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REVIEW ARTICLE

Peyote Constituents: Chemistry, Biogenesis, and Biological Effects

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Keyphrases ☐ Peyote constituents—chemistry ☐ Biogenesis—peyote alkaloids ☐ Biological effects—peyote constituents ☐ Mescaline—behavioral effects ☐ Addiction, habituation, tolerance—mescaline ☐ Metabolism—mescaline ☐ Structure-activity relationships—mescaline derivatives

CONTENTS

BACKGROUND

Peyote represents one of the earliest known hallucinogenic drugs, the use of which was exclusively limited to the New World. Today much more potent hallucinogens, of natural and synthetic origin, are known, yet investigation into the chemistry and pharmacology of peyote constituents and their synthetic analogs does not seem to have relented. The literature contains several early surveys covering various aspects of peyote and its constituents. These include articles and monographs dealing with cactus alkaloids (1–7) and natural hallucinogens (8–27) in general and more specialized ones dealing mainly with peyote and its active principle, mescaline (28–40). Several of the earlier articles also cover, more or less adequately, such diverse aspects of peyote as history, cultic and modern uses, chemical composition, synthesis of its constituents—as phenethylamines (41) and tetrahydroisoquinolines (42)—and the pharmacology of these products and their synthetic analogs along with their possible medicinal applications (40).

In the past decade or so, there has been no such comprehensive coverage in one review. The need for one is accentuated by the fact that during the past 5 years alone, more than 31 new constituents of peyote were discovered (compared to six before 1900 and five during the 1930's), several synthetic methods were developed, and an important part of the pharmacological and clinical (as well as social) studies and practically all the biogenetic studies of the major peyote constituents were conducted, with impressive revelations made.

Names—Peyote, a member of the family Cactaceae, has received varied taxonomical treatments with time by different botanists. The first "scientific" name given to it was *Peyotl zacatensis* by Hernandez in 1638. The designation *Echinocactus williamsii* was used by Lemaire in 1840, *Anhalonium williamsii* by Engelman, *Lophophora williamsii* by Coulter in 1894, *Anhalonium lewinii* by Lewin, and *A. jourdanianum* by Rebut. Although the name *Echinocactus williamsii* appears in the *Kew Index* (vol. II, p. 813), it does not seem to be as commonly used as *A. lewinii* or *L. williamsii* (7, 37). The latter name is the one more commonly used in the current chemical literature. The introduction of these names, and there seems to be more, appears to be the result of confusion between the different types of peyote which actually belong to a single species (37, 39).* The confu-

* According to E. F. Anderson [*Brittonia*, 21, 299(1969)], the genus *Lophophora*, which has an extensive range within the Chihuahuan Desert of Texas and Mexico, consists of two species, *L. williamsii* and *L. diffusa*. The former is both wide ranging and highly variable morphologically, whereas the latter consists of a single, fairly small population restricted to an area in the state of Querétaro.

sion arises from the differences between the young peyote individual specimens, with eight straight ribs, and the mature ones, with about 12 sinuous ribs, and a third form with irregular ribs, in addition to slight morphological variations according to locality.

Peyote is a popular name given to the cactus under discussion; other less common names are peyotl, pellote, challote, and devil's root. The name peyote derives from peyotl which appears to be of Aztec origin. The sun-dried slices of the plant constitute the "mescal buttons" of commerce. It is this material, which can be preserved for a very long time, that is usually consumed[1] in ritual ceremonies or for nonreligious purposes to produce euphoric effects. The name mescal buttons[2] is incorrect, since the material is not related to the noncactus succulent, the mescal proper, from which fermented beverages are prepared. Another incorrect name is "mescal beans," which is also given to the buttons but in fact is the Red Bean, *Sophora secundiflora* (Leguminosae).

Habitat—The cactus (*L. williamsii*) grows wild on the Mexican plateau and in the southwestern United States in dry places, on cliffs, or on rocky slopes. These regions are very hot and the vegetation is subtropical. Peyote is encountered sometimes singly but more often in clusters. It is barely visible, except when in flower, since it is mostly covered with earth and looks like a pebble. Peyote, like most cacti, can be grown practically anywhere under glass or in a room. The plant seems to be capable of standing adverse conditions of drought, heat, and cold.

Description—The peyote plant is a small (rarely exceeding 15–20 cm. in total length), fleshy, spineless cactus, simple or cespitose, proliferous, turbinate with a thick napiform root. The cylindrical stalk, which has horizontal wrinkles, is suberized and grayish-fawn in color. At the top it becomes more chlorophyllose, globular, flattened, and sage-green in color and appears divided into 5–13 thick ribs, only slightly salient, rounded, and separated from each other by well-marked longitudinal grooves. In the center of the spherical portion (2–50 mm. in diameter) of the plant, there is a tuft of silky hairs from which the flowers (usually one or two) emerge; the latter are usually pink but are sometimes white or yellow. The fruit is a flesh-colored, or sometimes grayish-yellow, berry which contains a few small black seeds.

History—Peyote was used and revered—as a panacea, an amulet, and a hallucinogen—in the mountainous regions of northern Mexico centuries before the settlers arrived; it was probably known to the Chichimec tribe long before the Christian era (43). Bernardino de Sahagun (43), a Franciscan missionary and chronicler of the Spanish conquest of Mexico, wrote about peyote, which was eaten by local natives because "it gives them strength and incites them to battle, alleviates fear, and they feel neither hunger nor thirst, and they say it protects them from every kind of danger." At that time, missionaries and administrators tried to suppress peyote consumption for various social, political, and religious reasons, apparently without much success.

During the 17th and 18th centuries, peyote was used in vast areas stretching northward up to the Arkansas River (44), and it was consumed by many Indian tribes including the Apaches, Comanches, and Kiowas. Although a true peyote cult did not seem to have existed at that time, the drug was taken mainly: (*a*) by individuals as a medicine and to induce visions leading to prophetic utterances, and (*b*) collectively to obtain the desired state of trance for ritual dances.

During the 19th century, the ritual use of peyote (peyotism) extended among Indian tribes with their migrations northward and southward and gradually became more fully organized into isolated cult groups (44–46). This led, toward the end of the century, to the establishment of the "Peyote Church." With time, peyote votaries increased in number, variety, and distribution; the Church, founded in Oklahoma, gradually joined in a strange synthesis of old Mexican, Christian, and local religious rites (47). The advocates of this Church remained predominantly Indians, although they were joined by some Negroes, and the cult remained essentially an ethnographical curiosity rather than a serious movement.[3] The present believers worship God as the great spirit who, as a master of the universe, infused some of his being into peyote; Christ is regarded as the man who made the cactus available to them when they needed it. Usually the ceremony is conducted at Saturday night gatherings in a large Indian tepee. Participants then sit around a fire and spend the evening in ritual singing, prayer, and contemplation (39).

In the United States, peyote is not regarded as a narcotic drug, although its use is controlled by the federal government except in *bona fide* religious ceremonies of the Native American Church.

The history, economic importance, cultic use, and psychic effects of peyote are described at length by several authors (9–11, 31–33, 35, 38, 45, 49–58).

Constituents of Peyote—The first chemical investigations of peyote were made by Lewin in 1888 (52). While traveling in America, he collected peyote plants; these were identified by Hennings as a new *Anhalonium* species that was named *A. lewinii*. He was able to isolate the first crystalline constituent, an alkaloid which was called anhalonine and shown to be devoid of any hallucinatory action. This initial finding, however, aroused considerable interest in the drug and the possible constituents that would account for the sensory excitations produced in those who took it. Up to that time, the family Cactaceae was regarded as being free of alkaloids; as a result of Lewin's findings, more attention was directed to the study of several other cacti.

In 1894, Heffter (59–64), working with fresh plants, isolated another alkaloid which received the name pello-

[1] The drug is usually taken orally. The buttons, whole or chopped, are brewed with tea or chewed while drinking tea, coffee, wine, or milk (to conceal an unpleasant taste). Less commonly, a liquid concoction is injected intravenously.

[2] Other slang names include: tops, moon, full moon (a large button) and bad seed.

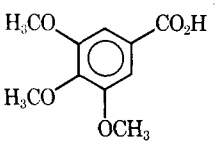
[3] In the United States, about 1950, some ethnologists protested strongly the idea that the use of peyote should be prohibited on the pretext that the Native American Church (practicing peyotism) is a legitimate religious organization with the same right to religious freedom as other churches (48).

tine. Shortly afterward he isolated three additional alkaloids. One, mescaline, was recognized—from pharmacological tests and personal experience—as the hallucinatory principle of peyote; the other two were named anhalonidine and lophophorine (61). In 1899, Kauder (65) discovered an additional alkaloid, anhalamine, besides the previously known pellotine in the mescal buttons. During or about the same period, other cacti yielded related alkaloids (nonhallucinogenic): anhaline (≡hordenine) from *Anahalonium fissuratum* and pectenine (≡carnegine) from *Cereus pecten-aboriginum* (66) and later from *Carnegia gigantea* (67).

Lewin (52, 53) also made the first pharmacological studies of peyote. His reports were followed by more elaborate and expanded studies made by Prentiss and Morgan (68), Mitchell (69), Ellis (70), Dixon (71), and Mogilewa (72), who described the physiological and special euphoric effects of peyote and its constituent alkaloids.

The elucidation of the structure and the synthesis of all these alkaloids had to wait until Späth made his contributions. He published the first of a series of papers on "Anhalonium alkaloids" in 1919 and continued his work up to 1939 (3, 73–90); his work also included studies on the alkaloids obtained from other Cactaceae. In addition to the previously mentioned alkaloids, Späth isolated from peyote five other products: anhalinine and anhalidine in 1935 (80, 81), *N*-methylmescaline in 1937 (83), *N*-acetylmescaline in 1938 (84), and *O*-methyl-*d*-anhalonidine in 1939 (85).

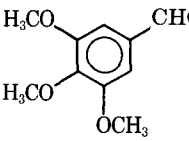
Interest in peyote, at least in research laboratories, remained dormant after the last contributions of Späth until very recent years, presumably with the resurge or increase of interest in the psychotomimetic agents and their sources which has become a hallmark of our days. Three tyramine derivatives were identified in peyote during 1965–1966; they are tyramine and its *N*-methyl and *N,N*-dimethyl (hordenine) derivatives (91, 92). The presence of candicine was suggested (92) on the basis of TLC evidence but could not be confirmed in later work (93). All these products were previously encountered in several cacti of other plant species. From 1967 onward, Kapadia and his coworkers examined the relatively minor alkaloidal and related nonbasic (quaternary, acid, and amide) constituents of peyote and identified 26 additional compounds. These include the alkaloids peyophorine (94) and 3-demethylmescaline (95); the quaternary bases anhalotine, lophotine, and peyotine (93); the amides *N*-acetyl-3-demethylmescaline, *N*-acetylanhalamine, and *N*-acetylanhalonine; *N*-formylmescaline, *N*-formyl-3-demethylmescaline, *N*-formylanhalamine, *N*-formylanhalonine, *N*-formylanhalinine, *N*-formylanhalonidine, and *N*-formyl-*O*-



$\longrightarrow$ ArCOCl $\longrightarrow$ ArCHO $\longrightarrow$

$$ArCH{=}CHNO_2 \xrightarrow{Zn/AcOH} ArCH_2CH{=}NOH \xrightarrow{Na{-}Hg} Ar(CH_2)_2NH_2 \quad (I)$$

Scheme I



$\xrightarrow{CH_2(CO_2H)_2}$ ArCH=CHCOOH $\longrightarrow$

$$Ar(CH_2)_2COOH \longrightarrow Ar(CH_2)_2CONH_2 \longrightarrow Ar(CH_2)_2NH_2 \ (I)$$

Scheme II

methylanhalonidine (96); six cyclic derivatives of mescaline [succinimide, malimide, maleimide (96), citrimide, isocitrimide lactone, and pyrrole (97)] in addition to two other cyclic amides, mescalotam and peyoglutam (96); and the acids peyonine (98), peyoruvic acid, and peyoxylic acid (99, 100). Agurell and Lundström also identified 3,4-dimethoxyphenethylamine (101) in addition to 3-demethylmescaline (102). Table I contains a list of the hitherto identified constituents of peyote.

CHEMISTRY OF PEYOTE CONSTITUENTS

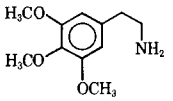
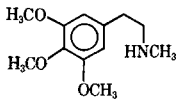
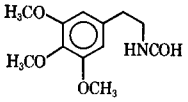
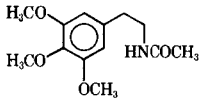
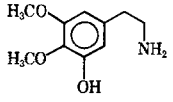
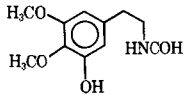
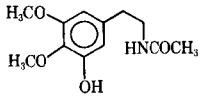
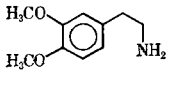
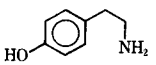
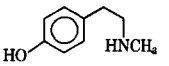
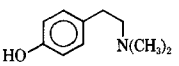
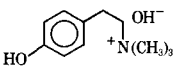
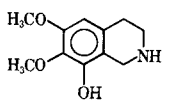
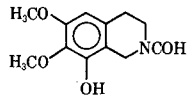
Phenethylamines—*Mescaline and Its Congeners*—Mescaline, 3,4,5-trimethoxy-β-phenethylamine (I), is the active hallucinatory principle of peyote (*L. williamsii*); it occurs in the drug to the extent of 6% and is the main constituent.

The principal synthetic approaches for mescaline and related β-phenethylamine derivatives are basically methods for the construction of the ethylamine side chain onto the appropriately substituted aromatic system.

The first synthesis of mescaline was realized by Späth in 1919 (73). 3,4,5-Trimethoxybenzoic acid was transformed into the corresponding aldehyde and subsequently, by reaction with nitromethane in ethanol solution containing alkali, into the ω-nitrostyrene, which was finally reduced to mescaline in two steps (Scheme I). 3-Demethylmescaline (V) was also prepared as an intermediate toward anhalamine (XIII) by Späth and Röder (90), using essentially the same method after temporary protection of the phenol group. This fundamental sequence was used by many later workers (114–129) in the preparation of mescaline and several of its isomers and analogs. Improvisations have essentially been concerned with the conditions of reaction in the individual steps. The reaction of the benzaldehyde with nitromethane can afford better yields of the ω-nitrostyrene derivative when performed in acetic acid containing ammonium acetate (121, 123, 126, 129, 130), as originally found by Raiford and Fox (131) and Gairaud and Lappin (132), or when an aliphatic primary amine is used as a condensation catalyst (122, 133), as suggested by Worrall and Cohen (134). Erne and Ramirez (118) and Ramirez and Burger (135) found that reduction of the nitrostyrene side chain can be performed with high yield in one step using lithium aluminum hydride[4] (119, 121, 130, 133). This reduction may also be achieved

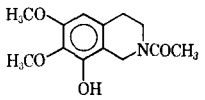
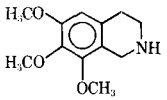
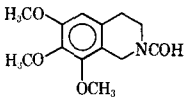
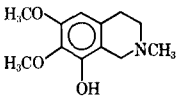
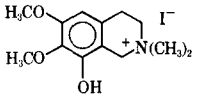
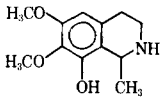
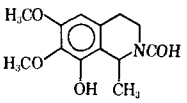
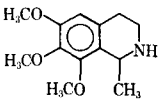
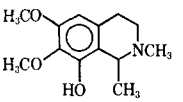
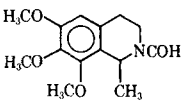
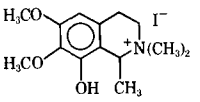
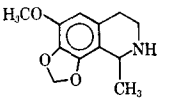
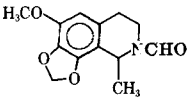
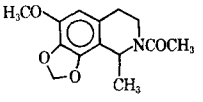
[4] Recently, Kapadia and Shah (136) found that this reaction can also lead to partial demethylation. Thus 4-demethylmescaline resulted, in low yields, from the lithium aluminum hydride treatment of the nitrostyrene discussed, the corresponding phenylacetonitrile, or mescaline itself; similar treatment of pyrogallol trimethyl ether and some of its derivatives also gave the corresponding syringyl phenols.

Table I—Peyote Constituents

Number and Name	Structure	Molecular Formula	M.p., b.p./mm., $[\alpha]_D$	References	Other Natural Sources (References)
I Mescaline		$C_{11}H_{17}O_3N$	30–32° 180°/12	7,40,139	*Trichocereus terscheckii* (103, 105), *T. pachanoi* (104, 105, 188), *T. werdermannianus* (105, 188), *T. bridgesii* (105, 188), *T. macrogonus* (105), *Gymnocalycium gibbosum* (106), *Opuntia cylindrica* (107, *cf.* 105)
II *N*-Methylmescaline		$C_{12}H_{19}O_3N$	177.5–178° (As picrate)	7, 83	
III *N*-Formylmescaline		$C_{12}H_{17}O_4N$	68–69°	96,108	
IV *N*-Acetylmescaline		$C_{13}H_{19}O_4N$	93–94°	7,84,96	
V 3-Demethylmescaline		$C_{10}H_{15}O_3N$	178–179° (As HCl)	95,102	*T. pachanoi* (105)
VI *N*-Formyl-3-demethylmescaline		$C_{11}H_{15}O_4N$	–[a]	96	
VII *N*-Acetyl-3-demethylmescaline		$C_{12}H_{17}O_4N$	–[a]	96	
VIII 3,4-Dimethoxyphenethylamine		$C_{10}H_{15}O_2N$	188°/15	101	*T. bridgesii* (105), *T. camarguensis* (105), *T. macrogonus* (105), *T. pachanoi* (105, 188), *T. werdermannianus* (105, 188), *Echinocereus merkeri* (113)
IX Tyramine		$C_8H_{11}ON$	161°	7,92	Several Cactaceae, *cf.* ref. 105, for other sources, *cf.* refs. 41, 109
X *N*-Methyltyramine		$C_9H_{13}ON$	127–128°	92	*T. camarguensis* (105), *T. schickendantzii* (105), also *cf.* refs. 41, 109
XI Hordenine		$C_{10}H_{15}ON$	117–118°	7,91,92	Several Cactaceae, *cf.* ref. 105; also *cf.* refs. 41, 109
XII Candicine[b]		$C_{11}H_{19}O_2N$	230–231° (As iodide)	7,92,93	*T. candicans* (110), *T. lamprochlorus* (111), *T. spachianus* (112)
XIII Anhalamine		$C_{11}H_{15}O_3N$	189–191°	7,64,65	
XIV *N*-Formylanhalamine		$C_{12}H_{15}O_4N$	–[a]	96	

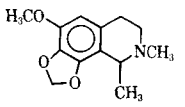
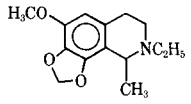
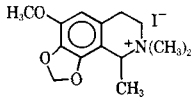
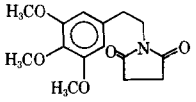
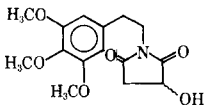
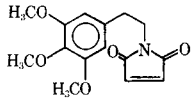
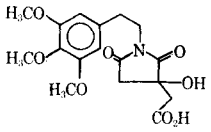
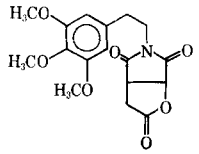
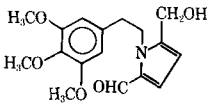
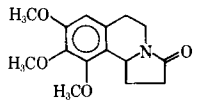
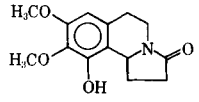
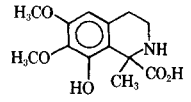
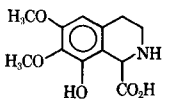
(*Continued*)

Table I—*Continued*

Number and Name	Structure	Molecular Formula	M.p., b.p./mm., $[\alpha]_D$	References	Other Natural Sources (References)
XV *N*-Acetylanhalamine		$C_{13}H_{17}O_4N$	–[a]	96	
XVI Anhalinine		$C_{12}H_{17}O_3N$	61–63°	7,80	
XVII *N*-Formylanhalinine		$C_{13}H_{17}O_4N$	–[a]	96	
XVIII Anhalidine		$C_{12}H_{17}O_3N$	131–133°	7,81	
XIX Anhalotine (iodide)		$C_{13}H_{20}O_3NI$	219–220°	93	
XX Anhalonidine		$C_{12}H_{17}O_3N$	160–161°	7,61	*T. pachanoi* (105)
XXI *N*-Formylanhalonidine		$C_{13}H_{17}O_4N$	–[a]	96	
XXII *O*-Methyl-*d*-anhalonidine		$C_{13}H_{19}O_3N$	140°/0.05 +20.7° (MeOH)	7,85	
XXIII Pellotine		$C_{13}H_{19}O_3N$	111–112°	7,60,65	
XXIV *N*-Formyl-*O*-methylanhalonidine		$C_{14}H_{19}O_4N$	–[a]	96	
XXV Peyotine (iodide)		$C_{14}H_{22}O_3NI$	185–186°	93	
XXVI Anhalonine		$C_{12}H_{15}O_3N$	85.5° –56.3° ($CHCl_3$)	7,52–54, 61	*T. terscheckii* (168)
XXVII *N*-Formylanhalonine		$C_{13}H_{15}O_4N$	–[a]	96	
XXVIII *N*-Acetylanhalonine		$C_{14}H_{17}O_4N$	–[a]	96	

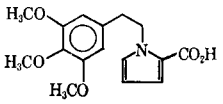
(*Continued*)

Table I—*Continued*

Number and Name	Structure	Molecular Formula	M.p., b.p./mm., $[\alpha]_D$	References	Other Natural Sources (References)
XXIX Lophophorine		$C_{13}H_{17}O_3N$	−47° ($CHCl_3$)	7,61	
XXX Peyophorine		$C_{14}H_{19}O_3N$	155–156° (As picrate)	94	
XXXI Lophotine (iodide)		$C_{14}H_{20}O_3NI$	240–242°	93	
XXXII Mescaline succinimide		$C_{15}H_{19}O_5N$	125–126°	96	
XXXIII Mescaline maleimide		$C_{15}H_{19}O_6N$	–[a]	96	
XXXIV Mescaline maleimide		$C_{15}H_{17}O_5N$	–[a]	96	
XXXV Mescaline citrimide		$C_{17}H_{21}O_8N$	–[a]	97	
XXXVI Mescaline isocitrimide lactone		$C_{17}H_{19}O_7N$	–[a]	97	
XXXVII Peyoglunal		$C_{17}H_{21}O_5N$	–[a]	97	
XXXVIII Mescalotam		$C_{15}H_{19}O_4N$	–[a]	96	
XXXIX Peyoglutam		$C_{14}H_{17}O_4N$	217–219°	96	
XL Peyoruvic acid		$C_{13}H_{17}O_5N$	233–234°	100	
XLI Peyoxylic acid		$C_{12}H_{15}O_5N$	237–238°	100	

(*Continued*)

Table I—*Continued*

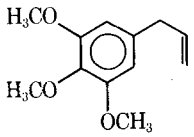
Number and Name	Structure	Molecular Formula	M.p., b.p./mm., $[\alpha]_D$	References	Other Natural Sources (References)
XLII Peyonine		$C_{16}H_{19}O_5N$	131–133.5°	98	

[a] Products identified by GLC–mass spectrometry in comparison with authentic preparations. [b] The presence of candicine was suggested (92) on the basis of TLC evidence but could not be substantiated in a later study (93); additional work is evidently needed to resolve this question.

electrolytically (115, 137) and by modified catalytic hydrogenation (117, 138–140).

Slotta (141) and Slotta and Heller (142) followed a different course for the synthesis of mescaline, which does not, however, seem to have attracted the attention of later workers. The appropriately substituted phenylpropionamide was prepared as indicated in Scheme II and finally subjected to Hoffmann degradation to give mescaline.

In another synthesis, Hahn and Wassmuth (116) and Hahn (143) obtained mescaline by reduction of the trimethoxyphenylacetaldehyde oxime which was prepared from the ozonization product of elemicine (Scheme III).



$\xrightarrow{O_3}$ $ArCH_2CHO$ $\longrightarrow$

$ArCH_2CH{=}NOH \longrightarrow Ar(CH_2)_2NH_2$ (I)

Scheme III

A successful and versatile method for the construction of the ethylamine side chain (144, 145) involves transformation of the substituted benzoic acid into the corresponding phenylacetamide *via* the Arndt–Eistert synthesis, followed by reduction with lithium aluminum hydride (Scheme IV). The use of appropriate amines in

$$ArCOOH \longrightarrow ArCOCl \longrightarrow ArCOCHN_2 \xrightarrow[(AgNO_3)]{NH_4OH}$$

$$ArCH_2CONH_2 \xrightarrow{LAH} Ar(CH_2)_2NH_2 \quad (I)$$

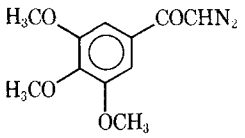
Scheme IV

place of ammonia, in the treatment of the diazoketone, affords *N*-substituted phenethylamines (144). This approach was recently used by Kapadia *et al.* (95) in the synthesis of 3-demethylmescaline (V), identified as a minor companion of mescaline in peyote. The suitably substituted phenylacetamide may also be obtained from the corresponding acetophenone *via* the Kindler modification of the Willgerodt reaction (Scheme V), which gives the intermediate phenylacetic acid derivative (146).

$$ArCOCH_3 \rightarrow ArCH_2COOH \rightarrow ArCH_2CONH_2 \rightarrow Ar(CH_2)_2NH_2$$

Scheme V

Perhaps of only historical interest is the mescaline synthesis of Hadáček *et al.* (147) in which the diazoketone group was transformed by a relatively long route to the ethylamine side chain (Scheme VI).



$\longrightarrow ArCH_2COOCH_3 \longrightarrow$

$ArCH_2COOH \longrightarrow ArCH_2COCHN_2 \longrightarrow Ar(CH_2)_2CONH_2 \longrightarrow$

$Ar(CH_2)_2NH_2$ (I)

Scheme VI

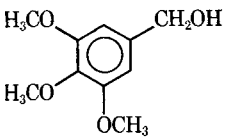
Mescaline was also synthesized, by Kindler and Peschke (139) and later by Amos (148), from the trimethoxybenzaldehyde through condensation with potassium cyanide, followed by acetylation of the formed mandelonitrile and catalytic hydrogenation (Scheme VII).

$ArCHO \rightarrow ArCH(OH)CN \rightarrow ArCH(OAc)CN \rightarrow$

$Ar(CH_2)_2NH_2$ (I)

Scheme VII

A convenient synthetic pathway of mescaline (Scheme VIII), which seems to be of general utility in the prepara-



$\longrightarrow ArCH_2Cl \longrightarrow$

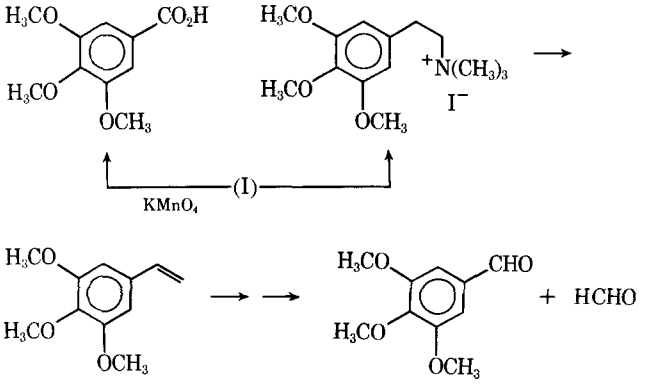
$ArCH_2CN \xrightarrow{LAH} Ar(CH_2)_2NH_2$ (I)

Scheme VIII

tion of analogous phenethylamines, involves use of the substituted benzyl alcohol which is transformed into the phenylacetonitrile, *via* the benzyl chloride, with final reduction using lithium aluminum hydride (149–154). Recently, Abdel-Rahman *et al.* (155) obtained excellent yields of mescaline by this route using thionyl chloride in the benzyl chloride preparation and potassium cyanide in aqueous formic acid or dimethyl sulfoxide in the subsequent stage. Benington *et al.* (123, 130, 145, 156) obtained the desirable benzyl chloride derivatives by chloromethylation (using aqueous formaldehyde and concentrated hydrochloric acid or chloromethyl ether in acetic acid) (130) of the appropriately substituted benzene derivative.

The recent review of Patel (40) on mescaline and its analogs gives a comprehensive listing of the various aromatic and *N*-substituted β-phenethylamines reported in the literature which have been obtained essentially by the foregoing methods (115, 137, 142, 157–162).

The most important degradative reactions of mescaline are those used in recent times in biosynthetic studies to determine the location of an introduced label. Cleavage of the ethylamine side chain (Scheme IX) may be



Scheme IX

effected by oxidation with potassium permanganate to give, for example, 3,4,5-trimethoxybenzoic acid from mescaline (163–167) and 4-acetoxybenzoic acid from *O*-acetylhordenine (166). Products comprising both carbon atoms of the side chain may also be obtained, as illustrated by Leete's (164) systematic degradation of mescaline. In the latter, the *N*,*N*-dimethyl methiodide derivative was subjected to Hoffmann degradation; the resulting styrene was oxidized to a diol with osmium tetroxide followed by cleavage with sodium metaperiodate, yielding 3,4,5-trimethoxybenzaldehyde and formaldehyde.

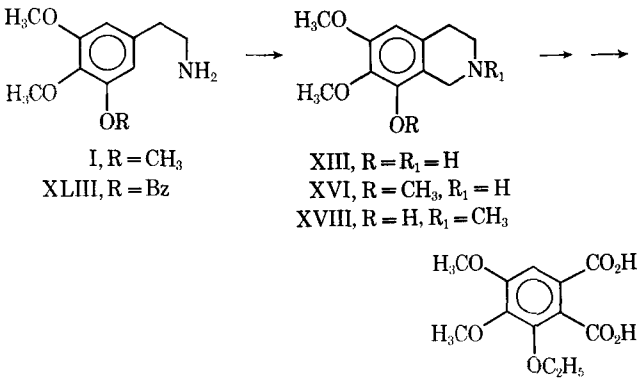
Several simple *N*-substituted derivatives of mescaline and 3-demethylmescaline are also known to exist in peyote. *N*-Methylmescaline (II) and *N*-acetylmescaline (IV) were identified by Späth and Bruck (83, 84) in 1937–1938; the first was synthesized (83) from mescaline by condensation with benzaldehyde followed by quaternarization with methyl iodide and hydrolysis. By using the technique of combined GLC–mass spectrometry, Kapadia and Fales (96) recently identified the *N*-formyl and *N*-acetyl derivatives of both mescaline (III and IV, respectively) and 3-demethylmescaline (VI and VII, respectively) in the nonbasic fractions of peyote. 3-Demethylmescaline (V) itself was more recently found to be a constituent of peyote, and its synthesis was realized as indicated before (95). 3,4-Dimethoxyphenethylamine (VIII) (≡homoveratyrlamine) was detected in trace amounts in peyote by Lundström and Agurell (101) using GLC.

Tyramine and Its Derivatives—The presence of tyramine (IX) and *N*-methyltyramine (X) in Cactaceae is an extremely rare event (7, 92). The first was detected by TLC and the second isolated by McLaughlin and Paul (92) from the phenolic fractions of peyote. Hordenine (XI) was isolated (91) from the phenolic fractions, and candicine (hordenine quaternary metho derivative) (XII) was detected by TLC (92) in the quaternary base fractions of peyote by the same workers (*cf.* 93). Both products are known to be constituents of other cacti (7, 168). In a recent report, Todd (169) showed that hordenine, unlike several other phenethylamine and tetrahydroisoquinoline constituents of peyote, occurs only in the roots.

Tetrahydroisoquinolines—The principal reported approaches for the preparation of the peyote tetrahydroisoquinoline alkaloids seem to have depended basically on the general Pictet–Spengler (170), Bischler–Napieralski (171), and Pomeranz–Fritsch (172) isoquinoline syntheses. In the first two types, the appropriately substituted (aromatic 3,4,5-trioxygenated) phenethylamine derivative is the starting material to be transferred into the desirable tetrahydroisoquinoline carrying a methylene or a $CH \cdot CH_3$ group at C-1. This additional unit is provided by reaction with an aldehyde in the first type of synthesis and by cyclization of the *N*-acyl derivative in the second type. In both, the unsymmetrically 3,4,5-trisubstituted phenethylamines are likely to follow either (or both) of two possible directions of cyclization. It remains, therefore, as an additional task, to ascertain the exact disposition of the resulting tetrahydroisoquinoline. This problem is not encountered in the syntheses depending on the Pomeranz–Fritsch method and its modifications (173), since the starting material, an *N*-benzylaminoacetaldehyde diethylacetal, can be so substituted as to give only one possible cyclization product. It is a fact that the structure elucidation of the principal tetrahydroisoquinolines of peyote—for which Späth must be credited—was realized largely by synthetic approaches, inspired by biogenetic considerations, rather than by degradative ones.

Anhalamine, Anhalidine, Anhalinine, and Anhalotine—Anhalamine (XIII) was first isolated from peyote by Kauder (65) and is estimated to exist in the cactus to the extent of 0.1% (64). Anhalidine (*N*-methylanhalamine) (XVIII) and anhalinine (*O*-methylanhalamine) (XVI) were discovered by Späth and Becke (80, 81) in peyote, where they exist as minor alkaloidal constituents; their yields are estimated to be 0.001 and 0.01%, respectively.

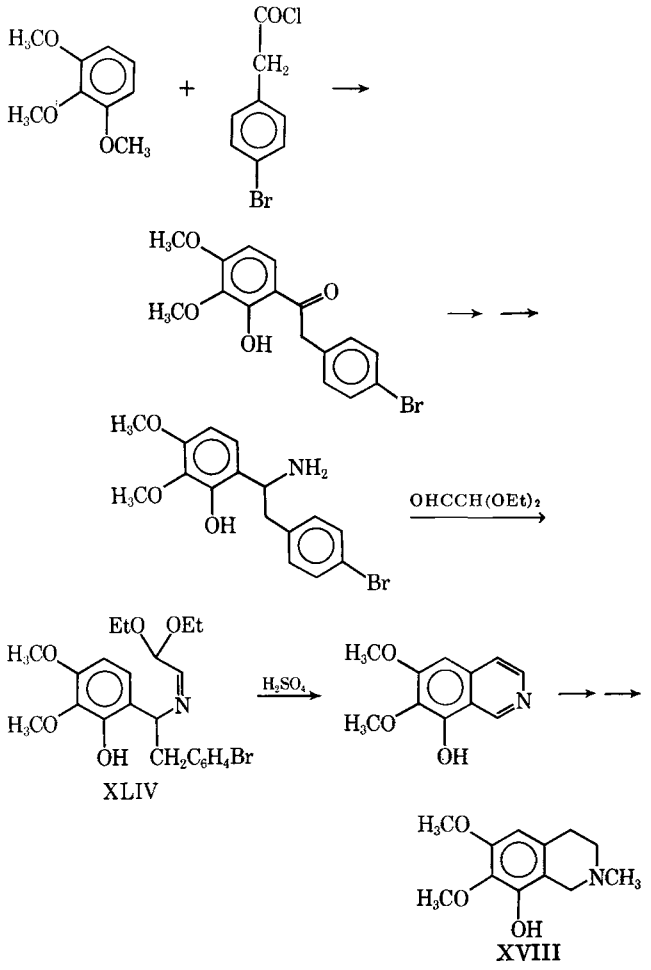
The first synthesis of anhalamine (XIII) was realized by Späth and Röder (90) through Pictet–Spengler condensation of 3,4-dimethoxy-5-benzyloxyphenethylamine (XLIII) with formaldehyde (Scheme X). The direction



Scheme X

of cyclization and, hence, location of the phenol group were determined by permanganate oxidation of the *O*,*N*-diethyl derivative which gave 4,5-dimethoxy-3-ethoxyphthalic acid (79). Anhalinine was also obtained by Späth and Becke (80) by a similar treatment of mescaline (I); anhalidine (XVIII) was obtained simply by treatment of anhalamine with methyl iodide and isolation from the complex reaction mixture (81). During a

Pomeranz–Fritsch reaction of the Schiff base XLIV, obtained as shown in Scheme XI, Inubushi and Fujitani

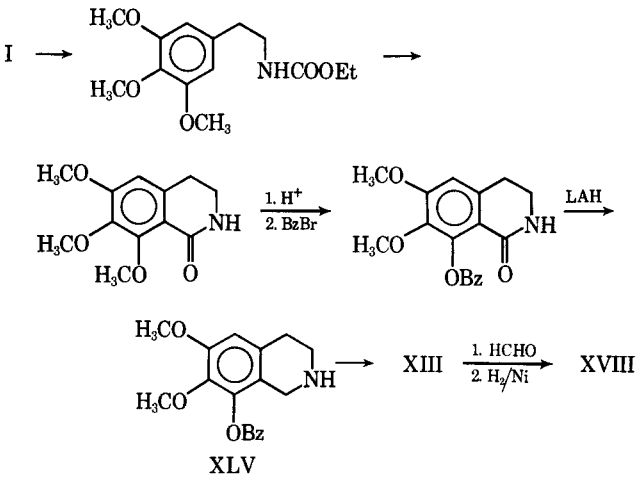


Scheme XI

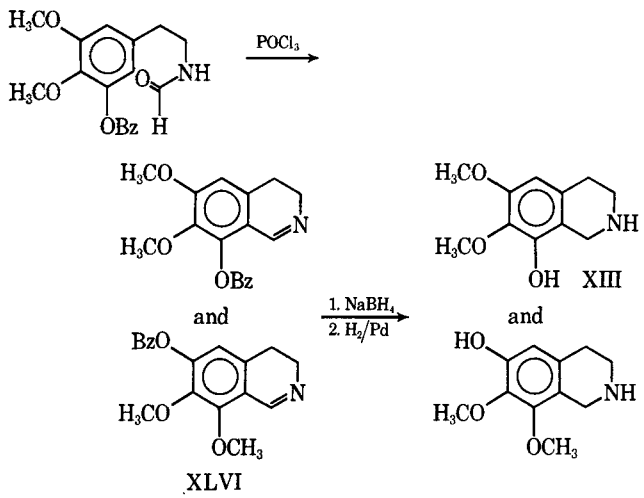
(125) found, unexpectedly, that the isoquinoline product had lost the C-1 substituent; they obtained anhalidine (XVIII) by subsequent quaternarization and reduction.

An interesting adaptation of the Pomeranz–Fritsch isoquinoline synthesis, originally developed by Bobbitt *et al.* (173) for the construction of tetrahydroisoquinolines by acid-catalyzed cyclization of the requisite *N*-benzylaminoacetaldehyde diethylacetal followed by hydrogenation, was recently used by Bobbitt and Dutta (174) in a novel synthesis of anhalamine, anhalinine, and anhalidine (Scheme XII).

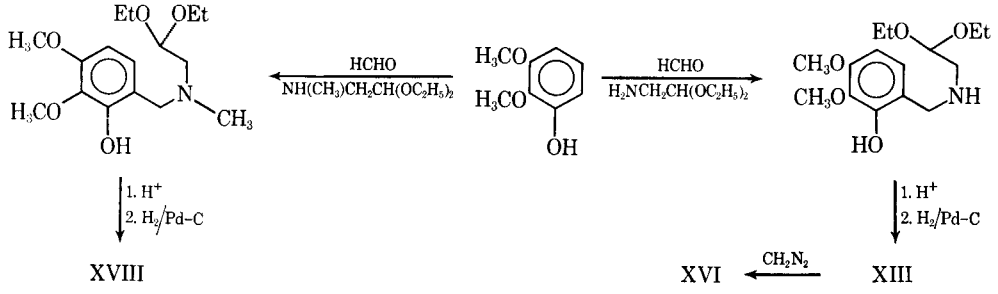
A relatively simple but less familiar method was earlier developed by Brossi *et al.* (175) for the construction of the heterocyclic ring by polyphosphoric acid cyclization of the urethan derivative obtained from the appropriate phenethylamine, followed by stages of reduction of the formed lactam system and introduction of the required substituents. Scheme XIII outlines the application of this route in the synthesis of anhalamine (XIII) and anhalidine (XVIII). The same sequence of reactions was also used by Kametani *et al.* (154) for the synthesis of the same compounds. In a later report, Brossi *et al.* (176) showed that the Bischler–Napieralski cyclization of *N*-formyl-3,4-dimethoxy-5-benzyloxyphenethylamine (Scheme XIV) occurs in both possible directions—unlike the 5-acetoxy analog (XLVII)—to give a mixture of two dihydroisoquinolines (XLVI).



Scheme XIII

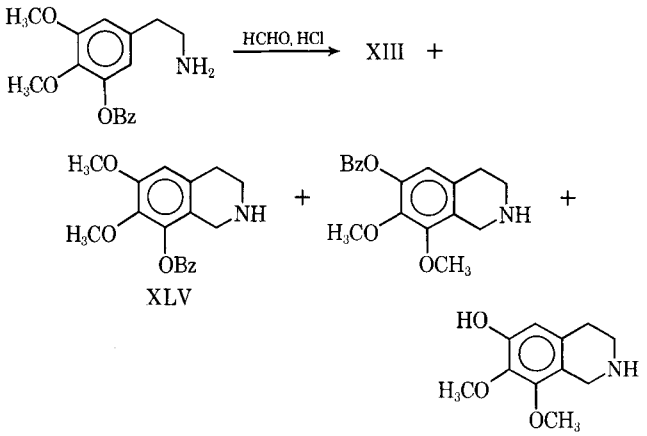


Scheme XIV



Scheme XII

Reduction and hydrogenolysis finally afforded a binary mixture from which anhalamine (XIII) was isolated. A Pictet–Spengler reaction of 3,4-dimethoxy-5-benzyloxyphenethylamine with formaldehyde was found by Brossi *et al.* (176) also to afford products, resulting from cyclization in both directions, including anhalamine (Scheme XV).

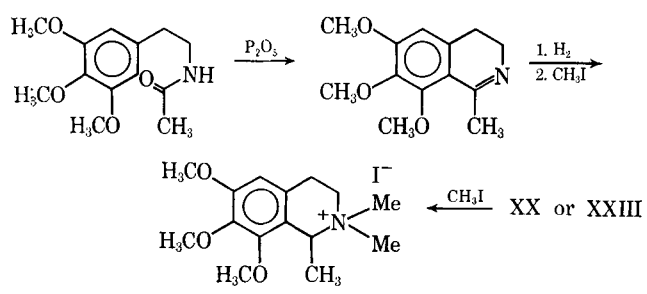


Scheme XV

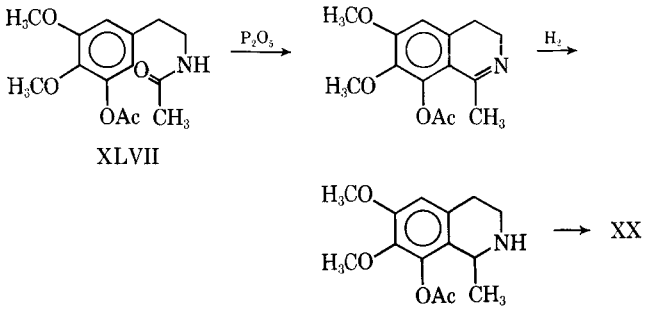
Anhalotine (XIX) was isolated from the fraction of quaternary bases of peyote by Kapadia *et al.* (93) and, as the iodide, was shown to be identical with anhalidine methiodide. *N*-Formylanhalamine (XIV), *N*-acetylanhalamine (XV), and *N*-formylanhalinine (XVII) were detected by combined GLC–mass spectrometry in the nonbasic fractions of peyote (96). Synthesis of the formyl derivatives (XIV and XVII) was achieved by treatment of the corresponding base with triethylamine and formic acid, a method recommended by Durand *et al.* (177).

Degradation of the heterocyclic system in tetrahydroisoquinolines was previously used in structure determination work and is currently a means to locate the label in biosynthetic studies. An example is the relatively recent degradation of anhalamine (178), as the *O,N*-dimethyl derivative methiodide, to 3,4,5-trimethoxyphthalic anhydride (loss of C-3 of anhalamine), using the conditions described much earlier by Späth and Becke (179).

Anhalonidine, Pellotine, and Peyotine—Anhalonidine (XX) was first isolated by Heffter (61) who found as much as 5% of it in peyote. *O*-Methyl-*d*-anhalonidine (XXII), an optically active alkaloid, was discovered in very small amounts by Späth and Bruck (85). Pellotine (XXIII) was discovered also by Heffter (60) in 0.74% yield and later by Kauder (65). Späth and Kesztler (89) prepared the optically active forms of pellotine



Scheme XVI

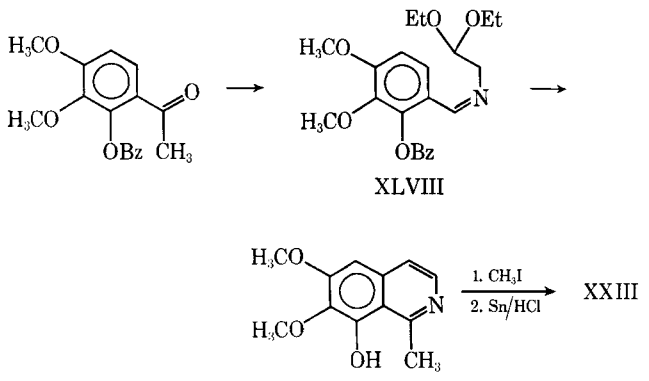


Scheme XVII

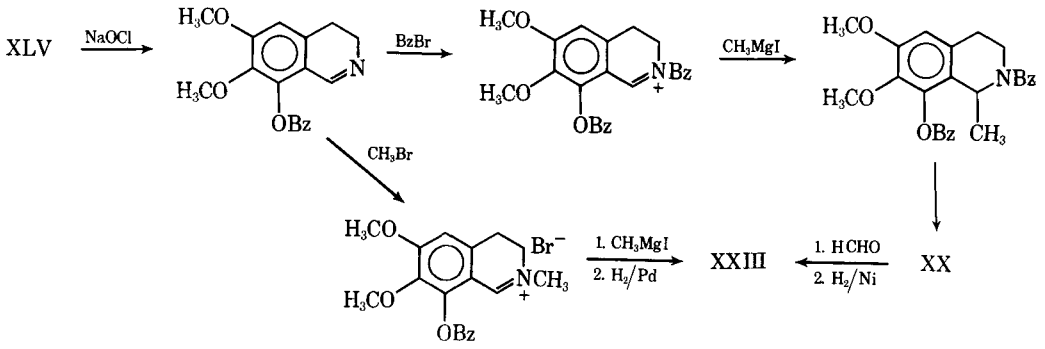
and, considering the ease with which they racemize, these authors thought that the natural product might be optically active and that racemization occurs by aging of the drug or during the process of isolation.

Anhalonidine and pellotine were the first peyote tetrahydroisoquinoline alkaloids to be synthesized—as early as 1921 by Späth (74). The synthesis was realized employing a Bischler–Napieralski condensation of *N*-acetylmescaline and leading, as indicated in Scheme XVI, to a quaternary iodide which was identical with *O*-methylpellotine methiodide. Anhalonidine (XX) was correlated to pellotine (XXIII) by complete methylation of both to the same product. In an independent synthesis of *rac.* anhalonidine, Späth (76) followed the same route using *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine after a temporary protection of the phenol group by acetylation (XLVII) as shown in Scheme XVII. The direction of cyclization and, hence, location of the phenol group were determined (86) by permanganate oxidation of the *O*-ethyl derivative of pellotine, which gave the known 4,5-dimethoxy-3-ethoxyphthalic acid; this was also confirmed by an analytical approach (82).

In another synthesis of pellotine (XXIII), Späth and Becke (78) subjected the Schiff base (XLVIII), obtained by condensation of 2-benzyloxy-3,4-dimethoxyacetophenone with aminoacetaldehyde diethylacetal, to Pomeranz–Fritsch cyclization using sulfuric acid (Scheme XVIII). The resulting isoquinoline was quaternarized and finally reduced to *rac.* pellotine. More recently, Brossi *et al.* (175) used the urethan derivative of mescaline (Scheme XIII) in a new synthesis of *rac.* anhalonidine and *rac.* pellotine *via* the 6,7-dimethoxy-8-benzyloxytetrahydroisoquinoline intermediate (XLV) as outlined in Scheme XIX. In a later report, Brossi *et al.* (176) obtained, in the Bischler–Napieralski cyclodehydration of *N*-formyl-3,4-dimethoxy-5-benzyloxyphenethyla-

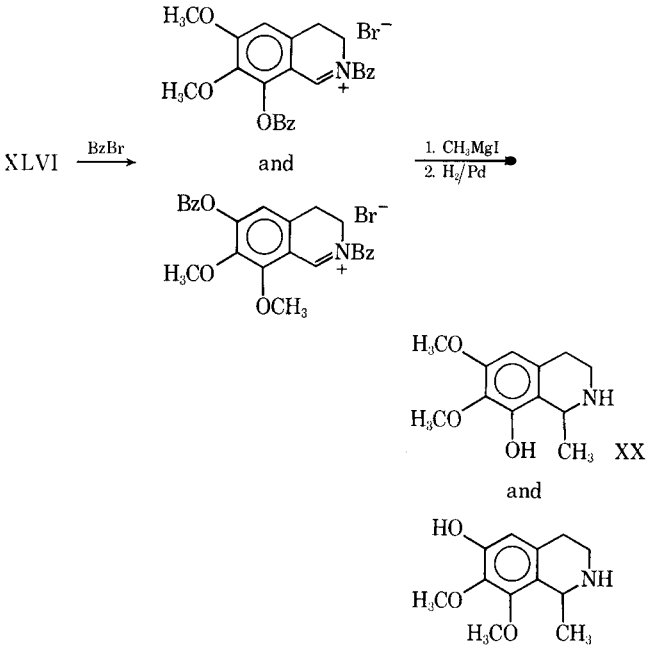


Scheme XVIII



Scheme XIX

mine, a mixture of the two possible dihydroisoquinolines (XLVI)—unlike the acetoxy counterpart (XLVII) (76, 86)—which was quaternarized and treated with methyl Grignard reagent to lead eventually to a mixture from which *rac.* anhalonidine (XX) was separated (Scheme XX).

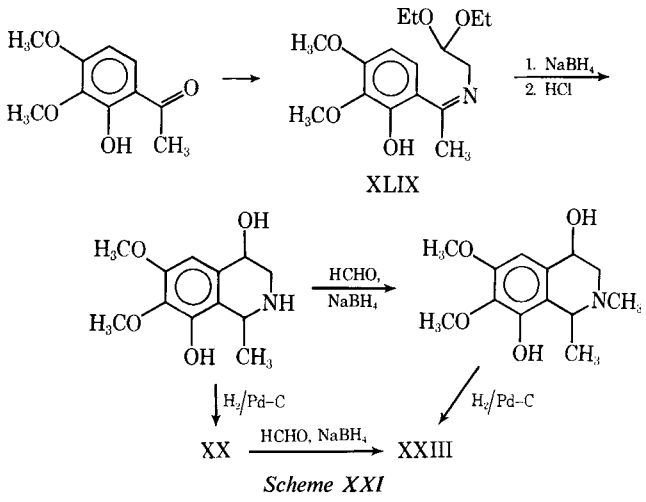


Scheme XX

Very recently, Takido *et al.* (180) made use of Bobbitt's modification (173) of the Pomeranz–Fritsch isoquinoline synthesis. The requisite Schiff base (XLIX), obtained from reaction of the appropriate acetophenone with aminoacetaldehyde diethylacetal, was cyclized to give *rac.* anhalonidine and *rac.* pellotine (Scheme XXI).

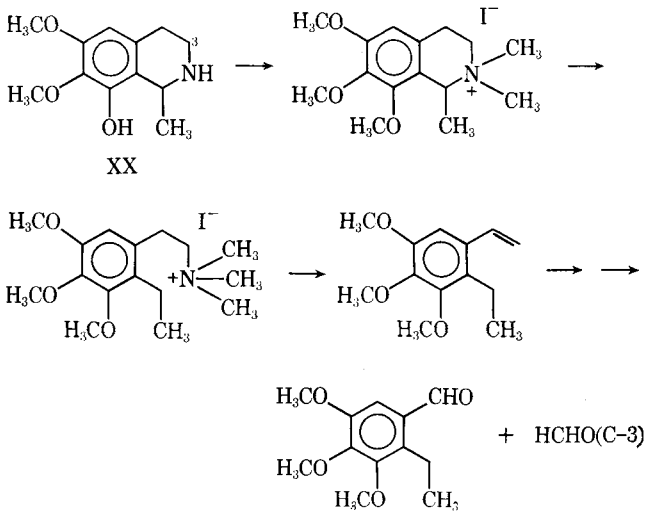
Peyotine (XXV) was recently isolated by Kapadia *et al.* (93) by fractionation of the quaternary bases obtained from peyote; it was shown, as the iodide, to be identical with pellotine methiodide. By combined GLC–mass spectrometry technique, Kapadia and Fales (96) proved the presence of *N*-formylanhalonidine (XXI) and *N*-formyl-*O*-methylanhalonidine (XXIV) in the non-basic fractions of peyote.

A useful degradative sequence of anhalonidine, reported by Leete (164), consists in reductive cleavage of the heterocyclic system in the methiodide of *O*-methyl derivative followed by quaternarization and Hoffmann degradation of the product (Scheme XXII). The resulting styrene derivative was oxidized to a glycol with osmium tetroxide and finally cleaved with sodium metaperiodate, giving 2-ethyl-3,4,5-trimethoxybenzaldehyde and formaldehyde. By use of this systematic degradation, it was possible to ascertain the location of the label



Scheme XXI

at C-3 in anhalonidine resulting from feeding of tyrosine-2-^{14}C to peyote (164). The Kuhn–Roth oxidative degradation of such alkaloids carrying a methyl group on C-1 is also often resorted to as a diagnosis of the label present

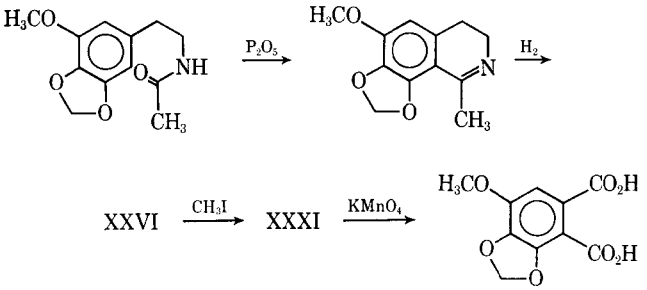


Scheme XXII

in this part of the molecule giving rise to acetic acid (100, 181, 182).

Anhalonine, Lophophorine, Peyophorine, and Lophotine—Anhalonine (XXVI) (as the *l*-form) was first isolated by Lewin (52–54) and was estimated (61) to occur to the extent of about 3% in peyote. Lophophorine (XXIX), as the *l*-form, was found by Heffter (61) to occur in peyote in 0.5% yield. Späth and Kesztler (88) resolved the synthetic racemic mixture of anhalonine (87) and showed that natural lophophorine results by *N*-methylation of *l*-anhalonine. Peyophorine (XXX) was discovered fairly recently by Kapadia and Fales (94) as a minor constituent of peyote. It was prepared (94) by *N*-ethylation of anhalonine with diethyl sulfate and by lithium aluminum hydride reduction of *N*-acetylanhalonine (XXVIII); the latter is itself a natural constituent of peyote (94). This is the only *N*-ethylated alkaloid so far found in peyote, and its presence is remarkable in view of the extreme rarity of such moiety in nature (183). *N*-Formylanhalonine (XXVII) is another minor constituent of peyote; it was identified by combined GLC–mass spectrometry in the nonbasic fractions (96).

The synthesis of *rac.* anhalonine (XXVI) and *rac.* lophophorine (XXIX) was realized by Späth and Gangl (87) by a Bischler–Napieralski cyclodehydration of *N*-acetylhomomyristicylamine followed by reduction and quaternarization (Scheme XXIII). The structure was

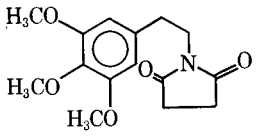


Scheme XXIII

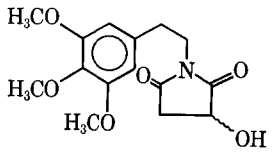
later confirmed by oxidation to 3,4-methylenedioxy-5-methoxyphthalic acid (80). The quaternary base (XXXI), corresponding to anhalonine and lophophorine and synthesized in 1923 (87), was quite recently shown by Kapadia *et al.* (93) to be itself a constituent of peyote; it was named lophotine.

Alkaloidal Amides—Very little attention has been given to the study of the nonbasic fractions of the alkaloid-bearing Cactaceae (and, in fact, most other alkaloid-bearing plants). This is testified to by the fact that only peyote has been found to contain *N*-formyl derivatives of its own alkaloids. It is also unlikely that *N*-acetyl alkaloidal derivatives have been found in cacti other than peyote. A discussion of these simple amide derivatives of the phenethylamine and tetrahydroisoquinoline constituents of peyote has already been given under the appropriate titles. The probable biogenetic implications of such one- and two-carbon units are discussed later.

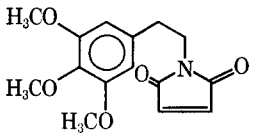
The recent GLC–mass spectrometric studies by Kapadia and Fales (96) showed that the nonbasic fractions of peyote contain more complex amide derivatives, the nature of which has been elucidated from mass spectral considerations and by comparison with synthetic materials. These include the succinimide (XXXII), malimide (XXXIII), and maleimide (XXXIV) derivatives of mescaline, which were synthesized simply by sublimation of the mescaline salts of the corresponding acids. Very recently, Kapadia *et al.* (97) characterized three additional products in the same nonbasic fractions.



XXXII

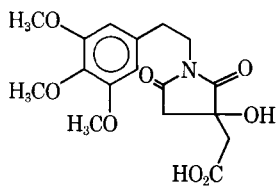


XXXIII

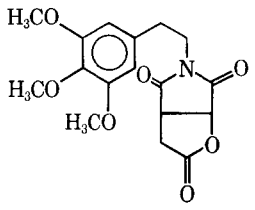


XXXIV

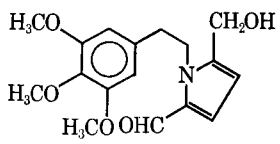
These were the citrimide (XXXV), the isocitrimide lactone (XXXVI), and the 2-formyl-5-hydroxymethylpyrrole derivative (XXXVII) related to mescaline. The structures of the first two products were evidenced by mass spectral data and supported by synthesis from mescaline through treatment with citric acid anhydride and isocitric acid lactone, respectively. The constitution of the isolated XXXVII, designated peyoglunal, was postulated from IR, NMR, and mass spectral evidence; its synthesis was attempted.[5]



XXXV



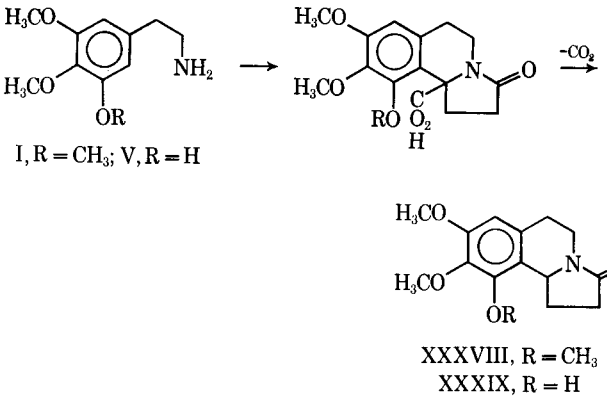
XXXVI



XXXVII

The nonbasic fractions of peyote were also found (96) to contain two structurally interesting lactams, XXXVIII and XXXIX, related to mescaline (I) and 3-demethylmescaline (V), which were named mescalotam and peyoglutam, respectively. Their constitutions, prompted by biogenetic considerations, were proven by synthesis from the corresponding bases by treatment with α-ketoglutaric acid followed by decarboxylation (Scheme XXIV). The direction of cyclization in

[5] While this manuscript was in preparation, a product containing XXXVII (GLC–mass spectrometry and other spectral evidence) was obtained by condensation of 2,5-dimethoxy-5-hydroxymethyltetrahydrofurfuraldehyde dimethyl acetal with mescaline. Treatment of desformyl-XXXVII under Riemer-Tiemann conditions also furnished XXXVII (97).



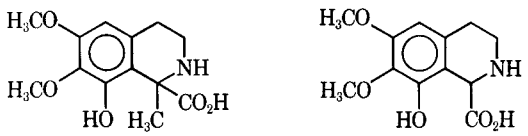
I, R = CH_3; V, R = H

XXXVIII, R = CH_3
XXXIX, R = H

Scheme XXIV

XXXIX was established by NMR evidence (96, 184).

Amino Acids—There does not seem to be any published data regarding the general proteinic amino acid content of peyote, significant and relevant to the biosynthetic processes as they may be. The presence of proline in the amino acid fraction was, however, demonstrated lately by Kapadia *et al.* (185). Among the complex composition of this fraction, containing at least 12 products, two nonproteinic amino acids, named peyoruvic and peyoxylic acids, were characterized by GLC–mass spectrometry and shown to have Structures XL and XLI, respectively (99, 100). Their presence was anticipated on biogenetic grounds, and their synthesis was realized by condensation of 3-demethylmescaline (V) with pyruvic acid and glyoxylic acid, respectively, under physiological conditions.

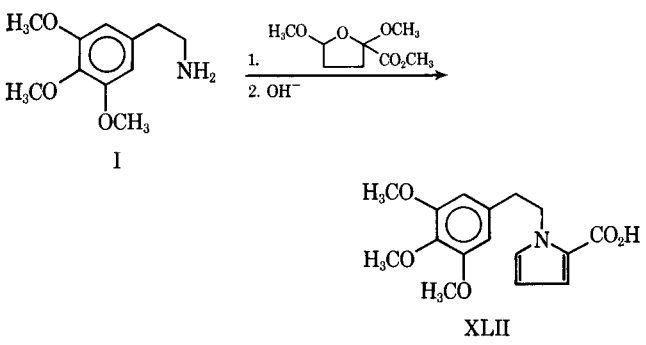


XL XLI

Peyonine (XLII) is another minor constituent of peyote which was recently isolated (186) from the nonbasic fractions. Its structure was determined (98) from spectral evidence and through synthesis by treatment of mescaline with methyl 2,5-dimethoxytetrahydro-2-furoate followed by saponification (Scheme XXV). Peyonine appears to be the first simple pyrrole-2-carboxylic acid derivative isolated from a natural source.

ANALYTICAL METHODS

Several reagents have been used in the detection and identification of mescaline and related compounds (187–192). Some are particularly useful in working with peyote alkaloid mixtures, for example, on thin-layer chromatoplates, such as dansyl chloride for nonphenolic products and tetrazotized benzidine (92) and tetrazotized di-*O*-anisidine (93) for detection and identification of phenolic ones. Also, a number of paper (193–198), thin-layer (92, 105, 169, 199–203), and gas (101, 105, 204–207) chromatographic methods have been reported for the separation and identification of mescaline and other cactus alkaloids. Kapadia and Rao (206) observed a relationship between the retention time and structure of peyote alkaloids and related bases.



I

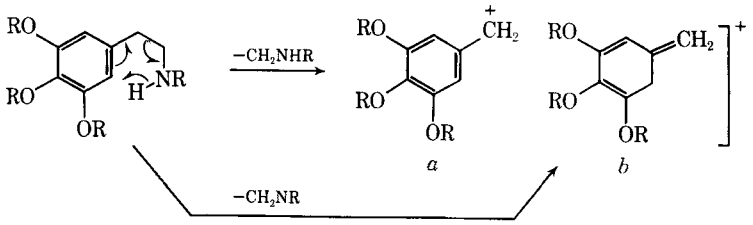
XLII

Scheme XXV

Several methods have been recommended for the quantitation of mescaline in biological fluids. They include colorimetric methods depending on measurement of the color formed by interaction with picric acid (208, 209), bromocresol purple (210), and *p*-nitrophenyldiazonium chloride (211, 212). In a fluorometric method (213), mescaline is transformed into a fluorescent isoquinoline derivative; another method (214) is based on the characteristic oscillographic behavior of mescaline in acid and alkaline solutions.

Mass Spectra of Peyote Alkaloids—The spectra of the phenethylamines and tetrahydroisoquinolines invariably exhibit molecular ions with very low intensities. The principal fragmentations result by cleavage of the β-bonds relative to the aromatic ring. The phenethylamines [such as I (215), V (95), and VIII (205)] and their *N*-alkyl-substituted derivatives thus give the benzyl ions *a* (which may also have tropylium structures) and, through transfer of a hydrogen atom from the departing fragment (arrows in Scheme XXVI), the equally important (and often stronger) ions *b*. In tertiary amines, such as peyonine (XLII), the latter type of breakdown obviously does not take place, and the predominant fragment ion is due to Species *a* (98). The spectra are complicated further only by combinations of losses from the aromatic substituent groups. The *N*-formylphenethylamines [III (216)] and *N*-acetylphenethylamines [VII (216)], as well as the related cyclic imide derivatives (XXXII–XXXIV) (96), give as principal fragmentation products ions of Species *a* in addition to styrene ions (*c*), resulting by scission of the C—N bond of the side chain with transfer of hydrogen (as depicted by the arrows in Scheme XXVII) in a McLafferty rearrangement.

The primary reactions exhibited by the tetrahydroisoquinolines [typified by XIII, XV, XVII, XVIII, XXIV, XXIX (216), and XXX (94)] involve expulsion of the C-1 substituent (217), giving the highly stabilized dihydroisoquinolinium ion Species *d* (Scheme XXVIII). The strongest peaks in the spectra are due to ions (Species *e*) formed by collapse of the heterocyclic system through the retro-Diels–Alder reaction. This type of breakdown does not seem to take place appreciably in those products carrying a methyl group on C-1, probably because the elimination of this substituent is more favored and becomes by far the most important reaction. Mescalotam (XXXVIII) and peyoglutam (XXXIX) (96) exhibit relatively strong M^+ ions and ones resulting by loss of the hydrogen atom on C-1 of the tetrahydroisoquinoline system. Fragmentation of the lactam

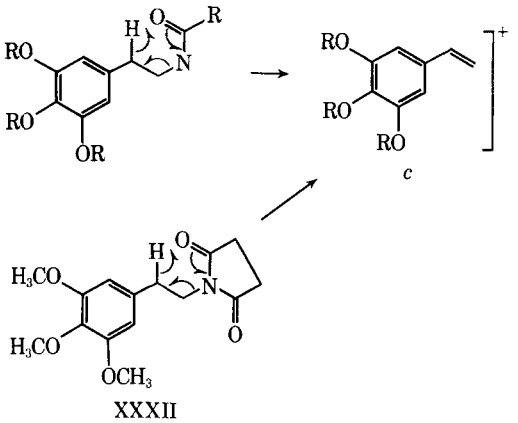


Scheme XXVI

ring by loss of CH_2CH_2CO gives ions with appreciable abundance which may have Structure *f* (Scheme XXIX).

BIOGENESIS OF PEYOTE ALKALOIDS

Phenethylamines—As with the general interest in peyote and its constituents, studies on the biogenetic origin of mescaline (I) and its companion alkaloids, using labeled substrates, were initiated during the late 1950's. Prior to this, Reti (7) expressed certain hypothetical views—fairly reasonable as they later proved—which were unsubstantiated by experimental evidence



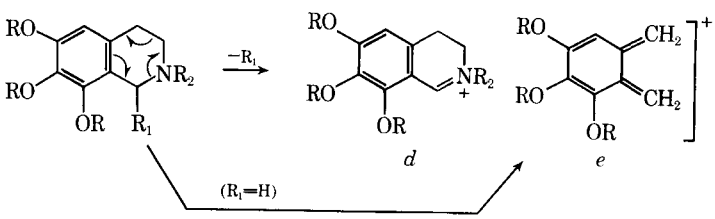
XXXII

Scheme XXVII

and largely based on Guggenheim's fundamental views regarding natural amines (218). It was already a matter of general agreement that the natural aromatic amino acids, such as phenylalanine (L), tyrosine (LI), and dopa (LII) must be biogenetically related to the phenethylamine and tetrahydroisoquinoline alkaloids. Reti visualized the transformations as "simple" processes of decarboxylation, oxidation, *O*- and *N*-methylation, and ring closure with formaldehyde or acetaldehyde equivalents. He thought that tyrosine, which "must" be present in peyote,[6] undergoes oxidation by tyrosinase to give dopa, which may then successively suffer decarboxylation to dopamine (LIII), oxygenation to 3,4,5-trihydroxy-β-phenethylamine (LIV), and *O*-methylation to mescaline (I). Scheme XXX shows these transformations; the postulated (7) stages, which in recent years became established by convincing experimental evidence (*vide infra*), are indicated by heavy arrows.

Reti (7) also offered a possible pathway for hordenine (XI) and candicine (XII) (of which the former is now proven to be a natural constituent of peyote), depending on the initial decarboxylation of tyrosine to tyramine (IX) followed—or perhaps preceded—by methylation. The source of the *O*- and *N*-methyl groups as well as the CH_2 in the methylenedioxy groups was assumed to be formaldehyde. It was shown shortly later, by other workers using tracer techniques, that the *N*-methyl groups of *N*-methyltyramine (X) and hordenine, found in germinating barley, originate from the *S*-methyl group of methionine (219–221) and also from formate (220, 222). In fact, several studies carried out predominantly during the 1950's showed that the methyl group of methionine serves as the source of *O*- and *N*-methyl groups of many alkaloids and that it may also be the origin of the carbon bridge in methylenedioxy groups (219). The extensive studies of the Marion group (220–226) on the biogenesis of hordenine and *N*-methyltyramine in barley rootlets showed that phenylalanine, tyrosine, and tyramine[7] are direct precursors.

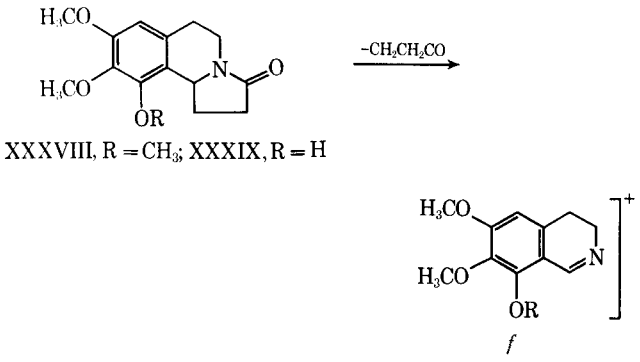
Working with peyote, Leete reported in 1959 (163) that the feeding of 2-^{14}C-DL-tyrosine gave mescaline in which all the activity was located on the α-carbon atom; this constituted the first experimental evidence that tyrosine is a precursor in the pathway to mescaline (I). It was only in 1966 that the next report, concerning the biogenesis of mescaline, was made by Leete (164) and later by McLaughlin and Paul (166) who had anticipated the existence of simple *N*-methylated tyramines on biogenetic grounds and actually isolated hordenine (XI) and *N*-methyltyramine (X) and detected tyramine (IX) itself (91, 92). Tyrosine (LI), which may result



Scheme XXVIII

[6] Reti (7) also assumed the presence of tyrosine in all cacti since the darkening of cut stems, preceded by a red phase, is characteristic for the whole family, probably due to advanced oxidations involving tyrosinase. Tyrosine and tyrosinase have been found in some cacti.

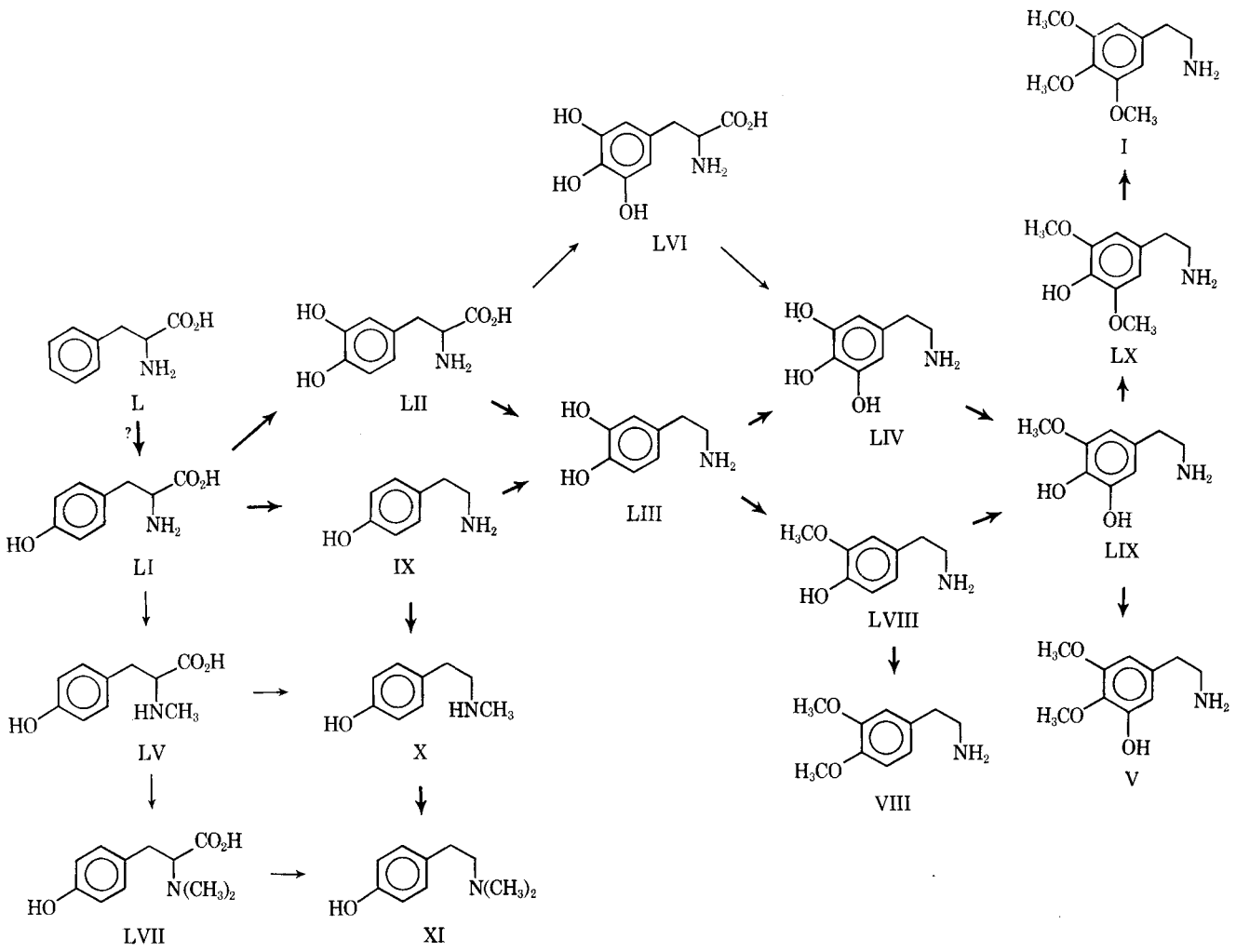
[7] The enzyme-controlled *N*-methylations of tyramine in barley were studied by Mudd (227, 228) who isolated a methionine-activating enzyme which converts methionine to *S*-adenosylmethionine, the actual methylating agent; he also purified the enzyme tyramine methylpherase (229).



Scheme XXIX

from phenylalanine (L), was regarded as the common intermediate leading to the production of tyramine and its *N*-methyl analogs by reactions involving decarboxylation and *N*-methylation, and also to mescaline by a different pathway involving decarboxylation and nuclear oxygenation. In these transformations, one may envisage two possible routes in each case: (*a*) decarboxylation occurs early in the biogenetic sequence, and (*b*) this process is preceded by *N*-methylations or ring oxygenation (Scheme XXX).

In his classical treatise, Guggenheim (218) held a view which was more in favor of the second alternative. In this proposal, he depended on the fact that 3,4-dihydroxyphenylalanine (dopa) (LII) and *N*-methyltyrosine (LV) are frequently encountered in nature; by extrapolation, 3,4,5-trihydroxyphenylalanine (LVI) and *N*,*N*-dimethyltyrosine (LVII) might also be expected to exist. However, McLaughlin and Paul (166), after administering α-^{14}C-tyrosine and α-^{14}C-tyramine to peyote, obtained incorporations which indicated that tyramine is a more direct precursor of mescaline and hordenine than tyrosine and that tyrosine is converted to tyramine. These findings seemed to offer more support to the alternative pathway (*a*). Rosenberg *et al.* (167) subsequently showed by similar feeding experiments that both dopa and dopamine are excellently incorporated in the biosynthesis of mescaline. Although quite expectable, they showed that also phenylalanine serves as a precursor for mescaline[8] and that it is converted in peyote into tyrosine. The latter conclusion, however, was not agreeable to Leete (164) who observed negligible incorporation of phenylalanine and suggested that peyote lacks the enzymes to convert it to tyrosine. However, the overall results clearly supported the earlier



Scheme XXX

[8] The low incorporation which they observed (167) is reasonable in view of the involvement of this amino acid in other biological roles; however, see *Reference 164*.

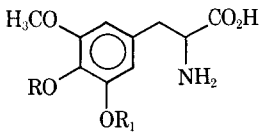
postulations of Reti (7) but indicated that two pathways are open from tyrosine to mescaline *via* dopamine,[9] with one proceeding through dopa and the other through tyramine. In fact, quantitative comparisons made by Rosenberg *et al.* (167) showed that tyramine and dopa appear to be about equally efficient as precursors to mescaline. Similar findings were obtained almost at the same time by Agurell *et al.* (165). However, they reported somewhat different incorporation values and demonstrated that the *O*-methyl groups of mescaline may be derived from methionine. The enzymatic transformations of tyrosine to dopa and then to dopamine are well established in plant systems (172), and the specific enzymes involved (a tyrosinase and a dopa decarboxylase) may be quite different from those that transform tyramine into dopamine and tyrosine into tyramine, respectively (167).

In more recent studies, Lundström and Agurell (178) showed that tyramine, dopamine, and 3,4,5-trihydroxyphenethylamine (LIV) (the latter so far has not been encountered in nature) are all efficient progenitors of mescaline on account of the observed high incorporations of the α-^{14}C-labeled materials. They also showed that phenethylamine and its 4-methoxy and 3,4-dimethoxy[10] (VIII)—a natural constituent of peyote (101)—derivatives are not significant precursors. These findings extend the previously established sequences a step further by showing that 3,4,5-trihydroxyphenethylamine[11] (LIV) may be a stage that follows dopamine *en route* to mescaline. 3,4-Dimethoxyphenethylamine (VIII) seems, however, to be a deadend product resulting from dopamine without being further metabolized to mescaline or to the tetrahydroisoquinoline congeners (*vide infra*).

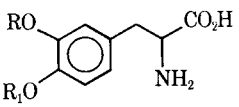
An alternative pathway from dopamine, namely that proceeding *via* the partially *O*-methylated derivative, was considered by both the Agurell (102, 233) and Paul (232, 234, 235) groups. Indeed, 3-methoxy-4-hydroxyphenethylamine (LVIII) was shown to be an important contributor to the mescaline of peyote; the 3-hydroxy-4-methoxy isomer, in contrast, was not significantly incorporated. Of the several possible pathways from 3-methoxy-4-hydroxyphenethylamine (LVIII) and 3,4,5-trihydroxyphenethylamine (LIV), the work of these two groups, using [α-^{14}C] (232–235) labeled compounds, afforded a definite choice. Whereas 3,5-dihydroxy-4-methoxyphenethylamine was hardly incorporated (233), the 3-methoxy-4,5-dihydroxy[12] analog (LIX) served as an efficient precursor (232, 233).

The subsequent metabolic stage beyond intermediate LIX *en route* to mescaline was shown to result by methylation of the *meta-* rather than the *para*-hydroxyl group. Thus, 3,5-dimethoxy-4-hydroxyphenethylamine (LX) was utilized to a higher degree, suggesting it as the immediate precursor to mescaline (232, 233, 235). 3,4-Dimethoxy-5-hydroxyphenethylamine (V), which is a constituent of peyote (95, 102), was, however, not significantly incorporated (233, 234). A complete biogenetic scheme is thus available from phenylalanine to mescaline (Scheme XXX, the heavy arrows indicate verified transformations). It will be noted that *meta*-methylations occur along the mescaline pathway from LIII, LIV and from LIX. *para*-Methylations, which also occur to give the natural constituents VIII and V, seem, however, to be the reactions involved in the pathways leading to the tetrahydroisoquinolines.

Kapadia *et al.* (185) carried out a special search by combined GLC–mass spectrometry in the amino acid fraction of peyote for products constituted as LXI–LXV, and they obtained no evidence[13] for their presence. This is significant since it may indicate that the carboxyl group probably does not survive beyond the stage of dopa in the sequence leading to the more complex alkaloids of the cactus.



LXI, $R = R_1 = CH_3$
LXII, $R = CH_3$, $R_1 = H$
LXIII, $R = H$, $R_1 = CH_3$



LXIV, $R = H$, $R_1 = CH_3$
LXV, $R = CH_3$, $R_1 = H$

Recent studies conducted with another mescaline-producing cactus, *Trichocereus pachanoi* Br. & R., revealed the presence of LVIII and LX (102); these products have so far not been encountered in peyote. Feeding experiments with labeled models (233) suggested that mescaline may be formed in this plant by the same biogenetic sequence operative in peyote (Scheme XXX). The comparatively much higher incorporations of the intermediates IX and LIV observed in *T. pachanoi* may tend to indicate that the LI → IX → LIII → LIV → LIX pathway is a better contributor to mescaline in this source than the alternative pathway(s).

Tetrahydroisoquinolines—In his review on cactus alkaloids, Reti (7) noted that the tetrahydroisoquinoline and phenethylamine alkaloids may be biogenetically related to each other on account of structural similarities and co-occurrence in plant sources. The same was suggested much earlier by Pictet and Spengler (238) who synthesized some simple tetrahydroisoquinolines by reacting the corresponding phenethylamines with formaldehyde; they suggested that a similar type of reaction may be operative in plant tissue. Späth (74) also expressed the same opinion during his earliest studies on peyote constituents. Specifically, formaldehyde and acetaldehyde were regarded as the possible biological sources of the one- and two-carbon units at C-1 of the natural tetrahydroisoquinolines of peyote. Schöpf (239, 240) and Schöpf and Bayerle (241) thought

[9] Dopamine (LIII) has not been encountered, as yet, in peyote; it is, however, a constituent of another cactus, *Carnegia gigantea* (236).

[10] 3,4-Dimethoxyphenethylamine (VIII) was contemporarily suggested by Paul *et al.* (231) as a direct precursor on account of the high incorporation percentage; later, Rosenberg *et al.* (232) revised this judgment and dismissed this product as an actual participant.

[11] The incorporation percentage of this compound reported by Paul *et al.* (231) was comparable to that given by Lundström and Agurell (178, 233), although both groups differed on its significance.

[12] In this connection, Benington and Morin (237) showed that enzymatic oxidation of LVIII in fact yielded LIX while VIII served as a poor substrate.

[13] It would still, however, be desirable to find out if amino acids corresponding to mono-*O*-methylated analogs of LIV (such as LIX) and LVI are present in the natural mixture.

that only the phenethylamines carrying free hydroxyl groups, which would activate the hydrogen atom involved in the ring closure, are capable of such condensation—a Mannich-type reaction which was demonstrated *in vitro* and shown to proceed at room temperature and in nearly neutral media. Hahn and Schales (242, 243), however, proved that other methoxy and methylenedioxyphenethylamines are also capable of condensation, although to a lesser extent. On the basis of other *in vitro* experiments, Hahn and his coworkers (244–247) suggested that similar condensation with α-keto acids, followed by decarboxylation, may lead in nature to the various tetrahydroisoquinolines.

Battersby and Garratt (182) were the first to show, by feeding experiments, that the tetrahydroisoquinolines of peyote, exemplified by pellotine, may originate from tyrosine. The finding was subsequently confirmed by feeding tyrosine-α-^{14}C to peyote and isolation of both radioactive anhalonidine (XX), in which all the activity was shown by degradation to reside in C-3 (164, 181), and lophophorine (XXIX) (181). It seemed reasonable that the phenethylamine portion of the tetrahydroisoquinolines would be biosynthesized by routes similar (or, in some stages, identical) to those that lead to mescaline. Lundström and Agurell (178, 233) found that tyramine and dopamine are efficiently incorporated into anhalamine (XIII), and Battersby *et al.* (181) showed the latter precursor to be a step on the pathway toward pellotine (XXIII). Available evidence (up to the time of writing this review) seems to indicate that beyond the stage of dopamine, different pathways exist for the different tetrahydroisoquinoline alkaloids. This may be the case since 3,4,5-trihydroxyphenethylamine (LIV), for example, was well incorporated into anhalamine (178, 233) but hardly in pellotine and anhalonidine (235). 3-Methoxy-4-hydroxyphenethylamine (LVIII) was an insignificant contributor for anhalonine (XXVI) (233) but a better one for pellotine[14] (248), anhalonidine (235), and anhalamine (233, 235). 3-Methoxy-4,5-dihydroxyphenethylamine (LIX), which served as an efficient precursor for anhalamine (233), was poorly incorporated into pellotine (248) and anhalonine (233). Further, 3,4-dimethoxy-5-hydroxyphenethylamine (V) was found to be well incorporated into anhalamine (233, 235) and anhalonidine (235) but insignificantly into pellotine (235, 248) and anhalonine (233). Mescaline itself was also considered as a possible precursor but found to be a poor contributor for anhalamine (178) and pellotine (248); the slight incorporation found may be due to previous partial demethylation.

It would appear, therefore, that the incorporations observed for the intermediates following the stage of dopamine are fragmentary and even inconsistent. Battersby *et al.* (248) suggested that cyclization of 3,4,5-trihydroxyphenethylamine (LIV) to the isoquinoline system precedes *O*-methylation. Lundström and Agurell (233), however, were of the opinion that partial *O*-methylation precedes cyclization and that 3-methoxy-4,5-dihydroxyphenethylamine (LIX) is a common precursor which, by further methylation on the *para*-hydroxy group, gives 3,4-dimethoxy-5-hydroxyphenethylamine (V); the latter may be the immediate progenitor of the tetrahydroisoquinolines or at least anhalamine. However, the situation, obviously confusing and difficult to explain, certainly calls for additional work to establish more rigorously the pathways followed, probably independently, in the elaboration of the phenethylamine portion of the different tetrahydroisoquinolines. Also, the possibility that they may evolve from each other by transformations involving *O*- and/or *N*-methylations or demethylations should not be overlooked. In fact, Battersby *et al.* (248) demonstrated that *N*-methylation of anhalonidine occurs *in vivo* to give pellotine and that the reverse also occurs to an even greater extent.

There seems to be general agreement that methionine is the sole or main source of the *O*- and *N*-methyl groups in the tetrahydroisoquinoline alkaloids. This was demonstrated by the high incorporations observed into pellotine (181, 248), anhalidine (XVIII) (248), anhalamine, and anhalonidine (178) following the feeding of [methyl-^{14}C]methionine to peyote.[15] Battersby *et al.* (248) concluded that the *S*-methyl group of methionine is transferred intact, which is in agreement with previous work (249) on nicotine.

The origin of the one-carbon (C-1) and two-carbon (C-1 and C-9) units, present in tetrahydroisoquinolines of the anhalamine (XIII) and anhalonidine (XX) types, respectively, would still have to be accounted for. From feeding studies with [1-^{14}C]- and [2-^{14}C]acetate, Battersby *et al.* showed that the *S*-methyl group of methionine cannot be a contributor (181) and that the acetate carboxyl (181, 248) and methyl (248) groups may contribute—but not through direct incorporation[16]—equally to each position in the two-carbon unit of pellotine. This unit in anhalonidine was also shown by Lundström and Agurell (178) not to originate from methionine.[17] Assuming that acetate suffers degradation prior to incorporation into the two-carbon unit (of pellotine, for example), Battersby *et al.* (248) studied the metabolism of bicarbonate and formate and found that only the latter could be incorporated into C-1 and C-9 with equal distribution. It became clear, therefore, that the two-carbon unit originates from a precursor to which both atoms of acetate and that of formate can donate and that other contributors must be involved. Battersby *et al.* (248) suggested that glycine, serine, and pyruvate may be considered as likely precursors and even that a C-5 side chain derived from mevalonate, in a suitable precursor akin to lophocerine (LXVI) (251, 252), may be involved by degradation.

[14] The incorporation value (1.5%) given by Battersby *et al.* (248) for this transformation, which those authors regarded as low, is higher than that (0.37%) found by Paul *et al.* (235).

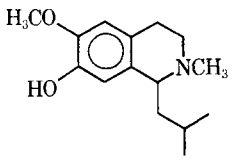
[15] The feeding of sodium ^{14}C-formate showed limited incorporation of this source into the *O*-methyl groups of pellotine (248).

[16] In fact, an appreciable proportion of the activity of the sodium [1-^{14}C]acetate fed to the peyote plant was scattered over the *O*- and *N*-methyl groups and the eight carbon atoms in the rest of the molecule (181). The acetate carboxyl group is known to contribute to the *O*-methyl groups and residues derived from the shikimic acid pathway (250).

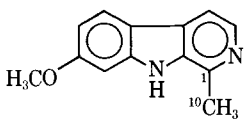
[17] With anhalamine, however, the same workers (178) found that the methyl group of methionine can be incorporated into C-1; this may be construed as evidence of a pathway involving the oxidative cyclization of an *N*-methylated derivative of phenethylamine.

Kapadia and Fales (96) recently suggested that the alkaloid amides mescalotam (XXXVIII) and peyoglutam (XXXIX) discovered in peyote may result *in vivo* by condensation of the appropriate phenethylamines with α-ketoglutarate[18] followed by decarboxylation of the resulting acids, reactions that were also realized *in vitro* (*vide supra*). These authors (96) extended their view, which was based on the original biosynthetic proposals of Hahn and his coworkers (244–247) to account for the origin of the one- and two-carbon units at C-1 in tetrahydroisoquinolines and suggested that they also arise from analogous condensations with the appropriate α-keto acids, namely, glyoxylate and pyruvate, respectively, rather than acetate. More recently, Leete and Braunstein (253) presented experimental evidence indicating that pyruvate can be involved since feeding sodium pyruvate-3-^{14}C to peyote cactus gave relatively high specific incorporation of the labeled atom into C-9 of anhalonidine. The two-carbon unit (C-1 and C-10) of harmine (LXVII) was similarly reported by Stolle and Gröger (254) to result from C-2 and C-3 of pyruvate; unspecific labeling was, however, obtained after feeding acetate-^{14}C to the *Peganum harmala* plant. In contrast, O'Donovan and Kenneally (255) found that the feeding of acetate-1-^{14}C to *Eleagnus angustifolia* plant yielded eleagnine (LXVIII) having predominantly all the activity at C-1.

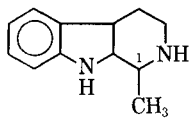
These facts, along with the recent report of Slaytor and McFarlane (256) that *N*-acetyltryptamine serves as a direct precursor of harman (LXIX) in *Passiflora edulis*, led Leete and Braunstein (253) to suggest that the two-carbon unit in the tetrahydroisoquinoline alkaloids (such as anhalonidine, XX) results by cycliza-



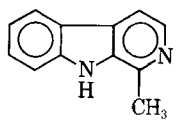
LXVI



LXVII



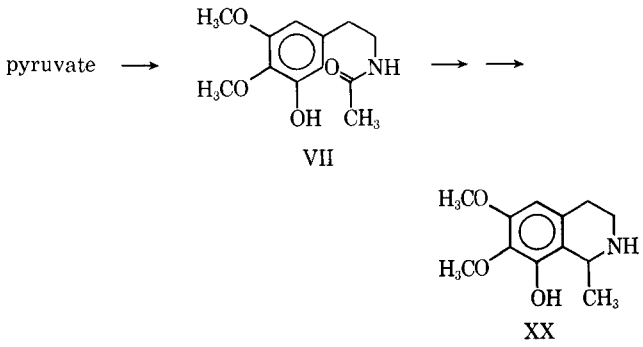
LXVIII



LXIX

tion from the *N*-acetyl moiety in the corresponding phenethylamine derivatives (such as VII) (Scheme XXXI).

For the origin of such *N*-acetyl groups, acetate must not be considered as the exclusive source since it failed to be incorporated directly into the tetrahydroisoquinolines of peyote (*vide supra*), a fact that may be rationalized by suggesting (253) that peyote contains no enzymes capable of utilizing acetic acid directly for the formation of such an *N*-acetyl derivative (as VII). A biosynthetic scheme was, therefore, proposed (253)

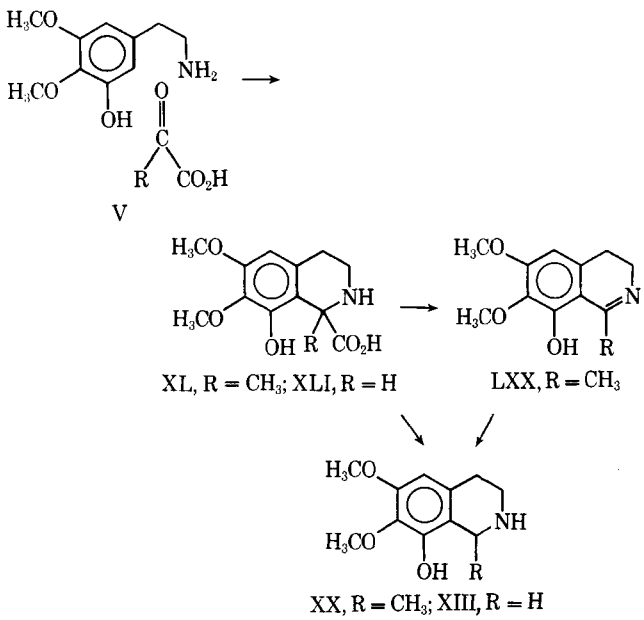


VII

XX

Scheme XXXI

whereby pyruvate acts as the primary source of the two-carbon unit and proceeds to acetylcoenzyme A, which then affords VII by contribution to the phenethylamine precursor.[19] The scheme centainly appears attractive, but its validity should be tested by the administration of *N*-acetyl- (and also *N*-formyl-) phenethylamines to peyote and determination of the degree of incorporation into the corresponding tetrahydroisoquinolines.[20] This pathway is a marked departure from the views of Hahn *et al.* (244–247) and Kapadia and Fales (96) who proposed that α-keto acids, as likely sources of the one- and two-carbon units, undergo Mannich condensation with the hydroxylated phenethylamines followed by decarboxylation of the intermediate acids (as XL and XLI) to yield the natural alkaloids; several *in vitro* simulations of such reactions were reported (Scheme XXXII).



V

XL, R = CH$_3$; XLI, R = H

LXX, R = CH$_3$

XX, R = CH$_3$; XIII, R = H

Scheme XXXII

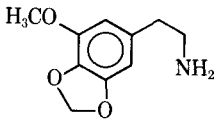
[18] It seems that the Krebs cycle acids conjugate favorably with mescaline (or a suitable precursor) in peyote, as evidenced by the proven (96) presence of the succinimide (XXXII), malimide (XXXIII), and maleimide (XXXIV) derivatives (see above).

[19] If taken literally, this would imply that glyoxylate is a source of the one-carbon unit in other tetrahydroisoquinolines (such as anhalamine) and that the *N*-formylphenethylamines, formed by a similar sequence, may be true precursors.

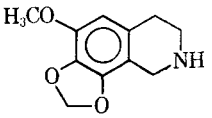
[20] It is pertinent in this connection to remember that peyote does actually contain several *N*-acetyl- (IV and VII) and *N*-formyl- (III and VI) phenethylamines (Table I) (96). While this manuscript was in preparation, Professor E. Leete (University of Minnesota, Minneapolis, Minn.) kindly informed the authors of his latest results (100) obtained from feeding *N*-[1-^{14}C]-acetyl-[α-^{14}C]-3,4-dimethoxy-5-hydroxyphenethylamine (VII) to peyote. These showed that the *N*-acetyl group was not involved significantly in the elaboration of the C-1 moiety of anhalonidine (XX) or anhalamine (XIII).

The actual presence of such nonproteinic amino acids, named peyoruvic acid (XL) and peyoxylic acid (XLI), in peyote was recently demonstrated by Kapadia *et al.* (99, 100, 185). Both were synthesized by condensation of 3,4-dimethoxy-5-hydroxyphenethylamine (V) with pyruvic acid and glyoxylic acid, respectively, at room temperature and physiological pH and resulted very rapidly in excellent yields. This intensified the belief that similar condensations may likewise operate in the plant tissue. Since normal physiological conditions were found (100) incapable of inducing subsequent decarboxylation, the transformation of both acids (XL and XLI) into the optically active anhalonidine and anahalamine, respectively, evidently necessitates the action of stereospecific decarboxylases. Experimentally, it was found (100, 185) that this could be true since facile decarboxylation of carboxyl-labeled *rac.* peyoruvic and peyoxylic acids (XL and XLI, respectively) could be brought about by short-term incubation with fresh slices of the peyote cactus, nearly half the activity was recovered as [^{14}C]-carbon dioxide. In a similar experiment in which [9-^{14}C]-peyoruvic acid was used, the decarboxylation product was isolated and found to be the Schiff base LXX, accounting for nearly half the activity. Moreover, feeding of [1-^{14}C]-peyoruvic[21] and [1-^{14}C]-peyoxylic acids to live peyote plants resulted in the incorporation of 6.0 and 6.8% of radioactivity in anhalonidine (XX) and anhalamine (XIII), respectively (100). The joint occurrence of 3-demethylmescaline (V), peyoruvic acid, and peyoxylic acid in peyote—in addition to the tracer experiments—would seem to suggest that the pathway indicated in Scheme XXXII can account for the C-1 moiety in the tetrahydroisoquinolines in addition or preference to that proposed by Leete and Braunstein (253). The isolation of the dihydroisoquinoline LXIII in the relatively short-term slice experiment may suggest that this product is a true intermediate, since it might be stereospecifically reduced to optically active anhalonidine (XX) with NADPH.

More work is certainly needed to establish rigorously the precise biogenetic route followed in the construction of the C-1 moiety in the various tetrahydroisoquinolines. Equally important is the work leading to the elucidation of the biogenetic interrelationships of the various tetrahydroisoquinoline alkaloids of peyote as well as the probable pathways that connect them with their phenethylamine precursors. In the latter, the biogenetic changes in the benzenoid oxygen substituents seem to be of special interest since a convenient explanation for the origin of the methylenedioxy system is still lacking. Kapadia *et al.* (95) recently anticipated the occurrence of homomyristicylamine (LXXI) in peyote and its probable biogenetic role. Whether the methylenedioxy group,[22] present in anhalonine (XXVI) and lophophorine (XXIX), is formed prior to or after cyclization remains to be established. The C-1 methylene counterpart (LXXII) of the latter compounds has not yet been found in peyote, although its presence is not unlikely from biogenetic reasoning.



LXXI



LXXII

BIOLOGICAL EFFECTS OF PEYOTE ALKALOIDS

General Pharmacodynamic Effects—*Mescaline (I)*—The effects of mescaline on the cardiovascular and respiratory systems were studied by several investigators (259–266). In general, low doses (~4 mg./kg.) of mescaline have no remarkable effects on blood pressure. Large doses (20–60 mg./kg.), however, produce a drop in blood pressure, bradycardia, respiratory depression, and vasodilation (259, 261–264, 266); the pressor and depressor effects persist after section of the vagi, greater and lesser splanchnic nerves, adrenalectomy, or atropinization. Moderate doses markedly inhibit the pressor effect of epinephrine without altering its accelerating effect on the cardiac rate. Grace (261), however, observed that the fall in blood pressure produced by mescaline in anesthetized cats could be prevented by vagotomy, decapitation, or atropine. Strong solutions of mescaline arrest the perfused frog heart in diastole due to a direct action on the cardiac muscle (261). Mescaline produces some sensitization to the cardiodepressant action of sodium EDTA (267). Its action on the cardiovascular system and on the nictitating membrane in cats and dogs is potentiated by pretreatment with reserpine (268). A threshold dose (152 mcg./kg. i.v.) causes slight potentiation of the effect of epinephrine on the nictitating membrane of anesthetized cats (269). Mescaline is slightly antagonistic to the vasoconstricting effect of serotonin perfused through the isolated rabbit leg (270).

In concentrations over 0.2%, mescaline causes gradual paralysis and shortening of the isolated gastrocnemius muscle of the frog. It stimulates the contractions of intestine and uterus *in situ* but not when excised (261). The intestinal muscle initially shows contraction but later is paralyzed (262). Other reports, however, show that mescaline causes respiratory stimulation, increases the tone of excised intestine, and slightly anesthetizes the cornea (260) and that it decreases the tonus of the smooth muscle at a concentration of 20 p.p.m. (264). The curarelike blockade of the dog peroneal tibialis anticus nerve-muscle preparation caused by mescaline is antagonized by epinephrine, prostigmine, and potassium chloride (271, 272). In rabbits and cats, it has no direct effect but it potentiates the inhibition of muscular contractions due to *d*-tubocurarine, gallamine, and succinyldicholine (273). Mescaline also stimulates the escape reflexes in mice in low doses and inhibits them in high doses (274).

Mescaline facilitates serotonin-induced contractions of the isolated rat uterus at lower concentrations and contracts the uterus at higher doses; atropine has no

[21] From the [1-^{14}C]-peyoruvic acid-fed plant, an unknown water-soluble basic substance, accounting for about 90% of the administered radioactivity, was isolated which from spectral (NMR and mass) data appears to be anhalonidine (or a derivative) attached to a polar moiety (100).

[22] It does not appear too unlikely that this group may arise from neighboring methoxy and hydroxy groups in the appropriate nucleus, since such transformation of aromatic substituents is a proven (257, 258) biosynthetic event.

effect but chlorpromazine inhibits these uterine contractions (275–278). Mescaline causes vasoconstriction of the umbilical vessels of the human placenta (279). In small doses, it enhances the potentiating effect of serotonin but blocks the prolongation action of reserpine on hexobarbital hypnosis in mice (280). It also augments cerebral serotonin levels and suppresses the protective effect of reserpine against toxicity of amphetamine in mice grouped in small cages (281). The favorable results obtained after administration of mescaline in a few cases of amenorrhea were attributed to an antagonism to serotonin (282).

Mescaline produces hyperthermia, and this effect in rabbits can be potentiated by pretreatment with iproniazid or reserpine (283–285). Jacob *et al.* (286, 287) observed a correlation between the mescaline-induced hyperthermia in rabbits, antianalgesia in mice, and hallucinogenic action in man. In rats, it lowers rectal temperature and is an effective antipyretic agent against tetrahydro-2-naphthylamine-induced fever (288).

A detailed discussion of the clinical pharmacology of mescaline and other related phenethylamines is given by Jacobsen (289).

The LD_{50}'s of mescaline in the rat are 330–410 mg./kg. i.p., 157 mg./kg. i.v., and 534 mg./kg. s.c. (259, 260). These values fall within the ranges given by other investigators for mice, frogs, and guinea pigs (290, 291). Flexor convulsions and respiratory arrest are the terminal events. Dogs fed with mescaline were reported (292) to develop capillary damage in the liver and nitrogen retention. Administration of sodium succinate to mice (0.5 g./kg. i.p.) was found to afford complete protection against mescaline (0.2 g./kg.) (290).

Hordenine (*XI*)—Heffter (59) gave the earliest description of the pharmacological properties of this compound; it was found to cause paralysis of the CNS in frogs without previous excitation. It was also reported to be highly antiseptic and to have an inhibitory effect on some soluble ferments (293, 294). Small doses of hordenine have no effect on blood circulation, but larger ones produce appreciable hypertension and accelerated pulsation; very large doses cause death by arrest of respiration. Rietschel (295, 296) found that the pressure effect of hordenine is not of central origin but results by stimulation of the heart muscle. Although much less active than adrenalin, it is analogous in its action, resembling ephedrine rather than adrenalin. Other workers reported that hordenine displays a nicotine-like action (297–299) and that in large doses it decreases or reverses the hypertensive effect of adrenalin (300).

Anhalonine (*XXVI*)—Heffter (62) described some aspects of the activity of this compound and the following ones after their first isolation from peyote. In the frog, injected doses of 5–10 mg. produced an increase in the reflex excitability after a phase of paresis. In the rabbit, similar symptoms resulted but general hyperexcitability predominated.

Anhalonidine (*XX*)—According to Heffter (62), doses of 20–25 mg. of the hydrochloride produced narcosis in the frog followed by increased excitability. Larger doses caused complete paralysis. Doses of 30–50 mg. provoked a curarizing effect. No significant symptoms have been observed in mammals.

Pellotine (*XXIII*)—Doses of 5–10 mg. caused temporary convulsions in frogs, dogs, and cats (62). Several authors, cited by Joachimoglu and Keeser (301), believe that pellotine could be used in man as a relatively safe narcotic.

Lophophorine (*XXIX*)—This base was shown by Heffter (62) to be the most toxic one in peyote; 0.25–1 mg. of injected hydrochloride provoked a long-lasting tetany in the frog. Although the animal recovers, the increased excitability may last for several days. There is no apparent action on the isolated frog heart. A dose of 7 mg./kg. in rabbits causes hyperexcitability and accelerated respiration; progressively higher doses induce tetany (12.5 mg./kg.) and lead to death (15–20 mg./kg.). Intravenous injection of 2.5 mg. causes an increase in blood pressure, but higher doses are hypotensive, without specific action on the heart.

More recently, Brossi *et al.* (176) examined anhalamine, anhalidine, anhalonidine, and pellotine and found all to be hardly active as anticonvulsants, tranquilizers, or muscle relaxants and to have no significant hallucinogenic effects.

Behavioral Effects of Mescaline—*On Animals*—In rats, mescaline (I) initially depresses the conditioned-avoidance response and then gives rise to a prolonged excitatory phase; the latter effect is dominant when lower doses are used (302). Harmine was found to augment the effect of mescaline (260). Maffii (303,304) observed the effect of mescaline on the secondary conditional response in an experimental avoidance situation and found the ED_{50} for blocking the response to be 32.5 mg./kg. i.p. Following an injection of 50 mg./kg., only 10% of the animals showed a loss of conditioned response. Dogs under the influence of large doses of mescaline reacted to conditioned stimulus as if it was the unconditioned one (305). Mescaline gave some protection to albino rats bred to have a high incidence of seizures when exposed to a standard sound (306).

Mescaline produced experimental catatonia in mice, guinea pigs, cats, monkeys, pigeons, and other animals (260, 307–314); the catatonic manifestations, however, could be inhibited by chlorpromazine, reserpine, and azacyclonol (315, 316). It caused reduction in the behavior patterns of contentment and sociability but increased excitement, aggressiveness, and defensive hostility (317). It was observed, however, that mescaline inhibited the isolation-induced attack behavior of mice (318). It produced a scratching response in mice, which was antagonized by tetrahydroberberine (319), various tranquilizers, serotonin, *d*-amphetamine, *etc.*, but not by barbiturates, meprobamate, azacyclonol, and mephenesin (320–322). Mescaline, given by intracerebral injection, produced aggressive tendencies and paroxysms of ear scratching in mice by doses that were ineffective by other routes (323). It also prolonged and potentiated the analgesic effect of morphine in mice (324).

In Humans—The onset, intensity, duration, and quality of the hallucinations produced in humans upon ingestion of mescaline or peyote depend both on the quantity of the drug and on the individual's cultural background. With mescaline, a latency period, de-

pending upon the route of administration, is followed by a number of disagreeable autonomic symptoms which are felt prior to the phase of inebriation. After an intravenous dose of 0.5 g. of mescaline sulfate, nausea, vomiting, sweating, generalized discomfort, dizziness, headache, palpitation, feeling of hot or cold, pupillary dilatation, and chest, neck, or abdominal cramps occur within 10 min. (325). A small rise in body temperature and systolic blood pressure are also experienced (326). Usually, the heart rate is accelerated somewhat, but sometimes a slight bradycardia is observed instead, as a reflex compensation of the hypertension. In general, the subjective vegetative symptoms like nausea and vomiting subside before the development of the psychic symptoms; the objective vegetative symptoms, such as pupillary dilatation, follow the time course of the psychic effects.

During the phase of mescaline-induced inebriation, the subject goes through abnormal mental states characterized by one or more of the following effects (37):

1. Visual hallucinations: Colors are at first intensified. Then, gradually, the subject shuts his eyes and entoptic phenomena appear, followed by true hallucinations with forms, shades, and movements. Flashing lights and complete scenes are seen, ordinary objects appear to be marvelous, and familiar sounds and music are "seen" in vivid colors.

2. Auditory hallucinations: These are fairly rare but frequently correspond to color and form visions. Hypersensitivity and pain at the slightest noise are also experienced.

3. Abnormal touch, taste, and smell: Paresthesias and alteration in perception of heat and cold occur.

4. Disturbances of personal judgement: The subject's perception of his own body, for example, is largely that it is changing shape, and he becomes unable to locate some parts of it. The perception of space and time becomes altered and both appear to be immensely stretched.

5. Emotional disturbances: An ecstatic euphoria with laughter is usually observed, especially at the beginning of the intoxication. This state is sometimes followed by anxiety and, less frequently, depression. The subject may then become suspicious and hostile, especially toward the person conducting the experiment.

6. Disturbances of the will and thinking: The subject utters words and makes gestures which he simultaneously does not wish to speak or make. He cannot pursue an idea; in tests of concentration and reasoning, failure is almost sure (327).

7. Personality disturbances: These, being the most important effects of mescaline intoxication, are manifested by symptoms similar to those of schizophrenia (328–330). The effect has catatonic features (329, 331). An experienced clinical observer can easily distinguish between schizophrenic reactions and drug-induced psychoses (328). The disorganization of psychic integration was much more apparent in schizophrenics than in normal subjects given mescaline (332). The drug precipitated schizophrenic psychoses in persons suffering from latent schizophrenia and also reactivated the psychosis in patients who improved after psychosurgery (333).

Detailed descriptions of the mescaline and peyote inebriation are given by various authors (1, 31–33, 35, 38, 58, 63, 71, 292, 325, 328, 334–341).

The reactions induced by LSD, psilocybin, and mescaline are qualitatively similar (326, 342), but mescaline is the least potent. It was noted that mescaline and LSD and their combination produced an enhancement in primary suggestibility (343). In a comparison of the effects of taraxein, a protein fraction obtained from the serum of schizophrenics, with those of mescaline, psilocybin, and LSD, Silva *et al.* (344) found that taraxein produced more dysphoria, blocking, and thought deprivation than did the three psychotomimetics. Secondary symptoms evoked by the protein fraction were more typical of those seen in schizophrenics than those induced by other substances.

The mescaline-induced state of intoxication has been used as an aid in psychotherapy (345). It has been recommended that mescaline be used when it is desirable to shorten a course of therapy, reactivate a stalled treatment of neurosis, and break down memory blocks (345). The studies of Turns and Denber (346) indicate that psychotherapy with mescaline can be effective in carefully selected cases where other methods have failed.

Tolerance, Habituation, and Addiction—Several studies show that human subjects and animals receiving mescaline daily develop tolerance to mescaline (302, 326, 347–351) and crosstolerance to LSD (326, 350, 351). The tolerance, however, regresses rapidly, and initial responsiveness is attained 3–4 days after the drug is withdrawn. Generally, the tolerance for the vegetative phase does not develop to the same degree as for the psychic phase (352). Speck (259) reported that no tolerance to the hypoglycemia and bradycardia induced by mescaline is observed. Dogs given 5 g./kg. of mescal buttons acquired tolerance to the emetic effects during 1 year of daily ingestion (353). Doses of mescaline producing acute tolerance have no effect on development of the chronic type (354). There seems to be no evidence that peyote and mescaline cause habituation and addiction (37); very few investigators hold a different view (355). Slotkin (44, 49) found that "the habitual use of peyote does not seem to produce tolerance or accrued dependence," an opinion that is also endorsed by many specialists (37) who affirm that peyote should not be regarded as a narcotic drug.

Antagonism and Synergism—The systemic administration of the phenothiazine tranquilizers (356–358), reserpine (356, 358, 359), asarone (360), trioxazine (361), lithium carbonate (362), lysergic acid derivatives (320), benactyzine, methylnonyldioxolane, chlorphenoxamine, *etc.* (358), inhibit various components of the mescaline-induced effects in different animals. Model psychosis produced by mescaline in man can also be inhibited by application of chlorpromazine and meretran (363, 364). Reserpine, injected 24 hr. before the mescaline, was found, however, to potentiate the action of the latter in mice (365).

Distribution of Mescaline in Animal Body—Mescaline taken orally is readily absorbed from the intestinal tract. The studies of various workers seem to agree

about the distribution of mescaline taken by injection. Tarsitano (366), working on dogs injected subcutaneously, found the highest concentration in the liver and kidneys but much less in the brain and no appreciable amount in the blood. However, the plasma levels of mescaline were found (367) highest immediately following intravenous injection, and the drug disappeared from the bloodstream after 6–8 hr. The concentrations of mescaline in the liver, spleen, and kidneys were 3–6 times those in the plasma; the brain and blood levels were about the same. These findings were supported by Block and coworkers (368–372) who studied the distribution of mescaline-α-^{14}C in mice. They found that, shortly after intraperitoneal injection, the highest radioactivity resided in the liver and kidneys with almost none in the brain and spinal cord. It was thus evident that mescaline was rapidly incoporated in the liver proteins. The maximum tissue concentration of mescaline coincided with the period of marked autonomic stimulation, while the highest concentration in liver protein corresponded to the period of hallucinations (372).

From his studies on the incorporation of radioactive mescaline into isolated tissues, Block (373, 374) found that the drug was incorporated in liver homogenates only if the latter were kept under oxygen first and then under nitrogen, and that the reaction rate increased 10-fold by brief heating of the mixture to 55° or by addition of tyramine. These observations indicated that there was an inhibitor, probably amine oxidase, whose action could be blocked by conjugation with tyramine or destroyed by heat, thereby facilitating the incorporation of mescaline. The inhibitor was, however, shown not to be amine oxidase, since several known inhibitors of this enzyme failed to increase mescaline incorporation (373). Moreover, Block (375), working with isolated cell components, found that nuclei could incorporate mescaline readily regardless of the action of tyramine or heat, while mitochondria and microsomes behaved similar to the total homogenate. It was, therefore, concluded that the incorporation-inhibiting factor resides within mitochondria and microsomes but not in the cell nuclei. Block (374) concluded, in general, that mescaline may be incorporated into proteins by a different mechanism from that involved in the case of amino acids; he postulated the following pattern. Oxidation of mescaline to an aldehyde is followed by condensation of the latter with the free amino groups of protein. The resulting Schiff base may subsequently either be hydrolyzed to an aldehyde, which undergoes further oxidation to an acid, or dissociated to mescaline and the oxidatively deaminated protein.

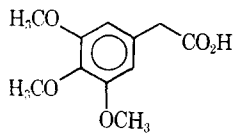
Fischer (376–378) used wool protein as a model surface to simulate the neuroreceptors involved in drug-induced psychoses. He demonstrated that the affinities (expressed in terms of absorption) of mescaline and other psychotomimetic agents, including LSD, for wool protein were parallel with their biological potency. Sympathetic overtones and subsequent adrenergic blockade seemed to contribute toward the precipitation of model psychosis. Neff *et al.* (379) found after administering radioactive mescaline intravenously into cats, which showed peak intoxication after 30 min., that the highest concentration of radioactivity was localized in the hypophysis, relatively high levels were in the cortical and subcortical gray matter, and very little was in the areas composed largely of myelinated fibers. The maximal mescaline concentration in the brain attained between 0.5 and 2 hr. roughly paralleled the period of maximal intoxication. The biological half-life of mescaline in plasma and cerebrospinal fluid was 1.5–2 hr. In human cerebrospinal fluid, however, Charalampous *et al.* (380) found significant concentrations of radioactivity throughout 9.5 hr. after administration of ^{14}C-mescaline.

Metabolism of Mescaline (I)—About one-half of the mescaline fed to rabbits was found to be excreted as 3,4,5-trimethoxyphenylacetic acid (LXXIII), a pharmacologically inactive metabolite (381, 382). Lesser amounts of the administered mescaline were recovered from dog urine (367). The studies of Block *et al.* (194) showed that rats and mice excreted intraperitoneally injected mescaline-α-^{14}C in the urine in the form of unchanged mescaline (18.4 and 79.4%), LXXIII (72.4 and 16.2%), and an unidentified product (9.1 and 4.4%), respectively. Spector (383) obtained qualitatively similar results by administering radioactive mescaline to dogs. Later, however, Neff *et al.* (379) found LXXIII to be the sole metabolite identified in the cat brain, plasma, cerebrospinal fluid, and urine. 2-(3,4,5-Trimethoxyphenyl)ethanol (LXXIV) was also found (384, 385) to be a metabolite in urine of rats fed with mescaline-α-^{14}C; its formation increases, at the expense of LXXIII, by calcium carbimide pretreatment, presumably because of the inhibition of aldehyde dehydrogenase. Pretreatment with iproniazid, however, markedly inhibits the formation of the acid (LXXIII), presumably by blockade of amine oxidase or a specific mescaline oxidase. Rabbits, estimated to be about 70 times as tolerant to mescaline as man, developed severe reactions by very small doses of mescaline when pretreated with calcium carbimide, implying that aldehyde dehydrogenase inhibition markedly enhances the pharmacological effects of mescaline. The intravenous administration of LXXIV to rabbits produced a mild mescalinelike effect, which was potentiated considerably when the alcohol was taken in combination with calcium carbimide. Based on these observations, it was suggested (385) that 3,4,5-trimethoxyphenylacetaldehyde (LXXV) is responsible for the pronounced pharmacological effects of mescaline.

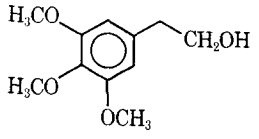
Musacchio *et al.* (386) and Musacchio and Goldstein (387) identified other mescaline metabolites, in the urine of rats, as *N*-acetyl-3,5-dimethoxy-4-hydroxyphenethylamine (LXXVI), *N*-acetyl-3,4-dimethoxy-5-hydroxyphenethylamine (VII), and *N*-acetylmescaline (IV), in addition to probably *N*-acetyl-3,4-dihydroxy-5-methoxyphenethylamine (LXXVII). They concluded that *N*-acetylation of mescaline may precede *O*-demethylation *in vivo*.

The early studies on metabolism of mescaline in man showed high recovery of the ingested drug in the urine of normal subjects and lesser amounts in psychopathic patients (388), with no evidence for the production of 3,4,5-trimethoxyphenylacetic acid (LXXIII) (382). Different figures for the recovery of mescaline in

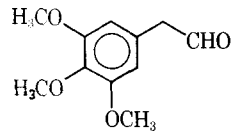
the urine were given by various workers (208, 389), depending on the route of administration and duration of the drug. Later studies (381, 390), however, showed that LXXIII was a metabolite which could be detected in human urine. 3,4-Dihydroxy-5-methoxyphenacetylglutamine (LXXVIII) (391) and 3-hydroxy-4,5-dimethoxyphenethylamine (V) (127) were other metabolites of mescaline found in small amounts in human urine. In more recent reports (40), orally taken mescaline was recovered substantially unchanged, in addition to LXXIII, VII, and IV, found in decreasing amounts



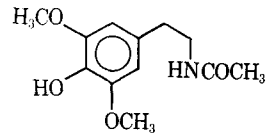
LXXIII



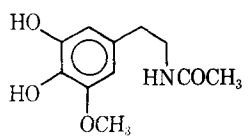
LXXIV



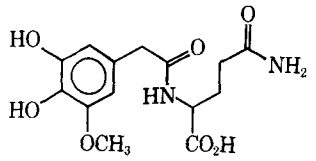
LXXV



LXXVI



LXXVII



LXXVIII

in both urine and cerebrospinal fluid. The appearance of LXXIII in human urine also was recently confirmed (392). A discussion of the metabolic fate of mescaline in man is given by Charalampous *et al.* (380).

Several *in vitro* studies (393, 394) showed that rabbit liver contains an enzyme system which oxidizes mescaline readily and that some factor other than oxidase might be involved. Amine oxidase was shown (394, 395) to have little or no effect on mescaline, and this was assumed (396) to be the reason for the high tolerance of rabbits to mescaline; a specific mescaline oxidase was claimed to have been isolated from the rabbit liver which was different from monoamine oxidase (397). Some authors (398) postulated that mescaline oxidase is identical with diamine oxidase, while others (399–401) believe that the oxidative deamination of mescaline can be effected by monoamine oxidase or diamine oxidase or both. However, mescaline was found to be a poor substrate for highly purified human plasma monoamine oxidase (402) and for dopamine-β-oxidase (403). According to Seiler (404), who treated mescaline with mouse brain homogenates, the oxidation is not caused by diamine oxidase but by a monoamine oxidase leading to 3,4,5-trimethoxyphenylacetic acid (LXXIII). Enzyme preparations obtained from rabbit lung produced *N*-methylation of mescaline (405, 406), while rabbit liver preparations caused *O*-demethylation to VII and LX along with oxidation to LXXIII (407). The formation of this acid (LXXIII) was inhibited by iproniazid, semicarbazide, nicotinamide, and triphosphopyridine nucleotide.

The excellent review of Patel (40) gives examples of the numerous studies made on various aspects of biochemical effects of mescaline with ample documentation.

Mode of Action of Mescaline—The following observations were enumerated by Patel (40) as reasons for doubting that mescaline *per se* is psychotomimetic and in support of the assumption that its action is caused by some metabolite.

1. Mescaline inhibited the oxidation of glucose, lactate, or pyruvate only if it was preincubated with brain homogenates for 2–3 hr. (408, 409).
2. In mice it was rapidly incorporated into liver proteins; during the phase of active CNS effects, the brain was almost devoid of it (371).
3. It stimulated the contractions of intestine and uterus *in situ* but not when excised (261).
4. No correlations were observed between the degree or type of behavioral responses and blood levels or rates of excretion of mescaline in man. The period of maximal behavioral changes followed the period of maximal blood level and excretion after 1–2 hr. (390).
5. The effective dose (400 mg.) was much higher than that of other hallucinogens; the effects took 1–2 hr. to develop and 5–6 hr. to reach a maximum (391).
6. The combined effect of mescaline and iproniazid could not be distinguished from that of an equivalent dose of mescaline (385).

Various explanations have been offered by different workers. Quastel and Wheatley (408) assumed that malfunction of the liver may give rise to abnormal amine metabolites which would affect brain respiration and subsequently produce CNS disturbances. It is not very likely that the hallucinogenic effect of mescaline is directly related to its sympathomimetic action on humans, since some substances possessing both the CNS and sympathomimetic properties are not hallucinogenic. The competition for adrenergic receptors leading to the disturbance of adrenergic mechanism was suggested by Speck (259). Quite recently, Clemente and Lynch (410) gave evidence suggesting that mescaline does not act *via* a cholinergic mechanism but rather through catecholamine mechanisms. The disturbance of histamine catabolism in the brain was suggested by Carlini *et al.* (411). Marrazzi and Hart (412) hold the view that "cerebral synaptic inhibition plays a part in the action of hallucinogens either by the direct disruption of normal patterns of synaptic activity as a result of alteration in the normal balance between cholinergic excitation and adrenergic inhibition at susceptible cerebral synapses."

Fischer (413) hypothesized the mode of action of mescaline, which he regarded as inactive *per se*, by suggesting that a metabolite produced *in vivo* by transformation into an indole derivative[23] resembling LSD is actually the active species. The hypothetical LSD-like compound results in very small amounts, perhaps from partially demethylated mescaline or through the condensation of mescaline with norepinephrine or serotonin. Other authors (9, 416) also postulated the *in vivo*

[23] Working on this assumption, Morin *et al.* synthesized 5,6,7-trimethoxyindole (414) and its 2,3-dihydro derivative (415) but found them to be devoid of mescalinelike activity.

Table II—Biological Data for the Isopropylamines

Compound	LD_{50} in Mice, mg./kg.	Effective Dose in Man, mg./kg.	Mescaline Units in Humans
LXXIX	260	1700	2.2
LXXX	150	1400	2.7
LXXXI	120	220	17
LXXXII	120	>1900	<2
LXXXIII	130	180	21
LXXXIV	40	210	18

formation of an indole derivative as the active species from mescaline. Snyder and Merril (417) made molecular orbital calculations for a variety of hallucinogenic and structurally similar nonhallucinogenic analogs in the phenethylamine, amphetamine, and tryptamine series and for LSD. They observed a close correlation between the energy of the highest filled molecular orbital of compounds, an index of electron donation, and their hallucinogenic potency.

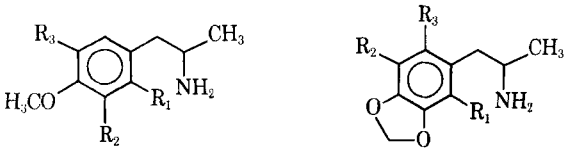
Although it appears attractive to suspect an intimate structural relationship among the active species that produce the same type of psychotomimetic effects, further and more thorough inquest should be made.

Structure–Activity Relationships—Several studies showed that alterations in the aromatic ring substituents (418–420) and the side chain can bring about substantial changes in the psychopharmacological properties of mescaline. Smythies and Levy (421), using the rope-climbing test for comparison, found that removal of the 5-methoxy group from mescaline caused about a 50% loss of activity, while demethylation of the 4-methoxy group resulted in a complete loss of activity. Substitution of the benzyloxy group for the 4-methoxyl was found to increase the activity. Ernst (422) confirmed that the presence of the 4-methoxyl group is essential for the manifestation of the hypokinetic rigid syndrome in cats. *N*-Methylation of mescaline seems to result in loss of the psychopharmacological properties of mescaline. Trichocereine (*N*,*N*-dimethylmescaline) was found (423) to produce no mental disturbances in man. However, it was observed to act on the CNS of normal cats to cause convulsions but to have no effect on decerebrated cats. This compound was shown (424, 425) to cause negligible inhibition of the conditioned-avoidance response but produced marked excitation similar to that induced by amphetamine; increase of the dosage delayed the onset of the excitation.

The introduction of a methyl group on the α-carbon of the phenethylamine system seems to maintain the hallucinogenic properties. In man, α-methylmescaline (LXXIX) (162) was found (426) to produce visual hallucinations in doses lower than that required for mescaline, without having significant effect on blood pressure or respiration. The peak urinary excretion occurred in 2–5 hr., with 20–35% of the ingested dose recovered unchanged in the urine. Several compounds analogous to LXXIX were also prepared and tested by Shulgin (427–429). The results showed that the presence of a 3,4-methylenedioxy group, as in LXXX,[24] does not result in loss of activity, while enlargement of this heterocyclic ring or increase in length of the aliphatic side chain in LXXIX results in decreased effect in humans. On the other hand, repositioning of the *meta*-methoxyl, in either LXXIX or LXXX, to an *ortho*-position produces an increase in potency (429).

Table II lists the effective dose (mg./kg.) of these isopropylamines in man, the LD_{50} (mg./kg.) in mice, and the mescaline units in humans (potency compared to mescaline = 1). The intoxication syndrome produced by these compounds in humans is qualitatively similar to that resulting from mescaline, except that the color effects and nausea are absent. In general, the methylenedioxy derivatives (LXXX, LXXXIII, and LXXXIV) gave more emphatic and pleasant responses. 2,5-Dimethoxy-3,4-methylenedioxyphenethylamine was found (431) to exhibit pharmacodynamic properties similar to those of mescaline. Schwachhofer *et al.* (432) and Schwachhofer and Chopin (433, 434) prepared several α,α-disubstituted derivatives of mescaline and found that the pharmacological properties (435) of only α,α-dimethylmescaline and α-methyl-α-veratrylmescaline are similar to those of mescaline.

A study of behavioral effects of mescaline, β-hydroxymescaline, and *N*-methyl-β-hydroxymescaline in mice performed by Friedman *et al.* (291) revealed that substitutions on mescaline did not substantially alter the biological activity of the parent compound.



LXXIX, $R_2 = R_3 = OCH_3$, $R_1 = H$ LXXX, $R_2 = OCH_3$, $R_1 = R_3 = H$
LXXXI, $R_1 = R_3 = OCH_3$, $R_2 = H$ LXXXIII, $R_3 = OCH_3$, $R_1 = R_2 = H$
LXXXII, $R_1 = R_2 = OCH_3$, $R_3 = H$ LXXXIV, $R_1 = OCH_3$, $R_2 = R_3 = H$

[24] Homomyristicylamine (LXXI) has recently been found by Shulgin (430) to be as potent as mescaline as a psychotomimetic in humans.

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RESEARCH ARTICLES

Synthesis and Biological Activity of Deuteriobenzyl-d_7-penicillin

PAUL A. LASKAR and ROBERT G. MRTEK

Abstract □ To investigate the deuterium isotope effect on the biological activity of penicillin G, this compound was chemically synthesized by first obtaining phenylacetyl-d_7-chloride from phenylacetic-d_7-acid and thionyl chloride, followed by condensation of the acid chloride with 6-aminopenicillanic acid. The penicillin was isolated as the 1-ethylpiperidine salt. Yield of the deuteriopenicillin was approximately 60% when a 2:1 (6-aminopenicillanic acid–acid chloride) molar ratio was used. The identity of the deuteriated penicillin was confirmed using several physical constants. From NMR data, the presence of deuterium in the benzyl moiety was found to be greater than 95 atom %. The biological activity of the deuteriopenicillin was compared to that of the protioanalog by a turbidimetric assay procedure using *Staphylococcus aureus*. The results of the biological assay indicate that a significant deuterium isotope effect operates in the antistaphylococcal action of benzylpenicillin. With the test organism chosen, the ratio of the antibiotic potencies was 125% H/D.

Keyphrases □ Deuteriopenicillin—synthesis □ Biological activity—deuteriopenicillin □ Turbidimetric assay—deuteriopenicillin antimicrobial activity □ NMR spectroscopy—identification □ IR spectrophotometry—identification

Deuterium (^{2}H), a rare stable isotope of hydrogen, was discovered by Urey *et al.* (1) in 1932. Extensive work by several investigators has felled the long-standing opinion that deuterium oxide (D_2O) is incompatible with life. The successful mass culture of algae, yeasts, and certain bacteria under conditions of full deuteriation has provided a useful source of fully deuteriated sugars, amino acids, proteins, and certain drugs (2–5). Substitution of deuterium for ordinary hydrogen and deuteriated substrates for protio metabolites has been shown to produce profound changes in biosystems. Isotope effects have been categorized as being either primary or secondary. Measurement of the magnitude of the effect is usually useful in distinguishing between the larger primary mass isotope effects and the smaller secondary effects.

The substitution of deuterium in several drug molecules has been the impetus for many recent research contributions. Isotopically altered drugs have shown widely divergent pharmacologic effects. Elison *et al.* (6) demonstrated a reduced analgesic potency of morphine deuteriated in the *N*-methyl group. Nona *et al.* (7) found an increased antifungal activity with fully deuteriated griseofulvin. Foreman *et al.* (8) investigated the *in vitro* Dutch rabbit liver metabolism of selectively deuteriated amphetamines. Their studies show that the ratio of apparent rate constants (k_H/k_D) is 1.9, indicating that the deuterioamphetamine is metabolized more slowly than the protioanalog. One major effect of deuterium substitution in drug-producing organisms has been a general suppression of most nonessential metabolism. Mrtek *et al.* (9) demonstrated an inverse effect between the level of deuteriation in *Claviceps* and the amount of clavine alkaloids produced in saprophytic culture. Multimilligram quantities of highly deuteriated elymoclavine were obtained only through the use of replacement culture techniques (10). Mohammed *et al.* (11) demonstrated a similar effect with several strains of *Penicillium*. Carlstedt (12) obtained small amounts of highly deuteriated penicillin from large numbers of shake