Chemistry of Phenethylamines Related to Mescaline

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This review will bring together a number of the known facts related to the cactus origins of the phenethylamine alkaloids, a comparison of their chemical structures, a listing of several synthetic variants that are known and a description of the psychopharmacologic intoxication that follows their administration to normal human subjects. This will be centered upon the drug mescaline which is the major active alkaloid of the North American dumpling cactus, known by the common name Peyote.

Anyone familiar with the mysteries of taxonomic binomial nomenclature must be aware of the confusion and frequently personal arguments that seem always to be underway amongst botanists. The area of Peyote assignment is no exception. The Peyote button, which is accepted as being the major hallucinogenic cactus in this area, appears to occur in two variations. Both contain some one to two percent alkaloids, but they differ in the composition of this fraction. In one, mescaline is the major component accompanied by some 60 other alkaloids in lesser amounts, most of them tetrahydroisoquinolines. In the other, the alkaloids are largely phenolic in nature and pellotine constitutes approximately 90 percent of this fraction. Mescaline is present in trace amounts at most. Thus when the buttons are collected at random, it is quite reasonable that there should be wide variations in composition reported. Heffter, in his seminal studies of various batches of Peyote buttons, employed the terms "mescalinogenic" and "pellotinogenic" to distinguish these two types on a chemical basis, but he claimed that there was no morphological distinction between them. There is, however, a distinct morphological variant called *Lophophora diffusa* which appears to contain largely pellotine. With apologies to the morphologists and for simplicity's sake, it would seem to be useful to make a temporary assignment of name primarily on chemotaxonomic grounds.

The dozen or so cacti that are associated with mescaline content are listed in Table 1. The distinction between the first two, both commonly known as Peyote, has already been commented upon, and the variant *Lophophora diffusa* is arbitrarily placed with *Anhalonium lewinii* due to the relative paucity of mescaline content in both. Of the many *Trichocereus* species listed, the first two are noteworthy due to their relatively large mescaline content. The first, *T. peruvianus*, on a weight basis probably exceeds peyote as a source of this alkaloid. The remainder of the species listed have not been quantitatively determined. Only estimates have been made, by mass spectral determination or by a combined gas chromatography-mass spectral procedure, and all contain unisolatable quantities of mescaline. These are listed as being less than 0.1 percent (the upper limit of assay) and may be considerably below this figure. The last two entries, *Pelecyphora aselliformis* and *Opuntia spinosior* (commonly known as the Hatchet Cactus and Cane Cholla, respectively) contain only microscopic quantities of mescaline. It can be calculated that the former, at

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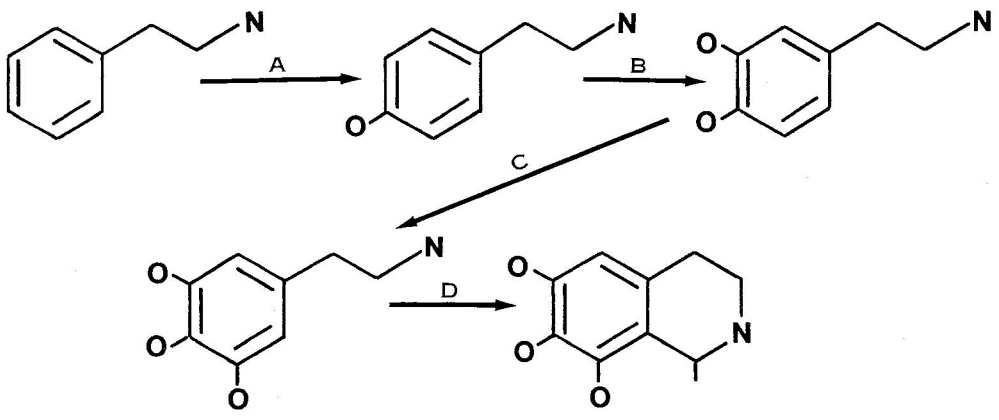
TABLE 1
CACTI SOURCES OF MESCALINE

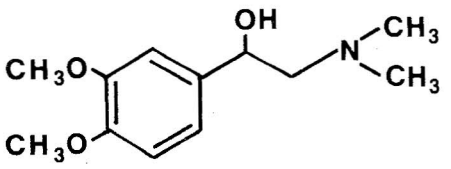
Botanical Name	Locale	Approximate Percent Mescaline Content
Lophophora williamsii	Texas, Chihuahua	1
Anhalonium lewinii (*L. diffusa*)	Queretaro	trace (1% pellotine)
Trichocereus peruvianus	Peru	1
T. pachanoi (San Pedro)	Peru	0.1
T. bridgesii	Bolivia	< 0.1
T. macrogonus	South America	< 0.1
T. terscheckii	Argentina	< 0.1
T. werdermannianus	South America	< 0.1
T. cuzcoensis	Peru	< 0.1
T. fulvilanus	South America	< 0.1
T. taquimbalensis	South America	< 0.1
T. validus	South America	< 0.1
Stetsonia coryne	Argentina	< 0.1
Pelecyphora asilliformis	San Luis Potosi	10^{-5}
Opuntia spinosior	Arizona, Chihuahua	10^{-5}

approximately two ounces per plant, would require the consumption of some 100,000 plants for central activity. The report of mescaline as a component of another *Opuntia* species (*O. cylindrica*) must be held as questionable as there are reports of plant misidentification.

The organization of the major alkaloids of Peyote is simplified by a preliminary consideration of the probable biosynthetic steps that are employed in the plant. This is outlined in Figure 1, with a progressive development of ring oxygenation and ring complexity. Although most of these pathways have been determined in Peyote itself, the general classes of alkaloids that are known to be in other cacti make it probable that these schemes are quite general. The first stage of oxidation is commonly found in microorganism and animal biosynthesis as well as in plant chemistry. This step, step "A," is best characterized by the formation of tyrosine from phenylalanine, in amino acid chemistry. Step "B," the introduction of a second oxygen adjacent to the first, is again common to both living kingdoms, and in the amino acid analogy represents the formation of dopa from tyrosine. At this point the animal and plant biosynthetic paths diverge. Most animal schemes introduce the third oxygen either adjacent to the aliphatic chain to form the 2,4,5-orientation pattern, or on the chain immediately adjacent to the aromatic ring, as in the enzymatic synthesis of norepinephrine. Cactus alkaloids such as macromerine (from *Corypantha macromeris*) indicate that examples of chain oxidation

FIGURE 1





macromerine

can occur in plants, but such products are completely unknown in Peyote. The indicated step "C," with the introduction of the third oxygen adjacent to the first two and the formation of the 3,4,5-orientation pattern, is unique to the plant kingdom. The mechanism of step "D" is variable. There is the necessary introduction of additional carbon to form the second ring of the tetrahydroquinoline system. An example of possible biosynthetic pathways is shown in Figure 2, for the synthesis of anhalonidine, employing compounds all of which are known to be present in Peyote. The study of such *in vivo* transformations is both difficult and inherently uncertain: difficult in that radioactively labeled precursors must be synthesized and employed, and the label in the product must be established as to its position; and uncertain in that the distinction between a plant's native synthetic process and its synthetic capabilities can only be inferred from the efficiency of the observed conversion.

Several of the some 60 known alkaloids present in Peyote are arranged in Tables 2-4 in increasing complexity, in agreement with the biosynthetic scheme presented. Not all of the known components are given, some being quite complex and having structures that have not been confirmed by synthesis but merely deduced by studies of physical properties. All of the compounds shown bear some family resemblance, showing varying degrees of 0-methylation, N-methylation (in one case N-ethylation), N-acylation and quaternization. The mono- and dioxygenated phenethylamine alkaloids that are established as being in Peyote are shown in Table 2. The oxygen function and the nitrogen function are given beneath the arrows from those atoms, and only when trivial names are commonly used are these names given.

Most of these simpler compounds are found not only throughout the cactus world, but widely distributed in both the plant and animal kingdoms. Three of these alkaloids, tyramine, hordenine and epinine, are known adrenergic agents and have been well explored pharmacologically. Epinine is also known as deoxyepinephrine. Hordenine may also occur in Peyote, although a confirming search for it independently has failed to show it to be present. The compound dopamine represents an interesting component: it is a normal neurotransmitter in humans along with being well established as a natural alkaloid of Peyote. A legal paradox might well exist here; in the current code of Federal regulations, under Title 21, Section 1308.11, there is an entry immediately following the listing of Peyote as a Schedule I drug. It defines Peyote as:

> . . . meaning all parts of the plant presently classified as *Lophophora williamsii* Lemaire,

FIGURE 2

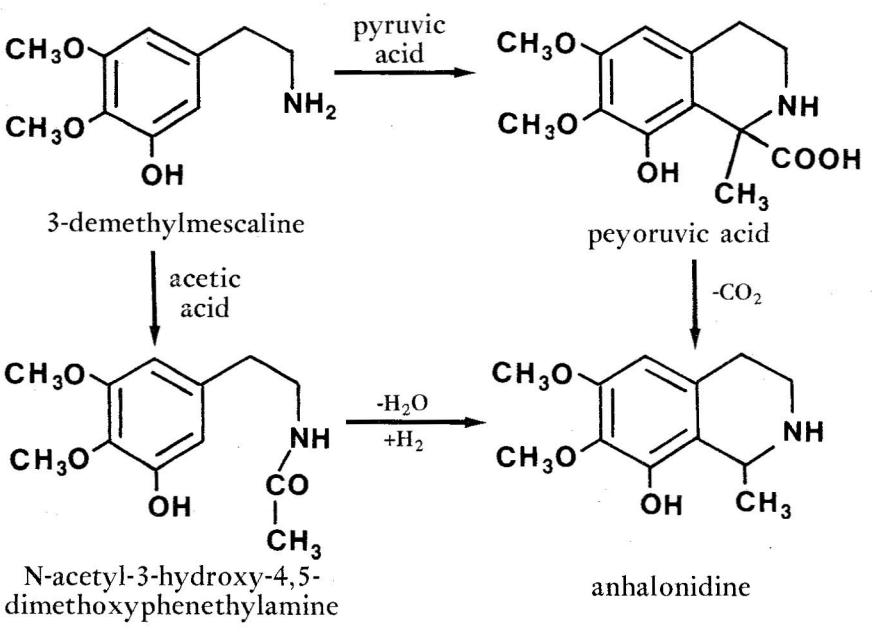
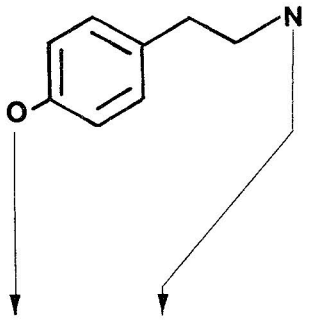


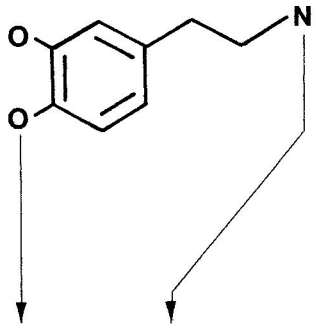
TABLE 2

PEYOTE ALKALOIDS (1)



HO	NH_2	Tyramine
HO	$NHCH_3$	N-Methyltyramine
HO	$N(CH_3)_2$	Hordenine

MONO- AND DIOXYGENATED PHENETHYLAMINES



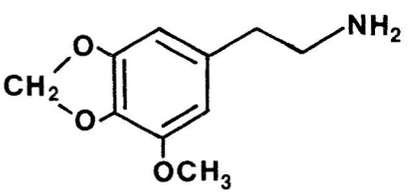
HO HO	NH_2	Dopamine
	$NHCH_3$	Epinine
CH_3O HO	NH_2	
	$NHCH_3$	
	$N(CH_3)_2$	
CH_3O CH_3O	NH_2	DMPEA

whether growing or not; the seeds thereof; any extract from any part of such plant, and every compound, manufacture, salt, derivative, mixture or preparation of such plant, its seeds or extracts.

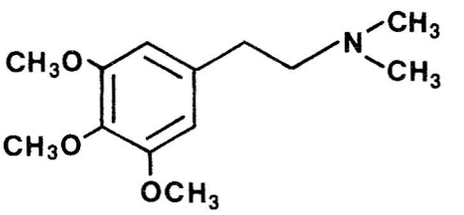
As the phrase "and every compound of such plant" is used, it is conceivable that a natural neurotransmitter essential to brain function could be argued in court as being a Schedule I drug!

Another noteworthy compound in Table 1 is DMPEA (3,4-dimethoxyphenethylamine). Although it is present as a trace component in Peyote, it has achieved broad notoriety as a component found in the urine of schizophrenic patients. Although there is presently some controversy as to whether it is validly a diagnostic or perhaps a dietary factor, it is nevertheless intriguing that a factor that may be implicated in mental health problems is also present in a plant that can affect mental integrity.

The several trioxygenated phenethylamines present in peyote are listed in Table 3. The first compound, 3,4-dihydroxy-5-methoxyphenethylamine, may be the possible precursor to the several methylenedioxy alkaloids that are mentioned shortly. The *in vivo* coupling of this compound with formaldehyde would give rise to homomyristylamine. This is a most logical compound to be found in Peyote; it would be a logical precursor to several of the known methylenedioxytetrahydroisoquinolines, and is centrally active in humans. And yet there is no report of its ever having been found in the natural cactus. In the second group, the monohydroxy-dimethoxy series, the first compound with the primary amino group serves as a prototypic precursor to some of the tetrahydroisoquinolines to be mentioned shortly. The N-acetyl derivative can be cyclized readily under laboratory conditions, and its possible role in the plant has been discussed in Figure 2. The simplest trimethoxy entry is mescaline itself, a beguilingly simple structure for a compound of such complex psychopharmacological properties. It is interesting that although the formic and acetic acid amides of mescaline are present in peyote, the simple methyl homologs probably are not. A recent report of the presence of N-methyl mescaline could not be confirmed.



homomyristylamine



trichocerine

The N,N-dimethyl homolog, trichocerine, is the major component of another cactus *Trichocereus terscheckii*. This compound is without activity in humans even in large quantities, as shown by direct experimentation and by the fact that the plant from which it comes is commonly used as a water source by both humans and animals. This alkaloid has never been reported to be in Peyote.

All of the tetrahydroisoquinoline alkaloids present in Peyote are trioxygenated, and they are presented in

TABLE 3

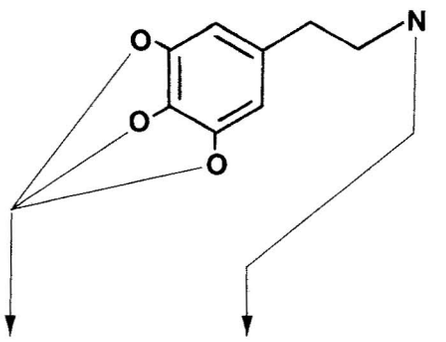
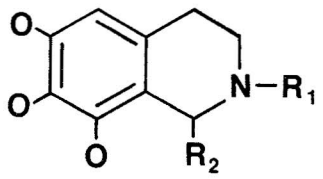
PEYOTE ALKALOIDS (2)	TRIOXYGENATED PHENETHYLAMINES	
		
HO HO CH_3O	NH_2	
HO CH_3O CH_3O	NH_2	
	$NHCH_3$	
	$N(CH_3)_2$	
	NHCHO	
	$NHCOCH_3$	
CH_3O CH_3O CH_3O	NH_2	Mescaline
	NHCHO	
	$NHCOCH_3$	

TABLE 4

PEYOTE ALKALOIDS (3) TETRAHYDROISOQUINOLINES



	R_1	R_2	
CH_3O, CH_3O, HO	H	H	Anhalamine
			N-formyl
			N-acetyl
	CH_3	H	Anhalidine
			Quaternary methyl (Anhalotine)
	H	CH_3	Anhalonidine
			N-formyl
	CH_3	CH_3	Pellotine
			Quaternary methyl (Peyotine)

	R_1	R_2	
HO, CH_3O, CH_3O	H	H	Isoanhalamine
	CH_3	H	Isoanhalidine
	H	CH_3	Isoanhalonidine
	CH_3	CH_3	Isopellotine

	R_1	R_2	
CH_3O, CH_3O, CH_3O	H	H	Anhalinine
			N-formyl
	H	CH_3	0-Methylanhalonidine

	R_1	R_2	
CH_3O, CH_2O_2	H	CH_3	Anhalonine
			N-formyl
			N-acetyl
	CH_3	CH_3	Lophophorine
			Quaternary methyl (Lophotine)
	C_2H_5	CH_3	Peyophorine

Table 4. The oxygen substitution patterns are again boxed, and the substituents found in the nitrogen ring are appropriately listed. In several cases, known acyl or quaternary homologs are entered below each parent compound, along with trivial names when they exist.

With the formation of this second ring system, the arrangement of the three oxygens relative to the chain substituent on the aromatic ring is no longer symmetrical, and so two patterns of monohydroxy-dimethoxylation can exist. The major group, with the free hydroxyl group adjacent to the heterocyclic ring, is shown in the upper left. The fourth compound, pellotine, has already been mentioned as a major compound in Peyote, and in some variants is present to the exclusion of mescaline. The isomeric compounds shown below them are present only in trace amounts, and have been established as present only through the employment of extremely sensitive analytical techniques. None of them have been studied pharmacologically. In fact, only four of the compounds listed on this table have been studied in humans. Most of this work was done before the turn of the century by Heffter at the time that he had isolated many of these materials and had determined their structures. Anhalonidine leads to sedation at levels of 100-250 mg, but with no sensory changes observed. Pellotine has been the best explored of these tetrahydroisoquinolines and was actually studied clinically in Germany in the 1920s. The oral administration of 15-30 mg leads to a calming of the patient and 50 mg subcutaneously leads to a quiet and uneventful sleep. At higher oral levels, up to 240 mg, there is the observation of dizziness and gastric upset, but other than extensive sedation there are no indications of central activity. Anhalonine at oral levels of 100 mg also failed to produce any central effects. Lophophorine is the most toxic of these chemicals, at least in cold-blooded animals. At 20 mg orally there was, in humans, abrupt vasodilation and the generation of an intense headache. At 50 mg there was a drop in heart rate with a compensatory increase in blood pressure, but no visual or interpretive effects that would relate it to mescaline. It would seem as if the family of

tetrahydroisoquinolines must be discarded as being major contributors to the action of Peyote in humans. It is always possible that they may play some augmentative or potentiating role but, within the limits of our present knowledge, mescaline must be assumed to be the major component of Peyote responsible for the action of the cactus.

Mescaline was first isolated from Peyote in 1896 and its psychopharmacological properties were reported the following year, although it was not successfully synthesized until 1918. Peyote and mescaline have usually been studied in one of several forms, and the following terms are often encountered in the literature:

Peyote: This is the cactus itself without any modification. It can be consumed either as the fresh plant or after having been dried for preservation and storage. The tufts of hair that are found on the cactus in place of the usual spines (and which have given rise to the Genus name *Lophophora* meaning "tuft-bearing") are devoid of alkaloids, and their removal before consumption can be justified only for esthetic reasons.

Tincture of Peyote: An extract of the ground-up Peyote button with 70 percent alcohol which has been clarified by filtration.

Basic Panpeyote: An extract of the ground-up Peyote button with chloroform. The term "basic" refers to its fundamental nature and not to the presence of organic bases. The prefix "pan" indicates that there has been no fractionation of the components.

Soluble Peyote: This term, which is used synonymously with the phrase "injectable peyote" is the hydrochloric acid extract of basic panpeyote, and thus contains those components that are inherently basic in property.

Mescaline Alkaloid: This is mescaline itself that has been isolated from Peyote, generally by the preliminary extraction of alkalinified aqueous material with ether (to remove alkaloids other than mescaline) and then with chloroform. It may be expected to contain traces of congener alkaloids.

Synthetic Mescaline: This is mescaline, usually as the hydrochloride or sulfate salt, that has been prepared by total synthesis.

The usual dosage of mescaline employed in experimental investigations has been between 300 and 500 mg of the sulfate salt, which is equivalent to 225-375 mg of the hydrochloride. It can be administered orally, subcutaneously, intramuscularly or intravenously. The dosage employed is independent of the route but in the case of intravenous administration the rate of onset is much faster. A generalized profile of the chronology and character of the intoxication is as follows:

> At a nominally active dosage level of 350 mg (orally, as the sulfate) there is a generally predictable chronology of events. The first signs of change are largely physical. At about a half hour following ingestion there is an onset of nausea, often accompanied with active vomiting. There is occasionally the development of diarrhea. A mild tachycardia and a rise in blood pressure is often seen during this initial phase, but this may be associated with anxiety and apprehension. The initial indication of sensory change is noted in about one hour. The development of central effects ends the "physical distress" phase of the intoxication, and this "sensory" phase continues to develop to a plateau of intensity during the next two to three hours. The physical changes noted during this period are minor. There is a cardiovascular quieting with the pulse rate and blood pressure dropping below their initial base levels, and a constant, extensive, and reactive mydriasis. A gradual diminution of the central intoxication over the following few hours leads to a complete recovery, generally within 12 hours. There is consistently an excellent recall of the impressions and the events that occurred during the experiment.
>
> Whereas this time pattern and sequence of events is quite predictable from one person to another and from one occasion to another, the content and the direction taken by a subject's imagination (as directed by his interpretative capacities) are completely unpredictable and unique to each experience. Some sensory changes are regularly noted and can be expected to contribute to the overall impact of the drug's effects. There is a shimmering and intensification of the visual field, far more intense than what one might expect from the mydriasis-induced photophobia. There is an intensification of color perception, and extreme amplification in minor differences in both color and texture. Frequently observed is the generation of patterned imagery, sometimes in a grid structure, sometimes with undulating shapes, but usually with some color contribution. There is a benign empathy shown to both inanimate and living things, especially to small things.

Much of this clinical data can be found in the

writings of Beringer and Rouhier and others, who have studied dozens of subjects usually with oral or intravenous administration of mescaline. More of the interpretive aspects of mescaline intoxication can be found in the writings of authors such as Huxley, in his well known book *Doors of Perception*. These readings will emphasize the variability that can be expected from one experiment to the next.

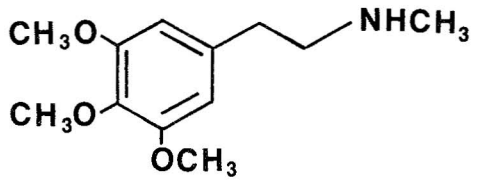
A question frequently arises as to differences that can be expected from the use of mescaline and the use of Peyote. There is no satisfactory answer. Peyote can contain largely pellotine which will not be hallucinogenic in any reasonable dose, but it can be the mescaline-containing variety which will produce largely mescaline-like responses. There have been no experiments reported that have compared mescaline directly with Peyote. There are almost always differences in the experimental protocol observed with the two materials. Peyote is almost always used in a sacramental rite and is usually ingested over a period of time; mescaline is usually administered in a single dosage and often parenterally. Peyote is often employed at night when there will be a restricted sensory input; mescaline is usually employed in the daytime when the sensory input is very rich. The nature of the setting can strongly influence the experience evoked. Peyote is classically used in an environment of social involvement and has the overtones of general acceptability; mescaline has frequently been studied in clinical surroundings with a flavor of some social unacceptability. All of these factors can contribute to the nature of the intoxication. In the absence of any study of the direct comparison of the two materials in some constant set and setting, they cannot be fairly compared.

Many hundreds, perhaps thousands, of compounds are known that can be considered as variants of mescaline. But only some 20 of these have been studied psychopharmacologically in humans, and these will be presented here with some emphasis on the structural and pharmacological differences amongst them. There are five general classes of structurally modified mescaline analogs: these include modifications of the nitrogen atom either by substitution or replacement; variations on the aliphatic chain of mescaline; positional variation on the aromatic ring, with the rearrangement or removal of methoxy groups; variations of the alkyl group attached to the ether function; and the introduction of a group or groups in place of a methoxyl function. These five classes will be considered separately.

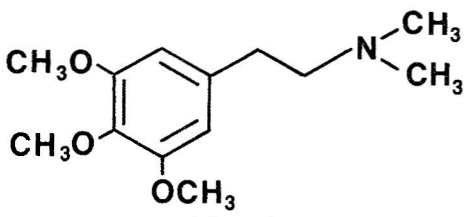
Some mention has already been made concerning the nitrogen substituted homologs of mescaline. Table 5 lists those compounds in this class that have been titrated in humans. N-methylmescaline, which may or may not be in Peyote, has been found to be without any pharmacological effects at dosages of up to 25 mg, a level that far exceeds its possible presence in reasonable amounts of the cactus. It cannot thus be a primary contributing factor to the action of Peyote. Trichocerine, although not in Peyote, is a major component of other cacti and is a valid nitrogen-substituted homolog of mescaline. In studies with acute dosages of up to 800 mg there is some gastric heaviness noted but no changes of the visual or interpretive state. One study of 400 mg administered sublingually led to the observation of some ill-defined psychotropic disturbances for about an hour, but it was felt that these might be ascribable to anxiety. N-acetylmescaline is found as a trace component of Peyote and, interestingly, also as a minor metabolite of mescaline in humans. Similarly, 3,4,5-trimethoxyphenylacetic acid, although technically not a nitrogen substitution analog of mescaline, is the major metabolite of mescaline (accounting for some 30 percent of the

TABLE 5

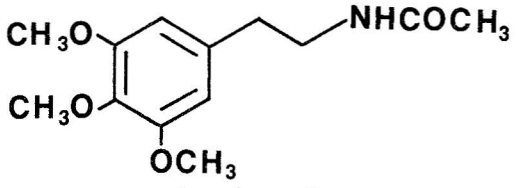
NITROGEN VARIANTS OF MESCALINE



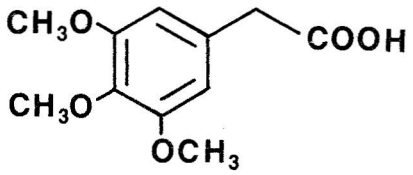
N-Methylmescaline



Trichocerine



Acetylmescaline



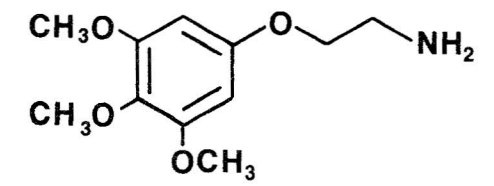
3,4,5-Trimethoxyphenylacetic acid

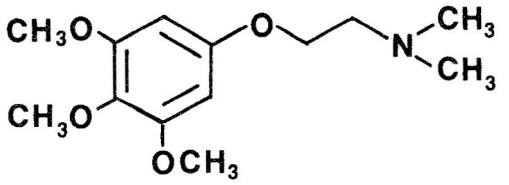
administered drug). These were assayed in humans to address the problem of whether some metabolite of mescaline rather than mescaline itself, might be responsible for its action. Acetylmescaline was assayed at varying levels between 300 and 750 mg, and was without effect except for some drowsiness in some subjects at the highest levels. The trimethoxyphenylacetic acid was without any effect when tried at these same levels (350-750 mg).

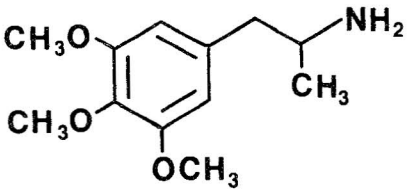
Four compounds can be considered as chain variations of mescaline maintaining the 3,4,5-trimethoxy substitution pattern. These are shown in Table 6. Two of these are compounds in which an oxygen atom has been inserted between the aliphatic chain and the aromatic ring. The first has been assayed at levels of up to 300 mg and the second to 400 mg; both are without any action at these levels. In these, as with all other materials mentioned in this brief structure-activity review, mescaline has been employed as a control measure of intoxicative susceptibility, usually at levels of 400 mg. The introduction of a methyl group alpha- to the nitrogen of mescaline yields TMA. This is the structural variation that is found in amphetamine and which affords it metabolic protection in the body. This was the first variant of mescaline which was found to be of similar psychotropic action and it proved to be about twice as potent. At dosage levels of between 50 and 100 mg, there is shown a giddiness lasting some four hours, with a decrease in inhibition and the loss of some motor control. At 125 mg structured visualizations are reported similar to those seen with mescaline at considerably higher dosages. Dosages of between 200 and 275 mg produce profound psychic changes largely devoid of the empathy so characteristic of mescaline. The alpha-ethyl homolog, quite unexpectedly, proved to be devoid of any action, either peripheral or central, at levels as high as 220 mg. The activity of the third of these compounds, TMA, has prompted an extensive study of related substituted amphetamine analogs, which has revealed compounds of very high intrinsic potency, but which lie outside the scope of this review.

TABLE 6

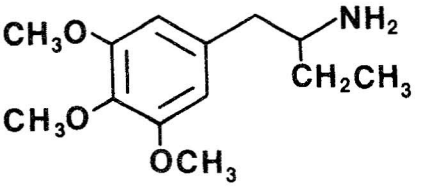
CHAIN VARIANTS OF MESCALINE







TMA



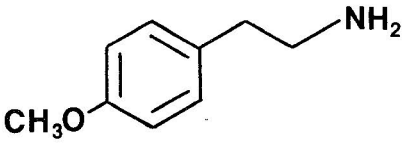
α-Ethylmescaline

Four compounds have been studied, which can be considered as positional variants of mescaline. These are shown in Table 7. The first compound, 4-MPEA, is a natural component of human metabolism and has been isolated from urine. Unlike DMPEA, there has been no pathological correlation with its appearance. It has been assayed at up to 400 mg orally and has shown no effect. DMPEA has already been mentioned in connection with its possible presence in the urine of schizophrenic patients. The theoretical interest in this compound stems from the fact that the counterpart without the methyl groups is dopamine. If there might be the transference of methyl groups to dopamine by enzymatic systems that are potentially available in the body, and if DMPEA is psychoactive, then it might be accorded some endogenous role in the origins of mental illness. For this reason, a number of groups have evaluated it in normal human subjects. However, at levels of between 400 and 1000 mg orally, there are no observable effects. It is only at the level of some 1500 mg, that some slight stimulation is noted, which is comparable to that seen from caffeine. Clearly the loss of a single methoxyl group from mescaline completely eradicates its intoxicative effectiveness. 2,3,4-Trimethoxyphenethylamine (2,3,4-TMPEA) has been studied under the name "reciprocal mescaline" and in the one published report has been found to have a paradoxical effect, depending on the mental health of the subject. The actual description of its action follows:

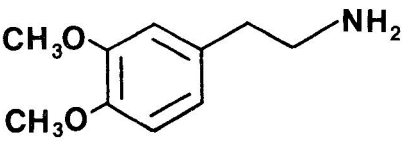
> We have discovered that the intoxicating action depends to a remarkable degree upon the position of the three methoxyl groups.

TABLE 7

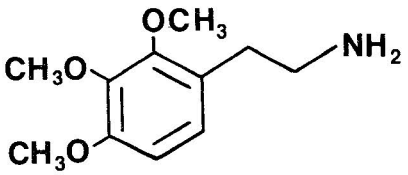
POSITIONAL VARIANTS OF MESCALINE



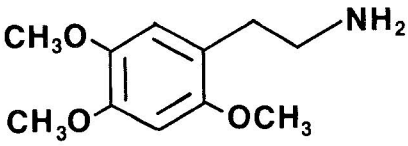
4-MPEA



3,4-DMPEA (DMPEA)



2,3,4-TMPEA



2,4,5-TMPEA

> Mescaline, the 3,4,5-trimethoxy-beta-phenethylamine, produces in the normal subject a much stronger overall intoxication than in the schizophrenic patient, whereas 2,3,4-trimethoxy-beta-phenethylamine has quite the opposite effect. It has little action in healthy individuals, being almost without intoxicating properties, but it is very potent in the schizophrenic. The metabolic conversion products of this "reciprocal" mescaline will be further studied as soon as the study of the proper mescaline is complete.

Unfortunately no dosages were given in this single report, but one might assume by the direct comparisons made with mescaline that they were perhaps 400 mg. Also, there have been no following reports of either metabolic studies or psychopharmacological details, and as there have been no confirming reports from other groups, this intriguing comment will have to stand on its own merits.

The last of the positional isomers of mescaline is interesting in that it has the substitution pattern of 6-hydroxy dopamine, an extremely potent neurotoxin in mammals. Also, it is now known that the 2,4,5-trisubstitution orientation is the most potent arrangement possible for hallucinatory efficacy. Only two reports on the action of this compound can be found in the literature. In one, the extent of the pharmacological data is:

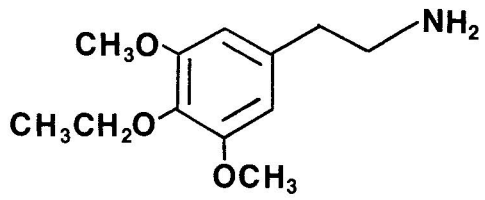
> The action of both these substances [mescaline and 2,4,5-DMPEA] agreed only to a limited extent to the effects described by Beringer. It may be concluded that the pharmacological action of beta-2,4,5-trimethoxyphenethylamine agrees to a large extent to that of mescaline. However, the new compound had more unpleasant secondary effects [nausea] and did not bring about the euphoric state caused by mescaline.

The dosage was not given, but as Beringer routinely employed between 300 and 500 mg of mescaline, it must be assumed that this was the dosage of 2,4,5-TMPEA. A second report states that the compound is without activity at 300 mg but that it potentiates the action of mescaline.

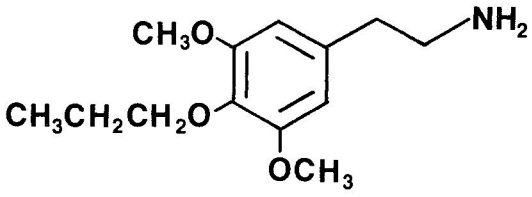
Three ether homologs of mescaline have been studied in humans, these are shown in Table 8. The first two have been called escaline and proscaline, based on

TABLE 8

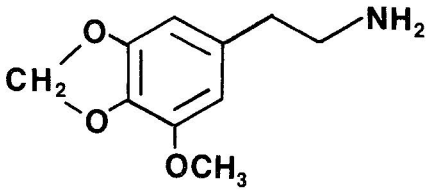
ETHER HOMOLOGS OF MESCALINE



Escaline



Proscaline



Homomyristylamine

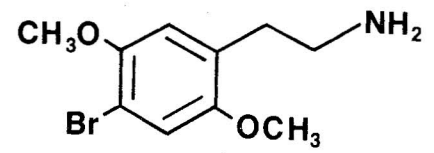
mescaline having a methyl group in the 4-position, replaced here with an ethyl and a propyl group respectively. Both compounds are active in the 40 to 80 mg dosage area, representing an increase in potency some 5-fold to that of mescaline. This demonstrates the importance of the substituent in the 4-position of this system, a fact that has been repeatedly demonstrated in the variously substituted amphetamine-derived hallucinogens and which will become more apparent in the final table. They appear to be qualitatively indistinguishable from mescaline in their action, so apparently the recognition of these materials at some active site within the body depends upon the intact nature of the rest of the molecule. Homomyristylamine has already been mentioned as a theoretical biosynthetic precursor to the tetrahydroisoquinolines in Peyote, although it does not appear to be present in the plant itself. It has the ring-substitution pattern seen in the essential oils of nutmeg and parsley and its alpha-methyl homolog is the hallucinogenic compound MMDA. It has about the same potency as mescaline (200 mg for threshold effects and 400 mg for intoxication). It produces a mood elevation and euphoric state with considerable visual enhancement, but with little distortion or nausea.

The last group of mescaline analogs are compounds that have substituent variations; methoxyl groups replaced with oxygen-free moieties. There are five materials in this set, and they are illustrated in Table 9. The first two compounds are the 2-carbon homologs of DOB and DOM, both potent substituted amphetamine analogs. Both have a more rapid onset of action than does mescaline and at effective dosages of about 10 and 20 mg, respectively, are some 20 times more potent. They lead to qualitatively uncomplicated intoxications that resemble one another closely. A description from the literature gives a qualitative portrait of their action:

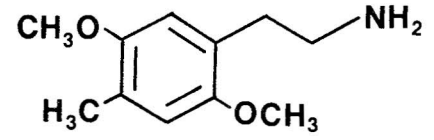
> Both of these bases lead to a similar state of intoxication, one quite separate and distinct from that usually associated with the "psychotomimetic" or "hallucinogenic" drug. Rather than showing signs of stimulation, the subject becomes passive and relaxed and is aware of an integration of sensory perception with emotional state [although not experiencing the lassitude characteristic of psilocybin]. Except for the constant perceptual enhancement noted, there are no effects that can be called hallucinogenic. At these dose levels there is a considerable euphoria with an increased body awareness and increased receptiveness of visual, auditory and tactile sensation. The integration of sensory and emotional states induces in most subjects a feeling of security and an ability to cope with incidents and experiences that might have led, with drugs such as LSD, to a state of anxiety and possible panic. At the end of the experience [six hours for 2-CD and eight hours for 2-CB] the subject appears to be alert, relaxed, and content.

TABLE 9

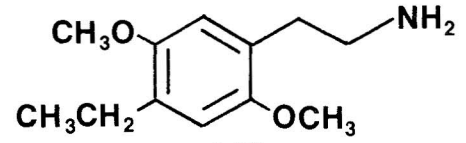
SUBSTITUTION VARIANTS OF MESCALINE



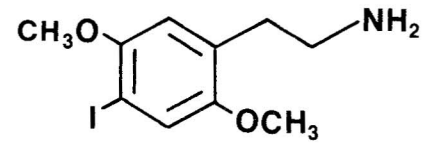
2-CB



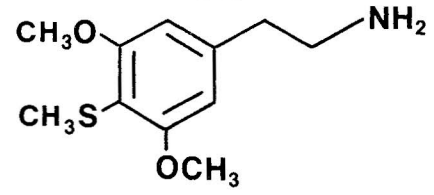
2-CD



2-CE



2-CI



4-Thiomescaline

The third of these compounds, 2-CE, is also active at about 10 mg and qualitatively at this level it is very similar to the first two. At twice this dosage, however, there is superimposed on this placid state a rather intense and somewhat frightening hallucinatory syndrome which is relatively long lasting. The fourth of these 4-substituted 2,4,5-ring patterned phenethylamines is the iodo analog 2-CI. Again the active level is approximately 10 mg, but there is no clinical detail reported in the literature. The last of these substituted variants is one of the most interesting from the

theoretical point of view. It has the precise structure of mescaline except for a single atom change, the replacement of a sulfur atom for an oxygen atom in the 4-position. It is active in humans at 10-25 mg so it represents a 12-fold increase in potency over mescaline. Of all the compounds mentioned in this review, it comes most closely to being what should properly be called a psychotomimetic. It produces a very intense and disorganized psychotic state that has some aspects of visual distortion but primarily disrupts the mental integrity.

This has been a brief review of one small portion of the fascinating world of materials that change our way of seeing things and thus change those things we see. It has been concerned with only one plant, the Peyote cactus, and has been centered on a single compound within that plant, mescaline. Many other plants are hallucinogens, each with its own unique chemical or chemicals and many of them have already led to similarly rich and complex stories. It will be incumbent upon the botanists and chemists, the shamans and psychiatrists, to tell their stories.

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