed as in a faulty mirror. Space and time became more and more disorganized and I was overcome by a fear that I was going out of my mind. The worst part of it being that I was clearly aware of my condition. My power of observation was unimpaired. I was not, however, capable by any act of will,

of preventing the breakdown of the world around me. At home the physician was called.

At the height of the experience, the following symptoms were most marked:

Visual disturbances, everything appearing in impossible colours, objects out of proportion. At times the floor seemed to bend and the walls to undulate. The faces of the persons present changed into colourful grimaces.

Marked motor restlessness alternating with paralysis. Limbs and head felt heavy as if filled with lead and were without sensation. My throat felt dry and constricted.

Occasionally I felt as if I were out of my body. I thought I had died. My ego seemed suspended somewhere in space, from where I saw my dead body lying on the sofa.

When the physician arrived, approximately $2\frac{1}{2}$ hours after I took the drug, he reported that my cardiac function was normal, pulse good, blood pressure normal, respiration deep and regular.

In the course of the evening the symptoms subsided gradually and then disappeared completely. Only the visual disturbances persisted somewhat longer. It was particularly striking how acoustic perceptions, such as the noise of water gushing from a tap or the spoken word, were transformed into optical illusions. I then fell asleep and awakened the next morning somewhat tired but otherwise feeling perfectly well.

That was the first experiment with LSD and rather a dramatic one. In spite of my caution, I had chosen a dose that was five to ten times too high.

In view of the wide application that LSD has since found in experimental psychiatry, this experiment is of a certain historical interest and would indeed justify the extract given here from my original report written 15 years ago.

One will have gathered that LSD was by no means a pure chance discovery, – I had actually been planning to synthesize an analeptic and in my work on this, I had made an observation, which was elucidated by a planned personal experiment.

LSD is by far the most active and most specific psychotomimetic. The effective oral dose in man is 0.03–0.05 mg, whereas

0.3 to 0.5 g of mescaline is required. LSD is 10'000 times more active than mescaline. With the minimal dose of LSD required to produce psychic phenomena, there are practically no side-effects. The first systematic study with LSD was carried out by W. A. STOLL (1947).

The following survey summarizes the main points of the pharmacological aspects of LSD as they have been established by different studies in the SANDOZ department of pharmacology.

Let us begin with the distribution and fate of LSD in the body. This study has been carried out on mice with the aid of 14-C-labelled LSD. Administered intravenously, LSD disappears rapidly from the blood and is then found in different organs. Surprisingly only a small portion of the total dose administered reaches the brain, and even after intracerebral injection, LSD disappears from the brain as rapidly as after intravenous administration. It could therefore be assumed that LSD is mainly responsible for triggering the central reaction.

The acute toxicity of LSD differs considerably according to animal species. Mice are relatively insensitive, while a high toxicity is observed in the rabbit. Furthermore, the oxytocic activity of LSD as tested in the rabbit is of the same magnitude as that of ergometrine. However, the oxytocic doses of LSD are far higher than those exerting a distinct central effect.

But there are interesting exceptions where several characteristic vegetative effects of LSD can be obtained in certain animals with similarly low amounts of LSD. A significant rise in body temperature of the rabbit, for example, is observed following the injection of 0.5 micrograms of LSD per kg bodyweight. Besides this pyrogenic action, small doses of LSD also cause mydriasis, hyperglycemia, piloerection, tachycardia, tachypnoea in rabbits. All these effects point to a distinct sympathomimetic action of LSD in rabbits, the central origin of which is demonstrated by the inhibitory effect of hypnotics, ganglionic and adrenergic blocking agents as well as by decerebration. In several tests the action of epinephrine, nor-epinephrine and amphetamine can be enhanced by LSD. All these findings suggest that LSD produces a predominant syndrome of central sympathetic stimulation. In addition a marked exaggeration of spinal reflexes is observed in the cat.

On the other hand, however, LSD exerts a distinct depressive effect in some instances: Barbiturate hypnosis in rats and mice can be potentiated by LSD. The body temperature as well as the oxygen consumption of rats is decreased by relatively small doses of LSD.

On consideration of all these vegetative effects, a two-fold action of LSD is observed: a predominant central sympathetic stimulation parallels a slight depression.

The mechanism of the psychotomimetic action of LSD is still unknown. A hypothesis has been put forward that serotonine is involved in this process. Indeed, LSD shows a marked and specific antagonism against the peripheral effects of 5-HT (serotonine), which is believed to play a part in the maintenance of normal mental processes. It is, however, not very likely that the serotonine antagonism of LSD has anything to do with the psychotomimetic property of LSD. This must be concluded from the observation that 2-bromo-LSD has no psychotomimetic effect in spite of the fact that its anti-5-HT potency is of the same magnitude as that of LSD. Many other derivatives could be added which have a potent anti-5-HT effect but which are devoid of any psychotomimetic effect, for example 1-methyl-ergometrine and 1-methyl-2-bromo-LSD.

In order to obtain some idea of the relationship between the chemical structure and the pharmacological or mental effects we have modified the molecule of LSD in the following three ways:

1) Variations in the amide grouping,
2) Substitutions in the ring system,
3) Variations in the spatial arrangement of the atoms.

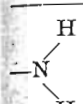
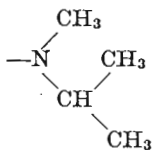
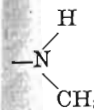
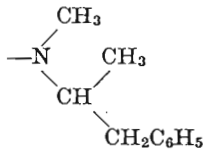
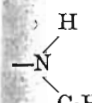
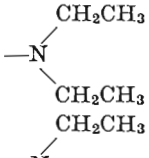
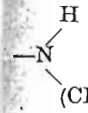
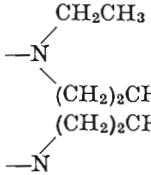
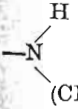
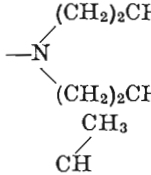
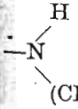
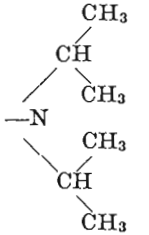
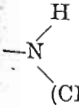
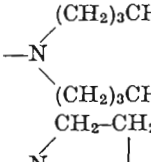
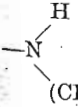
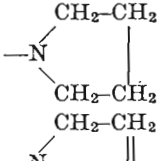
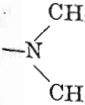
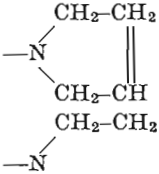
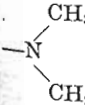
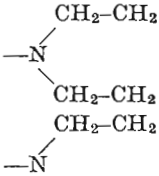
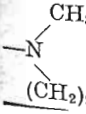
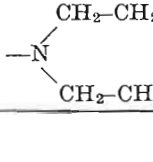
Systematic variations of the substituents in the amide grouping has resulted in the synthesis of a great number of substances (STOLL and HOFMANN, 1955) which are listed in table I.

Pharmacological and clinical investigations of this group of compounds have not yet been concluded.

None of these compounds shows the high specific psychic activity of LSD. The next higher and the next lower homologue of LSD, the lysergic acid dimethylamide and the dipropylamide,

TABLE 1 *Variations in the acid amide group of the LSD molecule*

Amides of d-lysergic acid ($C_{12}H_{15}N_2$–COR) prepared for pharmacological investigation

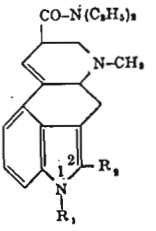
R	d-lysergic acid	R	d-lysergic acid
	amide		methylisopropylamide
	methylamide		(+)-methyl-(β-phenyl) -isopropylamide
	ethylamide		*diethylamide (LSD 25)*
	propylamide		ethylpropylamide
	butylamide		di-n-propylamide
	amylamide		diisopropylamide
	hexylamide		di-n-butylamide
	heptylamide		pyrrolidide
	dimethylamide		pyrrolinide
	methylethylamide		piperidide
	methylpropylamide		morpholide

are about ten times less active on the psyche, but the vegetative effects are the same as that of the diethylamide. But there are some derivatives which have other interesting psychic effects, for example the monoethylamide and the unsubstituted amide show some sedative or even hypnotic effects.

Table II summarizes the substitutions which have been made in the ring system of LSD (TROXLER and HOFMANN, 1957). 1-acetyl-LSD has a modified psychotomimetic activity which is

TABLE II

Substitutions in the ring system



$R_1 = COCH_3$	$R_2 = H$: Acetyl-LSD
$R_1 = CH_3$	$R_2 = H$: Methyl-LSD
$R_1 = CH_2OH$	$R_2 = H$: Oxymethyl-LSD
$R_1 = CH_2N(CH_3)_2$	$R_2 = H$: Dimethylaminomethyl-LSD
$R_1 = H$	$R_2 = Br$: Bromine-LSD (BOL 148)
$R_1 = H$	$R_2 = I$: Iodine-LSD

approximately as strong as that of LSD, but this derivative is weaker as a serotonine antagonist. 1-methyl-LSD is a stronger serotonine antagonist but a weaker psychotomimetic than LSD and again produces somewhat different psychic effects. 2-bromo-LSD possesses nearly the same antiserotonine activity as LSD but as a psychotomimetic is practically inactive.

Variations in the spatial arrangement of the atoms in the LSD molecule led to 3 stereoisomers (d-iso-LSD, l-LSD, l-iso-LSD) as shown in fig. 1. These proved to be practically inactive when compared with the ordinary LSD (d-LSD).

The author and his assistant have tested these 3 stereoisomers under medical supervision. They were found to be without any

psychotomimetic activity in doses up to 500 γ. This means that these stereoisomers are at least 20 times less active than the d-lysergic form.

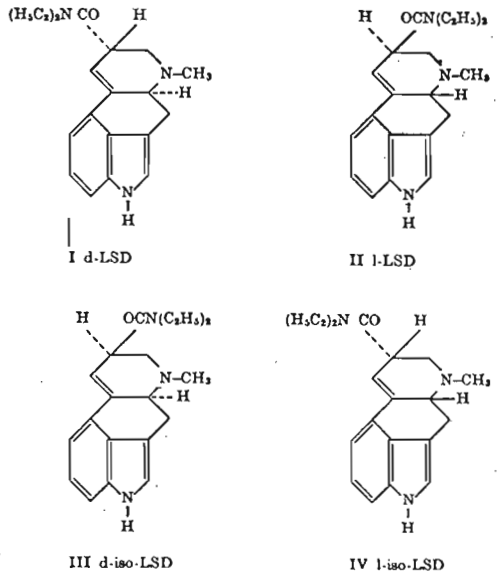


Fig. 1.
Stereoisomers of LSD

More extensive studies in human beings, using increasing doses, would be necessary to determine whether there are qualitative and quantitative differences between the three relatively inactive isomers. However, these preliminary studies clearly show that the mental effects of LSD are highly stereospecific.

We now present an account of our latest investigations on the so-called sacred or magic Mexican mushroom.

Since the pre-Columbian era, the Indians of Mexico, have made the eating of certain fungi a part of their religious rites; tribal soothsayers ate such fungi in the belief that they would acquire clairvoyance. An American ethnologist R. GORDON WASSON and his wife made several expeditions into the remote regions of Mexico between 1953 and 1955. They studied the

way in which these fungi are used and described their experience of the hallucinatory states occurring in the rituals (WASSON and WASSON, 1957). Prof. ROGER HEIM, the famous mycologist, Director of the Museum National d'Histoire Naturelle in Paris, accompanied R. G. WASSON on another expedition into the territories of the Mazatecs, Chatinos and Aztecs in the summer of 1956. He was able to classify and describe these fungi; the species were all pileate fungi (basidiomycetes) belonging to the family of strophariaceas (HEIM, 1956, 1957a, 1957b). R. HEIM together with R. CAILLEUX (HEIM and CAILLEUX, 1957a, 1957b) succeeded in growing cultures of several of these mushrooms in his Paris laboratory. Material from a particularly active fungus, psilocybe mexicana Heim, was sent to the SANDOZ research laboratories in Basle for chemical investigations.

Fig. 2.

Fig. 2 shows a culture of psilocybe mexicana grown in the *Sandoz* laboratory by Dr. A. BRACK (HEIM *et al.*, 1958). The natural size is about 3 to 5 cm.

When we started our isolation studies we had no idea to what group of chemical substances the active principle would belong, whether it would be a peptide or an alkaloid or a nitrogen-free compound. We therefore tested the fractions of our extracts on animals, selecting mice and cats for the purpose. These animals ate nearly all of the very rare material without showing any specific signs. On testing the fractions upon ourselves however, the results were clear and it was then possible to find and crystallize the active principle. We decided to call it psilocybin (HOFMANN *et al.*, 1958a).

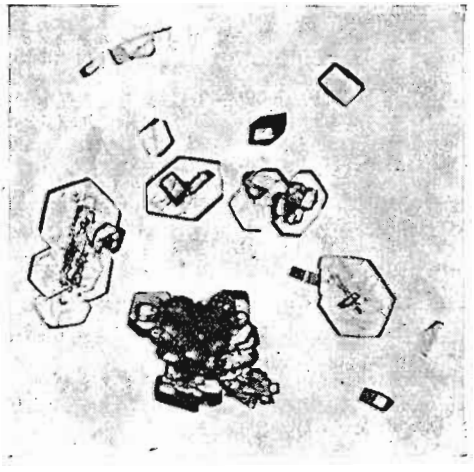


Fig. 3.
Psilocybin (crystallized from methanol).

Psilocybin forms white crystals which are fairly soluble in water or methanol but practically insoluble in the usual organic solvents.

Since then we have found psilocybin in other species of psilocybe and also in stropharia cubensis Earle, another sacred Mexican mushroom (HEIM and HOFMANN, 1958).

In addition to psilocybin, these fungi contain a second indolic compound in very small quantities. This compound is very

closely related to psilocybin and we have called it psilocin. Psilocin is easily destroyed and it has not yet been possible to crystallize it.

A. BRACK and H. KOBEL developed in our laboratory an improved method of cultivating the mycelium and sclerotia of psilocybe mexicana on a larger scale (HEIM *et al.*, 1958). From this material, which contains the same active principle, several grams of crystalline psilocybin could be isolated. This was sufficient for our chemical, pharmacological and preliminary clinical investigations.

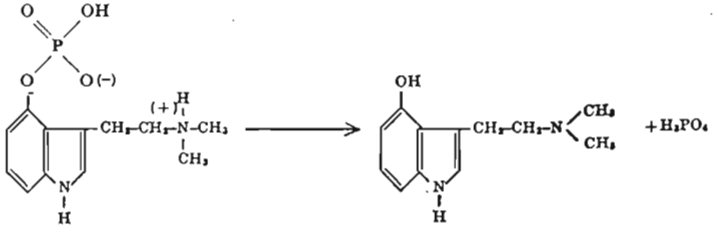
Crystalline psilocybin produces the same psychic symptoms as the fresh or dried mushroom, which proves that psilocybin is the genuine active principle of psilocybe mexicana and the related fungi. When taken orally, 5–10 mg of psilocybin elicit in man a state of drunkenness and euphoria, which lasts several hours. Furthermore, a feeling of bodily relaxation and peace is observed. The subject becomes indifferent to the events around him. Psilocybin therefore seems to be a promising aid in therapy. Profound and acute changes in the perception of reality, of space and time occur only with higher doses. The calming effect of psilocybin is in contrast to a certain psychotomimetic stimulation by LSD.

The pharmacological investigations on psilocybin in the pharmacological department of *Sandoz* reveal a number of interesting features:

Psilocybin is without marked peripheral effects. Only a slight antiserotonine activity is noted. This is about 1/100 to 1/80 of that of LSD. In vivo psilocybin exerts an overall effect which resembles a slight sympathetic stimulation. In unanaesthetized rabbits it produces mydriasis, tachycardia, hyperthermia and hyperglycemia. In unanaesthetized mice it causes mydriasis and piloerection. The EEG of the rabbits shows an alerting pattern after the administration of 1–2 mg/kg of psilocybin. It enhances the spinal reflexes of the cat. However, the motor activity of mice, rabbits and monkeys is unaffected or even slightly depressed. In anaesthetized cats and dogs psilocybin affects the blood pressure and heart rate, the effect depending on dosage and species.

The chemical investigation of psilocybin (HOFMANN *et al.*, 1958b) revealed a structure which is unusual and remarkable in many respects.

Psilocybin was difficult to analyse. The first provisional formula, which was incorrect, had to be modified and is now $C_{12}H_{17}O_4N$ P. Spectra and colour reactions revealed that it is an indole derivative. It is the first naturally occurring indole derivative known to contain phosphorus. On hydrolysis the psilocybin molecule is divided into two, giving 4-hydroxydimethyltryptamine and phosphoric acid.



Psilocybin — 4-hydroxydimethyltryptamine

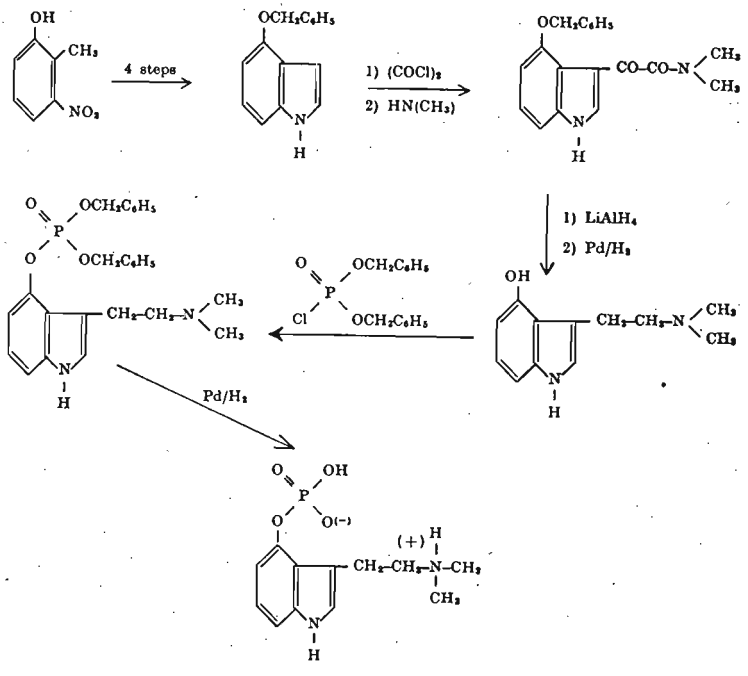
Psilocybin is an acidic phosphoric acid ester of 4-hydroxydimethyltryptamine. The phosphoric acid radical forms an inner salt with the basic dimethylamino group.

This structure could be confirmed by the total synthesis of psilocybin which is demonstrated by the following scheme:

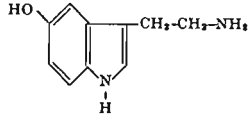
Being a hydroxy tryptamine derivative psilocybin is closely related to other naturally occurring biochemically important hydroxytryptamine derivatives such as: serotonine (5-hydroxytryptamine), bufotenine (5-hydroxydimethyltryptamine) bufotenidine (= quaternary base of bufotenine), dehydrobufotenine and bufothionine.

The comparison of the chemical constitution of the naturally occurring psychotomimetics with known structure reveals that nearly all are indole derivatives (see structural formulae fig. 4).

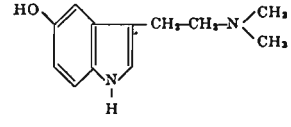
Only the active principles of hashish are nitrogenfree compounds of the type of the tetrahydro cannabinoles. It seems not impossible that mescaline is transformed in the body to some extent into an indole derivative which might be the true active principle and not mescaline. This might well be the reason



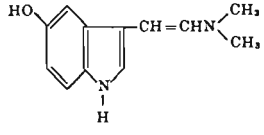
Psilocybin



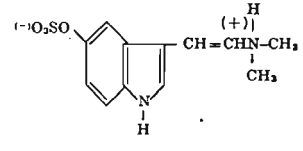
Serotonine



Bufotenine



Dehydrobufotenine



Bufothionine

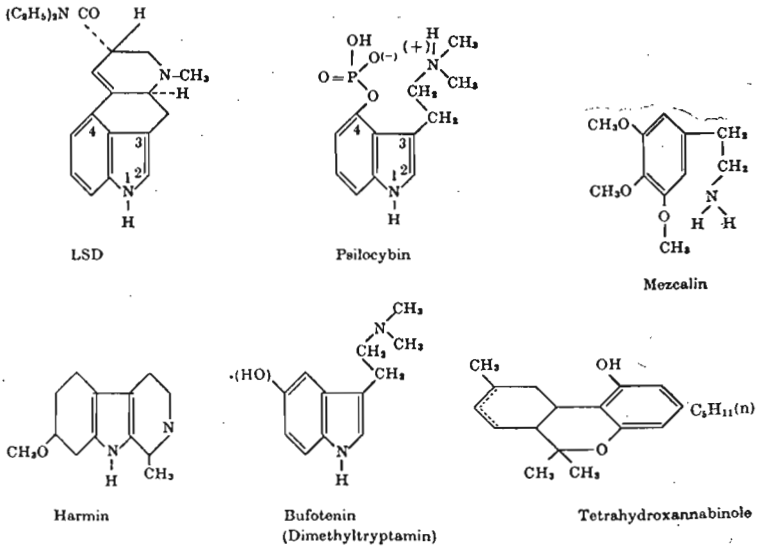


Fig. 4.
Structure formulae of psychotomimetics.

why such high doses of mescaline are needed. In every case, the importance of the indole structure in psychotomimetic compounds is evident.

A special structural relationship exists between LSD and psilocybin. Both these compounds are indole derivatives substituted in position 4. There are no natural indole compounds other than the lysergic acid derivatives and psilocybin which show this special structural feature.

Work is in progress to elucidate whether the position 4 is of importance for the psychotomimetic activity. Structural isomers and other chemical modifications of psilocybin have been prepared and are now under pharmacological and clinical investigation.

The explanation of the relationship between chemical structure and psychotomimetic activity is one of the methods which one day might shed some light on the chemical basis of psychic functions. The ultimate elucidation of this problem is a worthy, but still very distant goal of biochemical research.

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