TOPICS IN

THE CHEMISTRY OF

PSYCHEDELIC HALLUCINOGENS

By Pierre Mandel
Human Biology
Aspects of Drug Use

PREFACE: PSYCHOTOMIMETICS

A psychedelic experience is a journey to new realms of consciousness. The scope and content of the experience is limitless, its characteristic features are the transcendence of verbal concepts, of space-time dimensions, and the ego identity. (1)

To turn on means to find a sacrament which returns you to the temple of God, to tune you into your body, your mind, your ego self, to start a new sequence of behavior that reflects your vision, to manifest in oneself the religious experience one has had.

According to Hollister et al; Withdrawal from interpersonal contacts is characteristic of the schizophrenics and is atypical of the drug induced state. Schizophrenia and drug subjects communicate poorly, but the former seem not to care while the drug subjects are greatly concerned about it. The nature of the hallucinations are different. In schizophrenia they are auditory and generally threatening; while in the drug induced state they are visual and pleasant or impersonal. Drug subjects are easily suggestible, hence the cultogenic tendency of hallucinogens. Schizophrenics are resistant to suggestion etc. (2)

The experience of on scientific LSD user; sensory changes vary with dose. Low doses mild distortions appear, lights appearing brighter and sounds seeming clearer. Increasing the dose causes more sensory distortions, with extremely vivid coloration and such phenomena as moving walls and moving staircase. With larger doses, pseudohallucinations appear, and still very large doses give the occurrence of true hallucinations, with no loss of insight. Effects such as numbness, nasea. Emotionally the effects are quite variable. For some there is fear, and panic; for others there is diminuation of panic; for others there is diminuation of anxiety and feelings of a deep and transcendental experience. (3).

Fig 1.

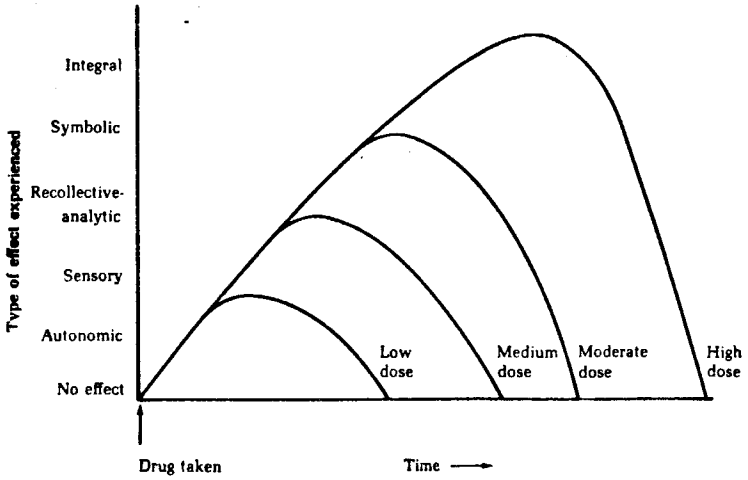


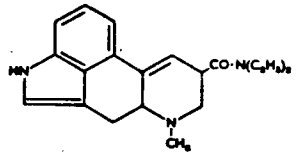
Fig. 16-2. Hypothetical dose- and time-response curve for LSD.

LYSERGIDE ***Hallucinogen***

Synonyms: LSD; LSD 25; Lysergic Acid Diethylamide. *Proprietary Name:* Delysid.

(+)-*N*'*N*-Diethyl-lysergamide

$C_{20}H_{25}N_3O$ = 323·4



A crystalline substance. M.p. 80° to 85°.

Extraction. Lysergide is extracted by organic solvents from aqueous alkaline solutions.

Chromatography. PAPER: system P1—Rf 0·47 (location under ultraviolet light, blue fluorescence; location reagents: *iodoplatinate spray*, weak reaction; p-*dimethylaminobenzaldehyde spray*, deep purple).

THIN-LAYER: system T1—Rf 0·66 (location reagent p-*dimethylaminobenzaldehyde spray*, blue); system T9—Rf 0·60 (location under ultraviolet light, blue fluorescence; location reagent p-*dimethylaminobenzaldehyde spray*, blue).

Genest and Farmilo (1964) have described a thin-layer chromatographic system which separates lysergide from the barbiturates.

Colour Tests. MICRO: sulphuric acid–formaldehyde test—grey (*sensitivity:* 1·0 μg); ammonium molybdate test—grey-green→grey-blue (*sensitivity:* 1·0 μg); ammonium vanadate test—grey (*sensitivity:* 1·0 μg); Vitali's test—brown/brown/purple-brown.

Quantitative Estimation. Methods of detection and estimation of lysergide involving thin-layer chromatography, elution, and subsequent

CLASSIFICATION:

I. Substituted Indole Alkylamines

1. D-Lysergic Acid Diethylamide (LSD). Synthesized from lysergic acid of the ergotamine of fungus ergot (Claviceps purpurea). A series of lysergic acid compounds are known. Ergotamines.

2. Lysergic acid amide and isolysergic acid amide. Weak hallucinogens found in species of American tropical morning glory seeds. (Ipomoec Violacea, Rivea Corynbosa).

3. Dimethyltryptamine. (DMT). Found in coliabu snuff from seeds of Piptadenia peregrina.

4. Diethyltryptamine. (DET). Synthetic variant of above DMT. Also DPT, dipropyltryptamine.

5. 6-Hydroxydimethyltryptamine. In vivo active form of DMT.

6. Bufotenine. (5-hydroxydimethyltryptamine). Found in cohaba snuff the skin of and parotid gland of the toad (Bufo marinus), and in agaric mushroom (Amanita muscarina).

7. Psilocbin. (4-phosphoryl dimethyltryptmine). Found naturally in Psilocybe mexicana. Psilocybe cubensis. Heim and related shrooms.

8. Psilocin. (4-hydroxy dimethyltryptamine). Found in Psilocybe cubensis and other Psilocybe species.

9. Ibogaine. Found in bean and root of Tabernanthe Iboga

10. Harmine. Also called telepathine and yageine from yage, caopi, and ayahuasea in S. Americ̣a. Found in seeds of Peganum Harmala, and in stems of Banisteria caopi.

II. Substituted Phenyl Alkylamines.

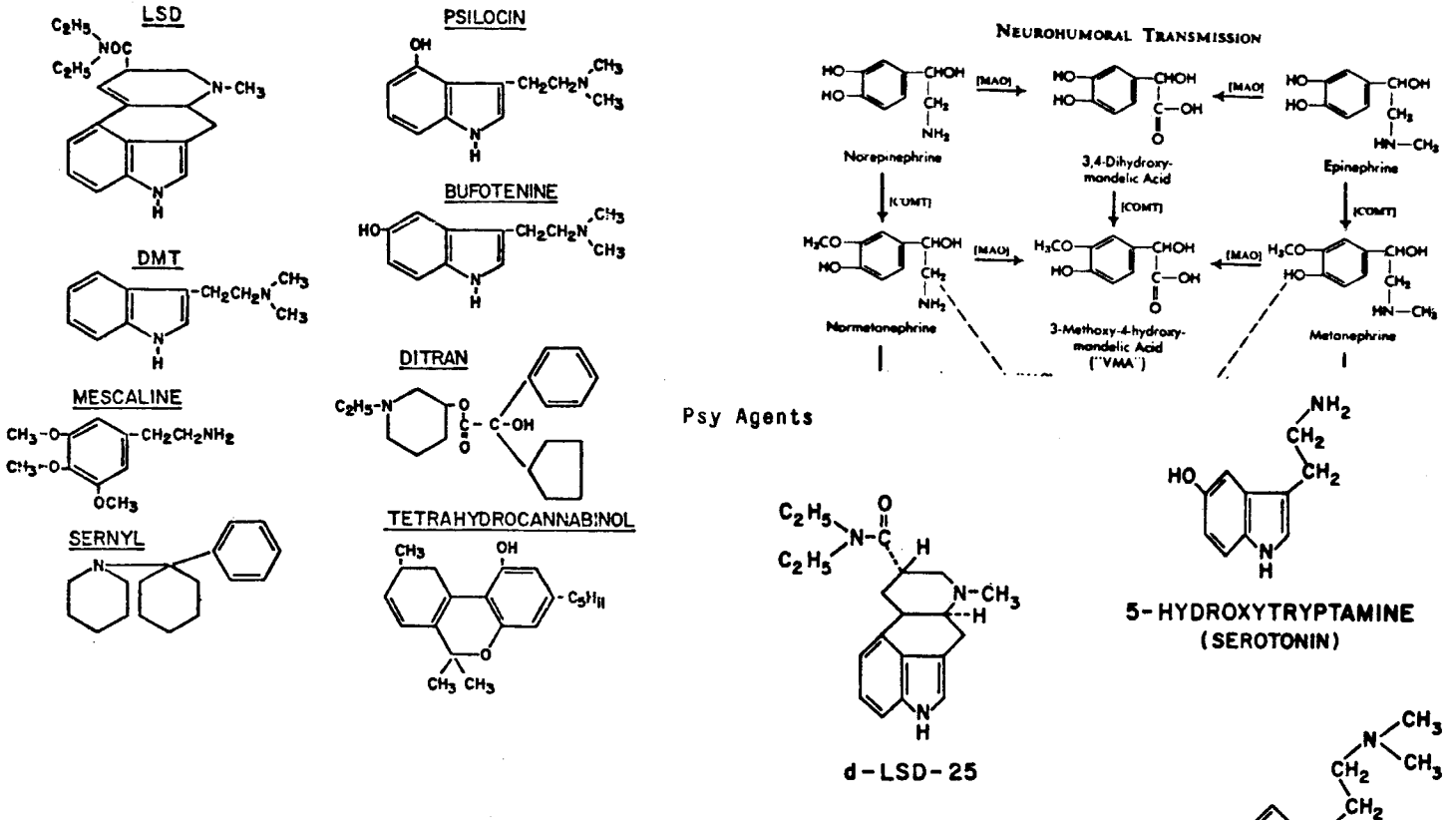
1. Mescaline (3,4,5 - Trimethoxyphenylethylamine). Found in buttons of the peyote cactus (Lophophora Williamsii).

III. Miscellaneous.

1. Tetrahydrocannabinol. Found in the resin, flowerering tops, and leaves of the Cannabis sativa var. indica. A non-nitrogenous hallucinogen from hashish (also marihuana, kef, gangha, etc.).

2. Ditran and analogues. Synthetic mixture of N-ethyl-3-piperidyl-phenylcyclopentyl glycolate and N-ethyl-2-pyrrolidyl methyl-phenylcyclopentyl glycolate.

3. Sernyl and its analogues. 1-(1-Phenylcyclohexyl)piperidine, a synthetic compound.



The close chemical relationships between the hallucinogens and the naturally occurring CNS neurotransmitters is noteworthy. (4,5)

Dimethylation of tryptamine gives DMT. Bufotenine is dimethylated serotonin. The metabolism of tryptamine and serotonin under certain conditions yields 6-hydroxytryptamine; Psilocin is an analogue of 6-hydroxy-DMT. Mescaline is a trimethoxyloted DOPAmine.

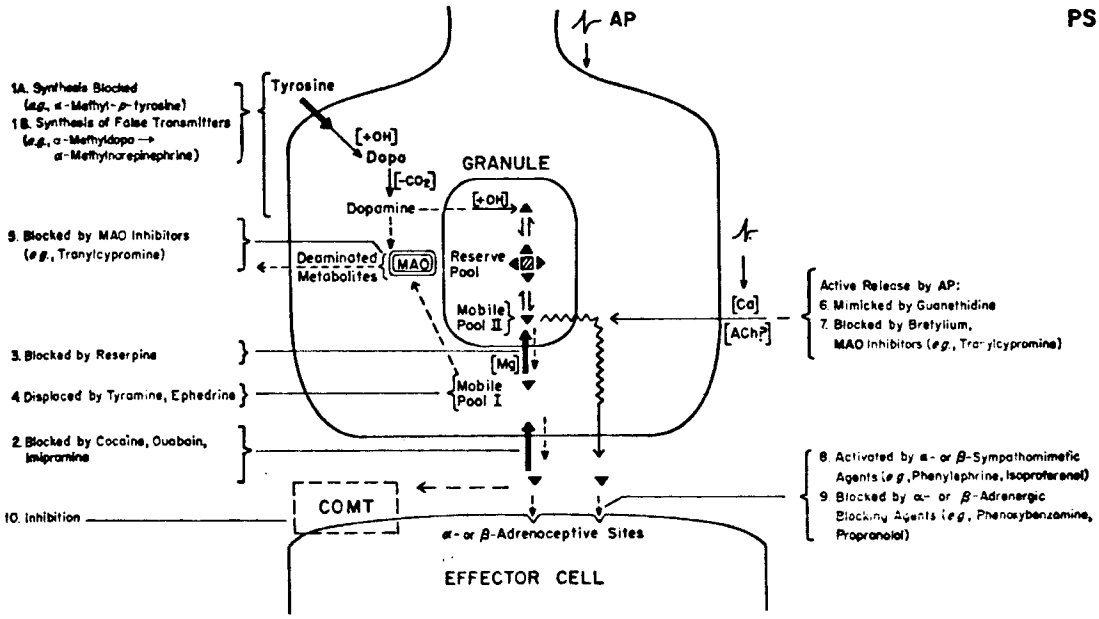


Figure 2 *Proposed sites of action of drugs that modify synthesis, uptake, release, and actions of norepinephrine at adrenergic nerve terminals.*

DMT, DET, DPT

This class of psychotogen has been labelled "the businessman's trip" because a dose of 20 mg. will cause onset of hallucinatory effects within two to five minutes, lasting up to an hour, and usually no longer. DMT is sold on the street as a semisynthetic, easily produced from common reagents, in a matter of hours. Very similar in structure to psilocin, the psychedelic agent of mushrooms, only non-substituted, and less potent. DET, DPT, close variants of DMT, may cause psychic dependence and is cross tolerant to LSD. In addition, the 6-hydroxylation products of these are even more active than the parent compounds. In man, DMT is converted into its 6-hydroxylated congener, although amine oxidation, not 6-hydroxylation is the major metabolic pathway in vivo. Most of the tryptamine is converted to the 3-indole acetic acid, and most of the serotonin to 5-hydroxyindole acetic acid.

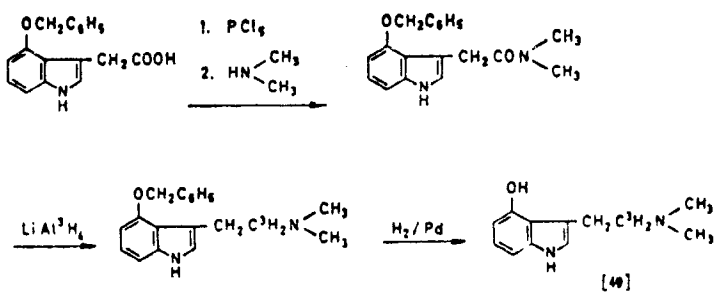
Treatment with an MAO inhibitor, reduces the effect of DMT, and a similar result is found with LSD. An increase in serotonin level in the brain prevents the DMT activity. Treatment with a serotonin antagonist, such as 1-methyl-D-lysergic acid butanolamide (UML), accentuates the DMT effect. DMT is inactive by mouth. It must be injected, sniffed, or preferrably smoked, to produce an effect.

The N-dimethylated analogue of serotonin is bufotenine, which provokes marked autonomic activity, and is a remarkably uncomfortable drug to take. Apparently, in South America the native use of bufotenin, from plant piptadenia peregrina, has in the past been as widespread as the peyote cult of the North American West.

PSILOCYBIN: Mushrooms

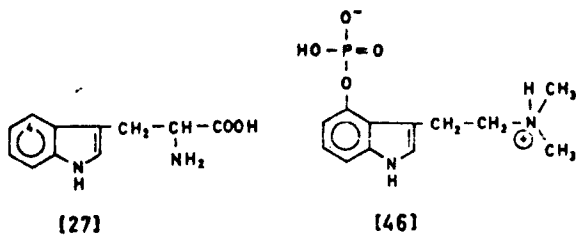
Albert Hofmann et al. who discovered LSD, isolated psilocybin, the hallucinogenic agent of Psilocybe mexicana, a small mushroom which grows in warm marshy environments. This mushroom has been used for centuries in religous ceremonies. The Aztecs, (and some groups of indians today), used it as a sacrament to produce visions and hallucinations. It permits you to travel in time, to enter other planes of existence, even to know God. The dried mushrooms contain 0.2% - 0.5% psilocybin. Psilocybin is unique because it is the most truly natural of the hallucinogenic compounds in existence, and the most compatible with the physiology of the body. The hallucinogenic effect of Psilocybin is quite similar to those of LSD, and mescaline. Cross tolerance between these three psychotogens does exist.

Psilocybin and psilocin are the active alkaloids in the Mexican magic mushroom. Psilocybin is the 4-O-phosphorylated, and psilocin is the 4-hydroxy ester of DMT. Hollister et al. estimates that LSD is over 100 times as potent as Psilocybin, or psilocin. Aside from the duration of the Psilocyb's effects, which last for up to 2-6 hours, the effects are similar to those of LSD. Again, many of these 4-substituted indole amines are readily found in nature by Psilocybe, have been successfully cultured, and harvested, from which the synthetic pathway had been elucidated. (Hofmann et al.).
To convert the tryptophan molecule to psilocybin would need the 1. decarboxylation, 2. methylation of the amino group, 3. hydroxylation of the indole nucleus, followed by phosphorylation. (6)



[49]

Synthesis of psilocin-^3H,



[27] [46]

Tryptophan [27] and psilocybin [46].

MESCALINE

Mescaline, one of a dozen alkaloids in the peyote cactus, was possibly the first of the hallucinogenic alkaloids to be extracted and synthesized in the lab. The active principle of peyote, mescaline, was isolated in 1896 from the peyote cactus Lophophora Williamsii. The drug was named after the Mescalero Apaches of the Great Plains who had also developed the religious peyote ritual. Peyotism is a religion, and its followers believe that God put some of His Holy Spirit into the peyote. The Indian eats the sacramental peyote in the same fashion that certain Christian sects eat the sacramental bread and wine as a catholicon or cure-all, accompanied by prayer and hymn ceremony.

Mescaline has a close chemical similarity to norepinephrine which implicates a catecholamine aberrant mechanism to account for the vivid hallucinations. The psychotomimetic dose for Mescal is 4000 times the equivalent dose of LSD. Mescal does not cause addiction; there is evidence for its use as an experimental tool for the investigation of schizophrenia. There has been some evidence to support the hypothetical biosynthetic mechanism of Mescal from phenylalanine -> tyrosine -> DOPA -> Dopamine -> Mescaline. Mescaline is the trimethoxylated DOPA-mine. (7)

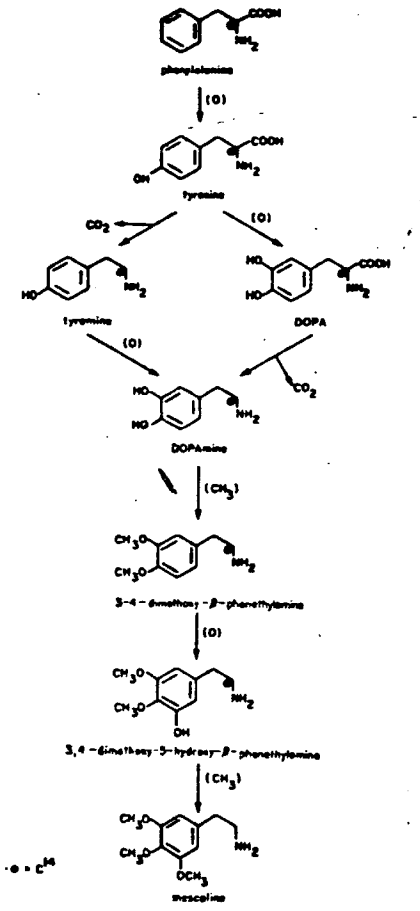


FIG. 1. *Proposed biosynthesis of mescaline.*

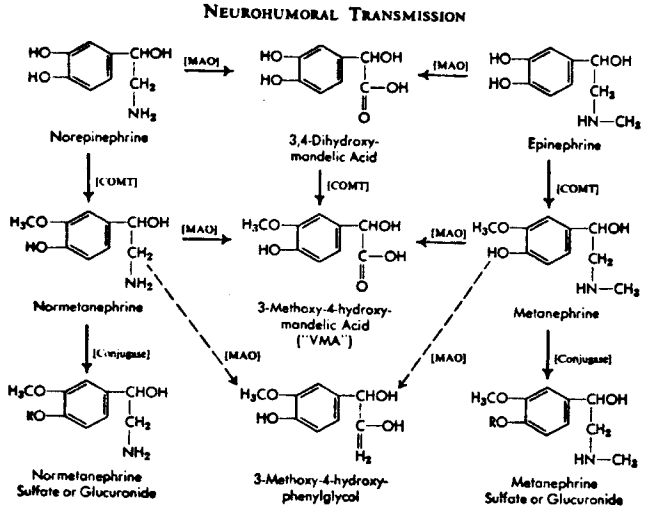
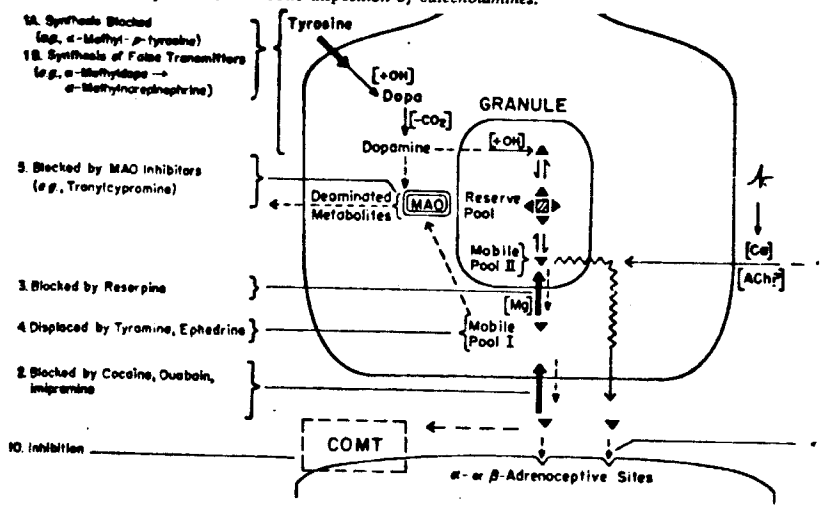


Figure 21–7. *Steps in the metabolic disposition of catecholamines.*



PSYCHIC AND PSYCHOTHERAPEUTIC EFFECTS

The psychological effects of LSD are numerous and diverse depending upon dosage, personality, and other nonspecific factors in the environment. For this reason, variation in setting, invariably elicited the effect of a "model psychosis". If the drug is taken with the idea that a transcendental state will ensue, there is high likelyhood that it will. The LSD state is a hypersuggestible one. The rational or critical functions of the ego are diminished and a passive spectator ego seems to take over. The enhancement of suggestibility and induction of hypnosis has been studied and confirmed by Hollister et al., noting the increased effects of trance like states during drug effect.

Changes in ego function are notable, with the usual ego defense mechanism interplay that take effect to cope with the peculiar mental changes. Eventually these defenses are dissolved, particularly in higher doses. Ego boundaries dissolve partially or completely, and separation of internal experience from sensory input is effectively lost. Drives are diminished, and the person is usually inclined to be passive, quiet, sitting, or lying, attempting to cope with the unusual state. But this depends again upon personality, and setting. The psychedelic state may be considered equivalent to a chemically induced sartori, or transcendental event. The perceptual alterations being most notable, the flat surfaces assume depth, fixed objects undulate and flow. Pseudohallucinations are common, with true hallucinations being infrequent at the common dosages. Also the phenomenon of 'synesthesia', or the overflow from one sense modality to another sensory mode, or a crossing over and fusion of perception and concept. Time perception is seriously altered, often time is put at a 'stand still'. Mood elation, blissful ecstacy, laughter, tears, anxiety, a range of emotional reactions may be encountered. Thought processes are non-logical, fantasy-prone, random and absent as oppossed tp a flood of thought. This may be due to inattentive preoccupation with sensory alteration. Orientation not usually impaired, although feelings of paranoia and persecution complexes are known.

PSYCHEDELIC PSYCHOTHERAPY; PSYCHOLYTIC THERAPY

The value of LSD-25 in clinical practice has become a very controversial topic of contemporary psychiatry. Some believe LSD is an excellent tool for explaining the hidden recesses of the mind, while others deny the diagnostic significance of the lysergide, as a disinhibiting drug.

LSD used in combination with the CNS amphetemine Ritalin, under the appropriate conditions, has been hailed an effective treatment of some neurosis. While other studies employ high dosages in treating chronic alcoholics, inducing a death-rebirth experience, allowing a new start with new values. Loosening of ego boundaries permits the patient a transcendental feeling of belonging. In the figure below the K scale indicates defensiveness, the SC scale schizophrenia, and the MF measure femininity, homosexuality.

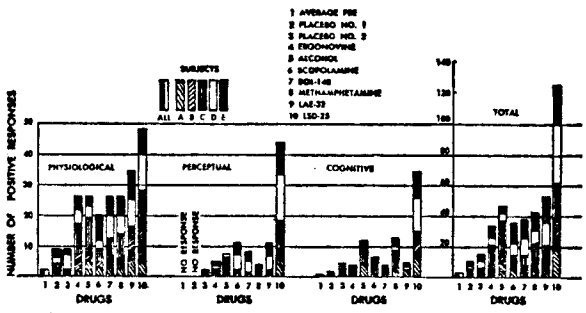
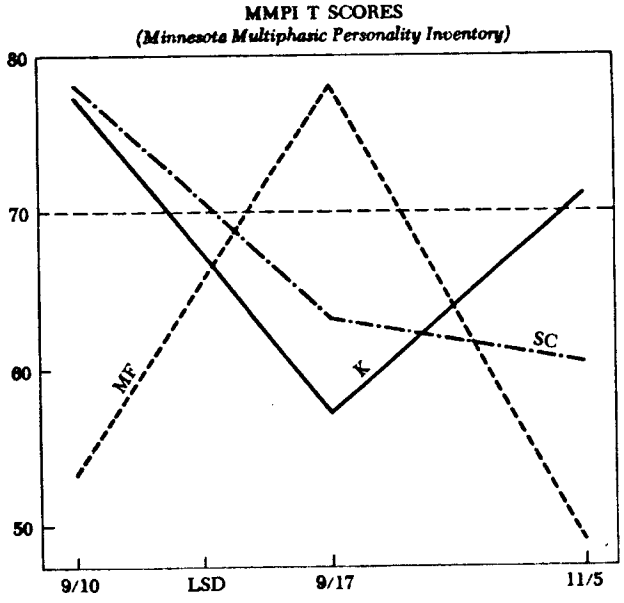


Fig. 5:* Number of positive responses to questionnaire given under ten different conditions.



1.

2.

3.

4.

7.

8.

9.

Figure 3. She has fallen into Hell. Her own rib cage was growing out to encase her. She feared the light, she was in terror and despair, she had seen death.

Figure 4. She was half skeleton, half woman, but she has recalled hope and now was seeking light. She stretched a hand out for help from the human world.

Figure 5. Her yearning for light and warmth were now so strong that her very ribs reached out for it. She could almost touch a wonder—"a living flame."

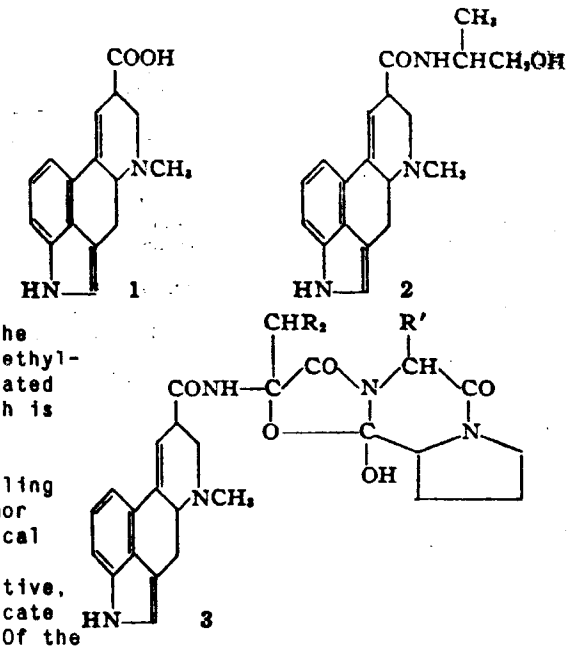
Figure 6. Still reaching for the light, her ribs were beginning to be clothed in human flesh once more. They stretched upward in striving or prayer.

Figure 7. Now her own skeleton detached itself from her body to become a cross. She was crucified on it, she felt one with Christ.

Figure 8. Free of the cross, buoyant in spirit, fully fleshed, she seemed to be afloat in a sea full of light. The fish were a symbol for Jesus Christ.

Figure 9. She attained a state of grace. Her sensations were what drug experimenters call "transcendental"—of freedom and white light.

LSD PHARMACOLOGY



LSD is a semi-synthetic compound, the lysergic acid moiety is the natural product of the ergot fungus Claviceps purpurea, and the diethylamide is usually added on synthetically in the lab. LSD-25 is related structurally to the uterine contractile stimulant ergonovine, which is the much studied, and well known isopropanolamide derivatives. (Stoll and Hofmann).

Incorporated into the LSD molecule is an indole nucleus, resembling their simpler psychotogens, psilocybin and DMT; the brain neurohumor serotonin, and 5-HT, which is implicated heuristically to biochemical function of the brain.

LSD is stereo specific. Of four stereoisomers, all optically active, only one, d-LSD (+), is pharmacologically active. This would indicate a high degree of specificity at the neuro-site within the brain. Of the different substited lysergic acid derivatives, only the mono-ethyl (LAE) and di-ethyl (LSD) are psychogenic. Brominated LSD, (BOL), has no psychogenic activity, yet retains serotonin antagonism; this finding has still to be clarified. The figures below help demonstrate the generalized pharmacology of LSD and its congeners. (10)

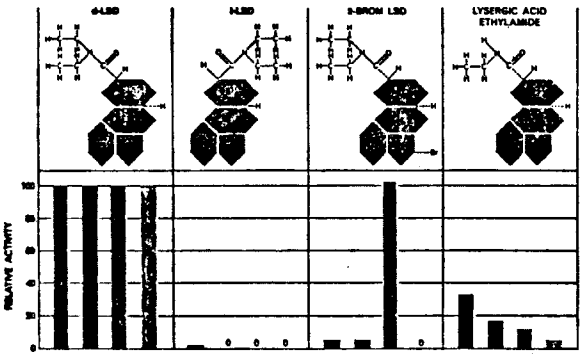
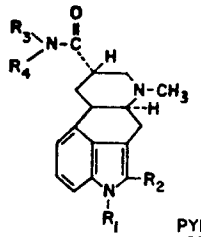


Fig. 3: Structure-activity relationships of congeners of LSD. Only a slight change in the molecule can markedly change the properties of the drug. Under each drug are shown four bar graphs depicting in order (1) toxicity, (2) hyperthermic effect, (3) anti-serotonin potency, and (4) psychotogenic activity.



COMPOUND	R_1	R_2	R_3	R_4	PYRETOGENIC ACTION	PSYCHOTOMIMETIC EFFECT	SEROTONIN ANTAGONISM
LSD-25	-H	-H	$-C_2H_5$	$-C_2H_5$	100	100	100
ALD-52	$-COCH_3$	-H	$-C_2H_5$	$-C_2H_5$	13	100	200
BOL-148	-H	-Br	$-C_2H_5$	$-C_2H_5$	5	0	103
MLD-41	$-CH_3$	-H	$-C_2H_5$	$-C_2H_5$	5	40	370
UML-491	$-CH_3$	-H	-H	$-CH(C_2H_5)CHOH$		0	400

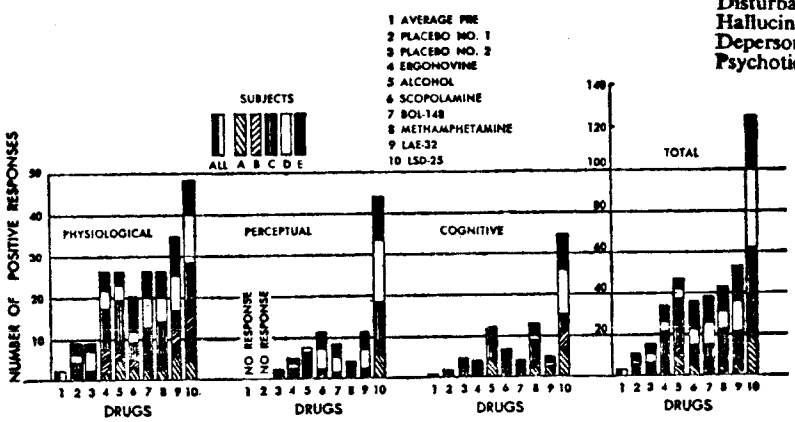


Fig. 5:* Number of positive responses to questionnaire given under ten different conditions.

CENTRAL ACTIONS UPON:

Psychic functions

Excitation
Mood changes: euphoria
depression
Disturbances of perception
Hallucinations
Depersonalisation
Psychotic states

Somatomotor functions

Pyramidal and extrapyramidal effects: ataxia and spastic paralysis

Autonomic nervous functions

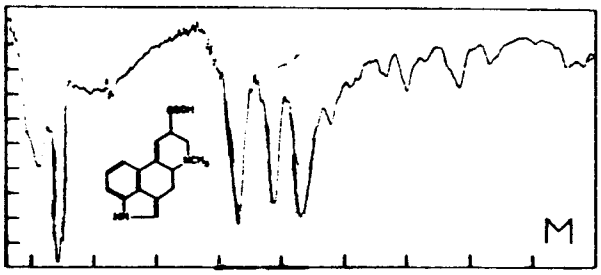
(*a*) Meso-diencephalic effects
Mydriasis
Tachycardia
Rise in body temperature
Hyperglycemia
Pilomotor reaction
(*b*) Medullary or bulbar effects:
Lowering of blood pressure
Bradycardia
Respiratory depression

LSD
Diethylamide of
(+)-lysergic acid

DIRECT PERIPHERAL ACTIONS UPON:

Constriction of:
- Uterus *in vitro* and *vivo*
- Blood vessels artificially perfused
- Bronchial musculature in high doses
- Blood vessels of spinal cat

Adrenolytic action on isolated uterus and seminal vesicle
Inhibition of 5-HT on different organs *in vitro* and *in vivo*



LSD AND THE ERGOT ALKALOIDS (+)-NN- Diethyl-lysergamide

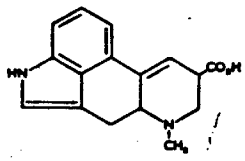
9,10-didehydro-N,N-diethyl-6-methyl-ergoline-8-beta-carboxamide,

d-lysergic acid diethylamide (LSD), (LSD-25), Lysergide

The unusual psychological effects of LSD were discovered by Hofmann and Stoll, in 1943. They had previously succeeded in synthesizing d-LSD and also ergonovine. This work was accomplished at the Sandoz laboratories in Switzerland. This particular workup was synthetic in nature, although there are biosynthetic means of accomplishing the same end-products with less effort, and with greater assurance of product stability.

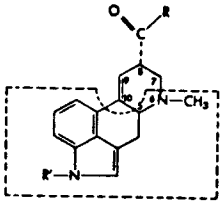
The biosynthetic production of LSD was originally synthesized from ergot alkaloids extracted from various high yield strains of Claviceps pupurea. This mold grows on rye grains, and injesting the infected grain results in the disease ergotism. During periods of famine infected grain may be used in making bread, and historically, there has been many outbreaks of ergotism, resulting from the eating of the infected bread. In 1676, ergot was identified as the causative agent of the dreaded gangrenous ergot intoxication nicknamed St. Anthony's Fire, after the hospital erected to treat the victims of the disease, which was built near the church of St. Anthony in France. In gangrenous ergotism, the ergot causes a vaso-constriction in the limb to become swollen and flamed experiencing violent burning pains, before eventual numbness, and actual separation or dropping of the limb in the severe and untreated cases. (8)

LYSERGIC ACID *Hallucinogen*
$C_{16}H_{16}N_2O_2 = 268{\cdot}3$



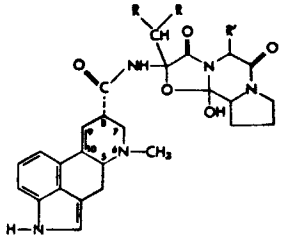
A white crystalline powder. M.p. 240°, with decomposition.
Solubility. Slightly soluble in water; soluble in dilute acids and alkalis.

A. LYSERGIC ACID AND AMINE ALKALOIDS*

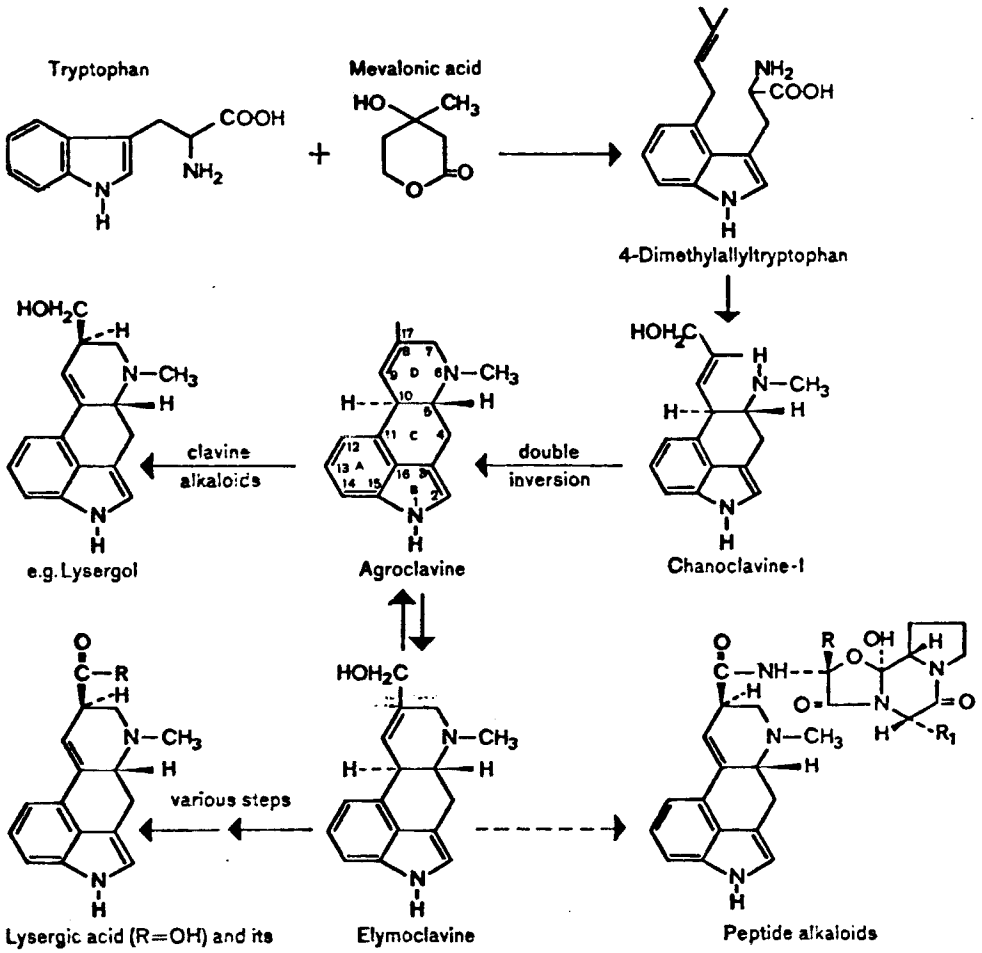


ALKALOID	R	R'
Lysergic acid	—OH	H
Lysergic acid diethylamide	—$N(CH_2CH_3)_2$	H
Ergonovine (ergometrine)	—$NH—CH(CH_3)CH_2OH$	H
Methylergonovine	—$NH—CH(CH_2CH_3)CH_2OH$	H
Methysergide	—$NH—CH(CH_2CH_3)CH_2OH$	CH_3

B. AMINO ACID ALKALOIDS†



R=H	R=CH_3	R'
Ergotamine	Ergocristine	—CH_2—⟨benzene⟩
Ergosine	Ergokryptine	—$CH_2CH(CH_3)_2$
——	Ergocornine	—$CH(CH_3)_2$



PHARMACOLOGICAL ASPECTS OF LSD -- KINETICS/DYNAMICS

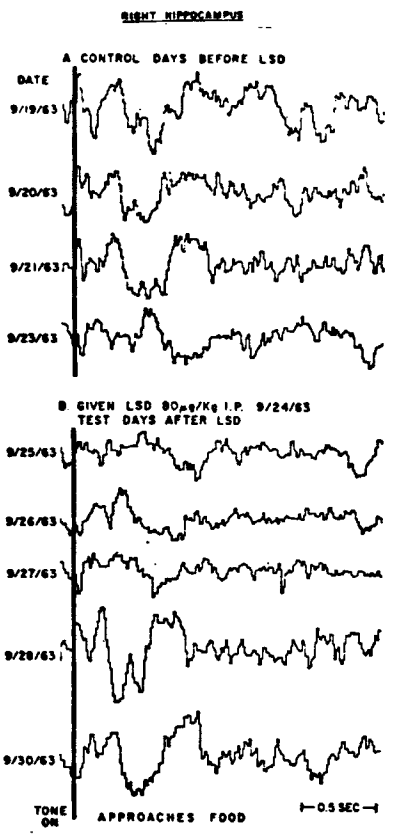
LSD is the most potent known psychotogen. The effective oral dose in a normal human is as small as 25 ug. LSD is 4000 times more potent than mescaline, and over 100 times more potent than psilocin, a substituted indole amine.

LSD is absorbed from the intestinal mucosa upon oral ingestion and is rapidly distributed to the body tissues via the blood proteins, and is found in highest concentrations in brain, liver, kidney, and highest in the liver bile. Within the brain, the highest concentrations are found in the pituitary, and the pineal regions. Other regions of high drug concentrations were the limbic centers, the amygdala, hippocampus, and septal regions, and the thalmic centers, the thalmus and hypothalmus. The concentration within liver bile may help explain the flashback phenomenon.

Another striking aspect of LSD, is the rapid onset of tolerance, so after a few days of steady usuage, a previously effective dose is no longer producing a response. There is also cross-tolerance with mescaline and psilocybin. This may point to a common chain reaction pathway, mediated perhaps by similar class of receptor.

There are two hypothetical mechanisms of action for LSD, a neurophysiologic one and a neurochemical one, but neither adequetly accounts for the observed phenomena. While LSD is antagonistic to 5-HT, it is speculated that excesses or deficiences of 5-HT, at the receptor site might govern normal or abnormal mental activity. However, when other nonpsychotogenic analogues of LSD were tested, it became clear that psychotomimetic action could not be correlated with peripheral 5-HT antagonism. (11)

Interestingly, when brain monoamines are depleted by reserpine the behavioral effects of LSD are enhanced, and prolonged. And, when biogenic amine concentration is elevated by MAO inhibition, the behavioral effects of LSD are diminished. (12)



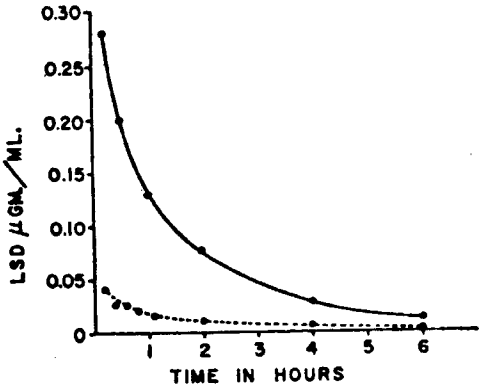


Fig. 5. The rate of clearance of LSD from blood (solid line) and cerebrospinal fluid (broken line) of the monkey after a dose of 200 μg/kg administered intravenously. Reproduced by permission from Axelrod *et al.*, 1957.

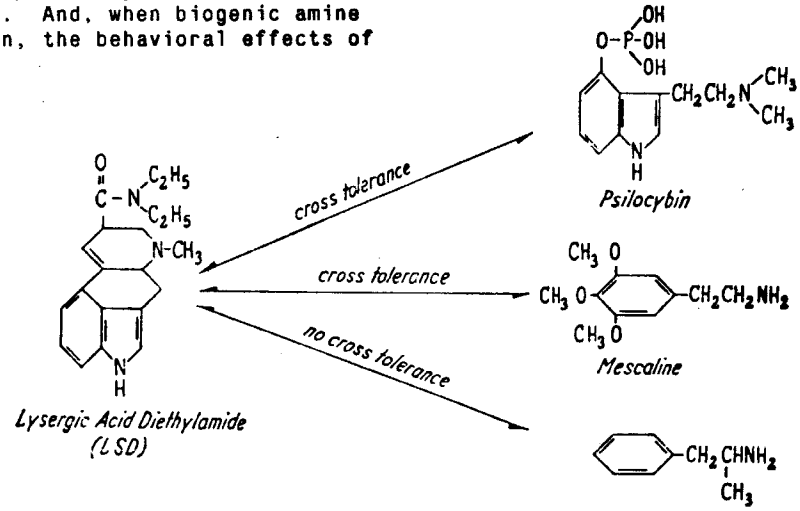


Fig. 8. Cross-tolerance and structural relationships among LSD,

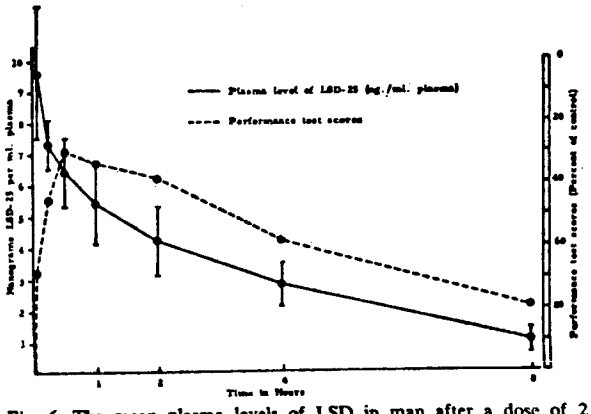


Fig. 6. The mean plasma levels of LSD in man after a dose of 2 μg/kg administered intravenously are expressed as ng/ml of plasma and appear on the scale at the left.

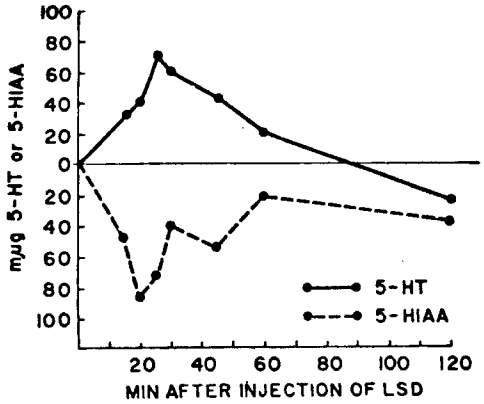


Fig. 9. The response of brain levels of 5-HT (solid line) and 5-hydroxyindole acetic acid (5-HIAA, broken line) in the rat after administration of LSD. Reproduced by permission from Freedman,

BIOSYNTHETIC ASPECTS OF ERGOT ALKALOIDS AND RELATED PSYCHOTOMERS

Ergot is produced by the parasitic fungus, Claviceps purpurea, which used to be prevalent in rye fields of Europe, and North America during moist, warm summers. Upon the young ovaries of rye, the spores of ergot germinate, and develope into mycelia, and later sclerotium. These sclerotia fall to the ground and the following spring produce ascospores which infect rye ovaries, only to start the new life cycle. There exist some 30 species of the genus Claviceps, that infect over 300 species of Grasses (Gramineae).

From the early 19th century ergot preparations have found an increasing medical use. Pure ergot alkaloids and semi-synthetic derivatives are used widely in medicine. Ergotamine is used for treatment of migraine, ergometrine is used frequently in obstetrics, and LSD as a psychotherapeutic agent.

The chemistry of ergot alkaloids has been the subject of numerous investigations. Since 1906, over 40 ergot alkaloids have been isolated. And their structures determined via chemical methods. Many of these ergot alkaloids have been reviewed by Hofmann and Stoll.

The ergoline skeleton is derived from the mevalonic acid conversion to isopentyl pyrophosphate, which is enzymatically incorported into the tryptophan receptor, in the following. (13)

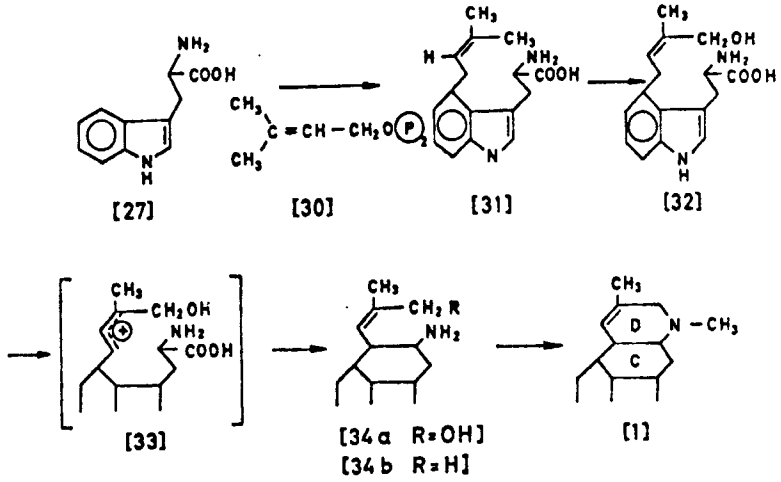


Fig. 6. A hypothetical mechanism for formation of the ergoline skeleton (48).

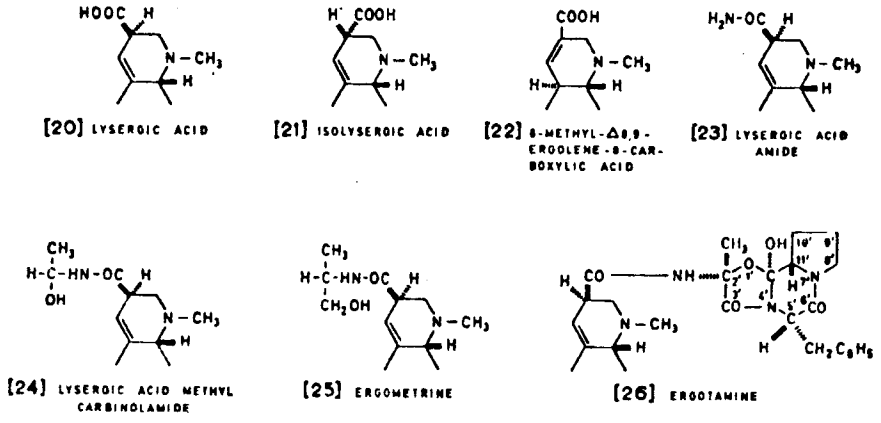
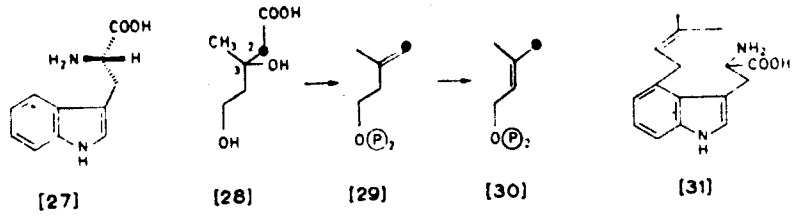
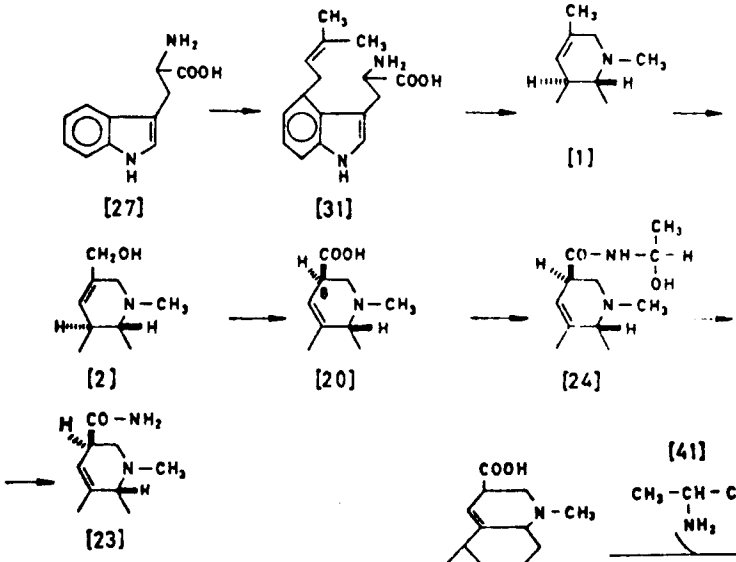


Fig. 2. Some naturally occurring lysergic acid-type alkaloids.

The biosynthetic relation between the clavine type and lysergic acid type ergot alkaloids has been the object of much research. In Claviceps paspali, or ergot, it appears that lysergic acid methyl carbinolamide is the primary product, which decomposes to lysergamide. The existence of a number of substituted lysergamides such as ergometrine, ergotamine and other peptide alkaloids suggests that lysergic acid joins in linkage with an amino acid such as alanine, in peptide linkage and under subsequent reactions in vivo. (14,15)

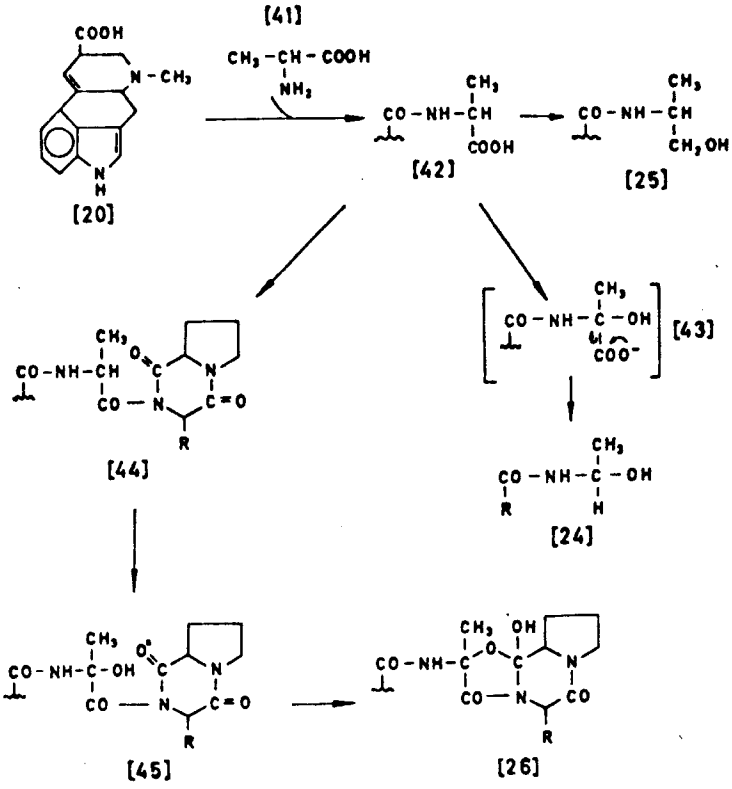


[27] [28] [29] [30] [31]



[27] [31] [1] [2] [20] [24] [23]

13. Probable biogenetic pathway found in C. paspali.



[20] [41] [42] [25] [44] [43] [24] [45] [26]

Hypothetical biogenetic pathways to ergometrine [25], acid methyl carbinolamide [24] and ergotamine [26].

The production of the important lysergic acid derivatives by different strains of Claviceps paspali, in quantitative yield of 1 mg/ml has been achieved with production in submerged culture and isolation of high yield strains of Claviceps in standard culture media. The product D-lysergic acid alpha-hydroxyethylamide can be easily converted to the psychotropic lysergide, in high yield. (16)

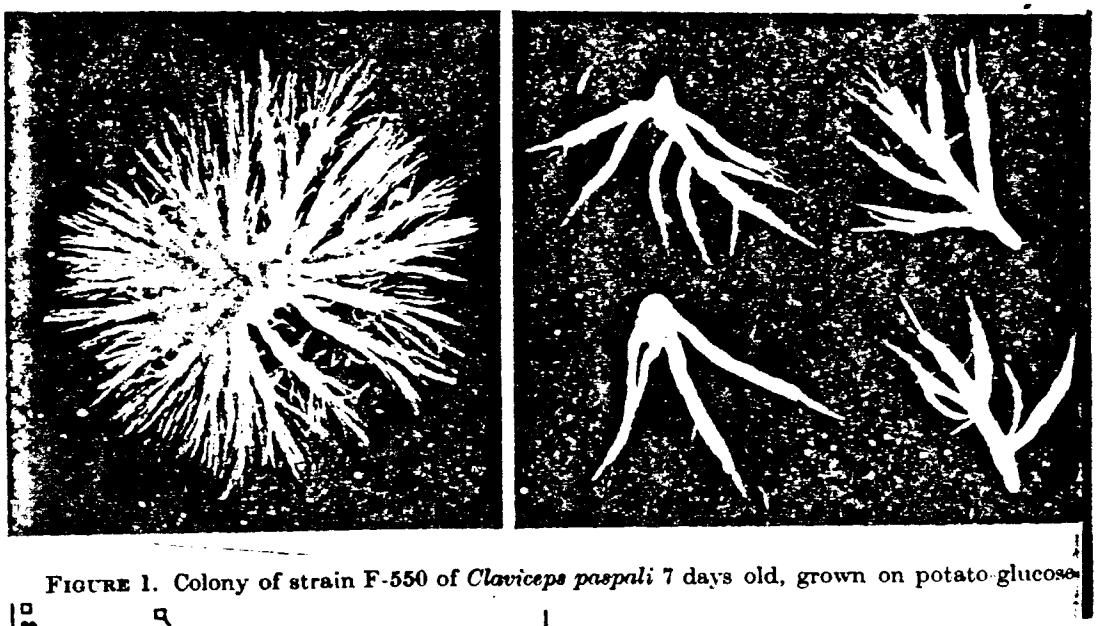
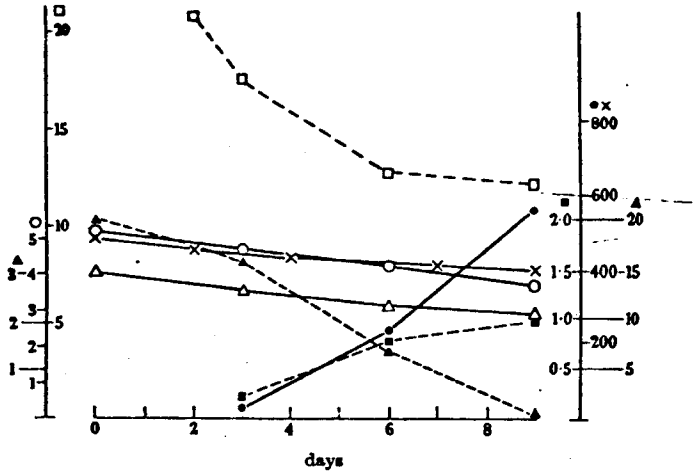
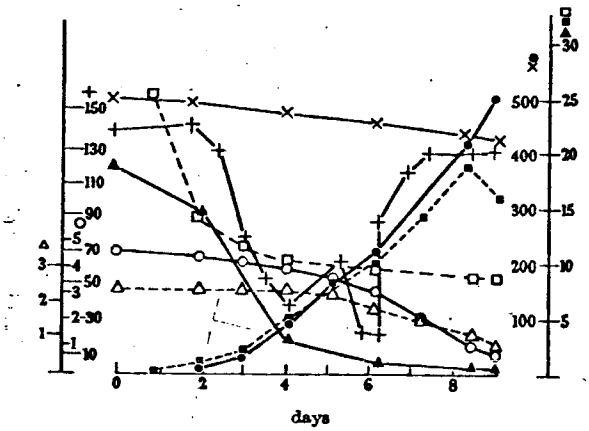


FIGURE 1. Colony of strain F-550 of *Claviceps paspali* 7 days old, grown on potato glucose



Course of a typical *LAD* fermentation by *Claviceps paspali*, strain F-550, in shake flasks in medium *B*. △, Succinic acid, g %; ○, mannitol, g %; □, Q_{O_2}; ■, dry weight, g/100 ml.; ▲, inorganic phosphate, mg P %; ●, *LAD* μg/ml.; ×, ammonia, mg N %.



Course of a typical *LAD* fermentation by *Claviceps paspali*, strain F-550, in a 500 l. stirred fermenter in medium *B*. △, Succinic acid, g %; ○, mannitol, g %; □, Q_{O_2}; ■, dry weight, mg/ml.; ▲, inorganic phosphate, mg P %; ●, *LAD*, μg/ml.; ×, ammonia

LAD PRODUCTION AFTER FIRST STRAIN SELECTION

colour of mycelium	percentage distribution	average yield (μg/ml. after 9 days)
white	28	10
brown	69	44
violet	3	120 ✓

LAD PRODUCTION AFTER SECOND STRAIN SELECTION

colour of mycelium	percentage distribution	average yield (μg/ml. after 9 days)
white	20	5
brown	70	55
violet	10	230 ✓

LAD PRODUCTION AFTER THIRD STRAIN SELECTION

colour of mycelium	percentage distribution	average yield (μg/ml. after 9 days)
white	9	50
brown	29	204
violet	69	450 ✓

Similarly, there have been several interesting chemical synthetic protocols for the workup of the tetracyclic lysergic acid moiety, including several patented solutions to the problem of creating the lysergide, or diethyl amide of the lysergic acid. However, as with many chemical syntheses, such techniques frequently suffer from one or more of the common drawbacks.

a. The reactions fail to go to completion.

b. The reactions require higher temperature, pressure, or other caustic conditions that are compatible with the stability of the lysergic moiety.

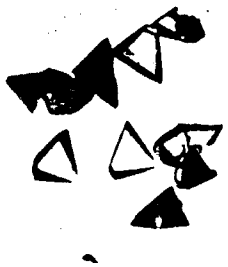
c. The reactions system decomposes lysergic acid or its amide due to the excessive acidic character.

d. The mixed anhydride(s) method of amide prep. undergoes non-specific acylation across the molecule.

e. Separation of the optical isomers, or incomplete isomeric resolution results in tautomerization of the solution

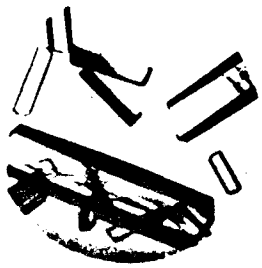
f. There are numerous other pitfalls underlying the chemical synthetic pathway, unless there is a complete chemical lab including raw materials access. Even under ideal conditions, numerous errors come into play.

However the biosynthetic pathway offers a potential supply of d-(+)-lysergic acid, through the cleavage of ergot alkaloids, via the following pathway. However, the methods of amide forming techneques must operate under mild alkaline conditions to be suitable, due to the sensitive nature conferred upon the lysergic acid moiety by their indolic ring moiety. (17)



1. *d*-Lysergs.-*l*-propanolamid-(2) *d*-Ergobasin (aus Essigester)

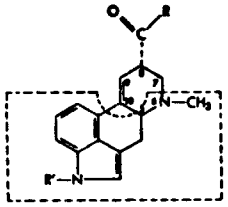
2. *l*-Lysergs.-*d*-propanolamid-(2) *l*-Ergobasin (aus Essigester)



3. *d*-Isolysergs.-*l*-propanolamid-(2) *d*-Ergobasinin (aus Aceton)

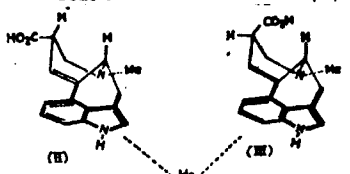
4. *l*-Isolysergs.-*d*-propanolamid-(2) *l*-Ergobasinin (aus Aceton)

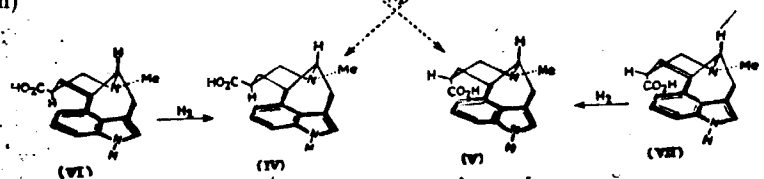
A. LYSERGIC ACID AND AMINE ALKALOIDS*



ALKALOID	R	R'
Lysergic acid	—OH	H
Lysergic acid diethylamide	—$N(CH_2CH_3)_2$	H

boat structure Structures (II) and (III)





Lysergic and isolysergic acid therefore, have the structures (VI) and (VII) respectively, in which saturated ring D adopts the more stable chair conformation

SOCIAL AND LEGAL ISSUES OF LSD

The use of LSD by students and other young people constitutes a serious problem as in this group there is the least control in the use of the drug. LSD poses a far greater roblem than carefully controlling bona fide research projects with the drug. Controlling the use of illicitly obtained substance by those of college age or younger. The attraction of the drug is great, and it is no surprise that statistics reveal the extent to which this is true.

Playboy magazine -1966, When Dr. Goddard, Head of Food and Drug Admin. announced in a senate hearing that ten percent of college students are taking LSD.

Besides the administrators, justifiable and genuine concern with illicit use on campus, college officials are also faced with interesting and meaningful legal questions relative to search and seizure of drugs found on campus. These guidelines should prevent student prosecution, while at the same time prevent wholesale student violation of the law.

LSD provides challenges to every level of our society. It is a great challenge to medicinal research. It is a great challenge to the law, which accomplishes little when the result is making felons out of young thrill seekers of the day. (20,10).

LSD LEGISLATION

State	Category of the law concerning LSD	Penalty for illegal use	Penalty for illegal sale	Penalty for illegal manufacture	Penalty for illegal possession	Penalty for illegal sale to minors	Exemption for research purposes
California Hlth. & Sfty. Code § 11901-11916; 1966 Supp.	LSD treated as dang. drug in separate ch. by that name.	No provision.	First offense: 1-5, st. prison. Subsequent: 2-10, st. prison; see note 1 for limitations.	No provision.	Poss. & poss. w/ intent to sell = separate offenses; see note 1.	First offense: 1-5, st. prison. Subsequent: 2-10; see note 1.	Exception for research limited to "investigational use" by experts who are exempted by §§ 26228 & 26292 of Hlth. & Sfty. Code.

LSD LEGISLATION

State	Category of the law concerning LSD	Penalty for illegal use	Penalty for illegal sale	Penalty for illegal manufacture	Penalty for illegal possession	Penalty for illegal sale to minors	Exemption for research purposes
Massachusetts[4] Mass. G.L. Ann. §§ 197-217e 1966 Supp.	Treated as narc. drug w/ marijuana & heroin.	No provision.	First offense: 5-10 yrs. Subsequent: 10-25 yrs.	First offense: $500-1000 or 6 mo. to 2 yrs. Second: $500-1000 or 5-10 yrs. Subsequent: $2000 and 10-20 yrs.	St. prison up to 3½ yrs; or hse. of corr. up to 2½ yrs. or up to $1000.	No separate penalty for sale to minor; see note 5.	Yes; to a person in *charge* of laboratory only, & only for use in that laboratory.

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