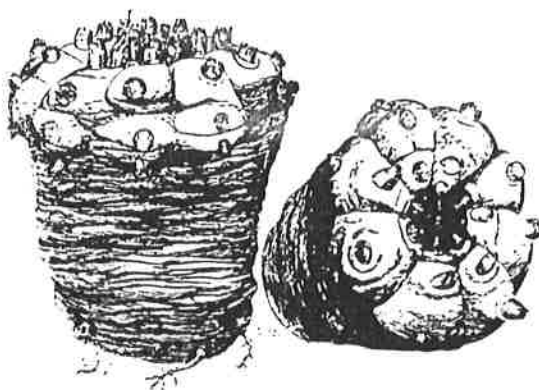


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PHARMACOGNOSTIC STUDIES OF PEYOTE
AND RELATED PSYCHOACTIVE CACTI

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Lophophora Williamsii var. *Lenini*.

Lophophora Williamsii.

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1975

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Chemical interest in cacti stems from 1888, when Lewin reported the finding of a pharmacologically active alkaloid in peyote (Lophophora williamsii). Further studies by Heffter resulted in the isolation of the hallucinogenic principle, mescaline. By 1940, structural studies had shown that the cactus alkaloids could be classified in two main groups, β -phenethylamines (e.g. mescaline) and tetrahydroisoquinolines (e.g. pellotine). With these findings, the first wave of interest in cactus alkaloids was gone.

Triterpenes (Djerassi, 1957) and lactone-forming acids (Kringstad and Nordal, 1975) have since been found in cactus species, but biosynthetic studies of mescaline in the 1960's brought a revival of interest in related alkaloids (cf. Lundström, 1971a). At the same time, the availability of gas chromatography-mass spectrometry (GC-MS) proved to be of great value and importance for the rapid separation and identification of the cactus alkaloids, and several new and interesting structures were found (Aguirell, 1969a; b; Kapadia and Fayez, 1970; Bruhn, 1971).

2. SCOPE OF THE PRESENT INVESTIGATION

"Some of the most interesting enigmas lurk in the desert stretches of northern Mexico, where what we might term the "prototype" of the New World hallucinogens - peyote or Lophophora williamsii - has long been the center of religious and curative rites in the Tarahumare and Huichol country".

R.E. Schultes (1967)

When the present investigation was started, biosynthetic studies of mescaline and related alkaloids in Lophophora williamsii and Trichocereus pachanoi were close to their completion. Relatively few other cacti had had their alkaloids structurally clarified, although many species had been listed among alkaloid-containing plants.

cult (La Barre, 1964; Furst, 1972), the chemistry and biological effects of peyote constituents (Kapadia and Fayez, 1970; Shulgin, 1973), and the biosynthesis of peyote alkaloids (Lundström, 1971a; Paul, 1973).

Lophophora is generally looked upon as a highly variable, monotypic genus. Recent field studies in Mexico have however indicated that there are two species, L. williamsii (Lem.) Coult. and L. diffusa (Croizat) Bravo, differing in distribution and chemical characters. No thorough alkaloid study of L. diffusa had been performed when the present investigation was undertaken (papers I and II).

During this investigation, a sample from 1887 of "mescal buttons" (the drug derived from L. williamsii), was made available for phytochemical examination. When the early papers were studied, it became apparent that the alkaloid analysis of L. diffusa provides an explanation of several controversial and much discussed points in the older research work.

3:1 Historical remarks on peyote research

The early history of peyote research from 1886 to the turn of the century is presented in paper I. Unpublished letters and notes have been drawn upon to clarify the events leading to the botanical identification of the drug and the finding of pharmacologically active alkaloids.

The first self-experiment with "mescal buttons" was performed in 1886 by Dr. John Raleigh Briggs of Dallas, Texas. His short report attracted the attention of the medical world and initiated an intensive research.

The pharmaceutical manufacturers Parke, Davis & Company distributed the new drug to scientists and also brought it on the market. In September 1887, the German toxicologist Louis Lewin visited Parke-Davis in Detroit and brought drug material with him back to Berlin. He was the first to publish the finding that the drug contained alkaloids and was very toxic in animal experiments. However, the first mention of alkaloids in peyote seems to be an unpublished laboratory

The two latter compounds are phenolic amines and as such rather unstable. Lundström and Agurell (1971) showed that 3-hydroxy-4,5-dimethoxyphenethylamine is present in fresh L. williamsii, but also that this amine is quickly destroyed. The lower mescaline content of the old material may likewise be due to degradation, but could also constitute a natural variation.

3:3 A chemotaxonomical problem

In paper I, reference is made to several 19th century chemical analyses of peyote under the names Anhalonium lewinii and Anhalonium williamsii. The most recent taxonomic treatments (Bravo, 1967; Anderson, 1969) consider these two species of Anhalonium as merely synonyms of Lophophora williamsii.

Interestingly, Heffter (1898) reported great differences in chemical composition between the two Anhalonium species. Anhalonium lewinii contained a mixture of alkaloids, among them anhalonine and mescaline. Present-day analyses (Todd, 1969; paper I) show that Lophophora williamsii contains the same alkaloids. Heffter found, however, that Anhalonium williamsii produced predominantly pellotine, and this has been a most confusing point in all peyote research.

Heffter (1898) noted that he could not distinguish the two species morphologically. Chemically, however, it was easy. He also found that the shipments he received were always homogenous, and this led Schumann to conclude that there were two local chemical forms. Thus, Schumann (1898) designated Anhalonium williamsii as Echinocactus williamsii α pellotinic and Anhalonium lewinii as Echinocactus williamsii β anhaloninic.

However, later investigations by Kauder of A. williamsii showed the same results as for A. lewinii. Kauder concluded: "The circumstances seem to me to call for further clarification, which will only be possible when we succeed in obtaining that cactus, which contains only pellotine. In spite of great effort, this has not yet been accomplished." The problem of the pellotine-containing Anhalonium seems not to have been further investigated.



Fig. 2. The distribution of *Lophophora*. *L. williamsii* is found from southern Texas to San Luis Potosi. *L. diffusa* is only found in Querétaro. Redrawn from Anderson (1969) with permission.

Biosynthetic experiments with 1, 4 & 5 (Fig. 3) lead Lundström (1971b) to postulate an independent metabolic pathway in L. williamsii, leading to pello-tine and anhalidine. The results reported in paper I with L. diffusa may then reflect an efficient N- and para-O-methylation of the alkaloid precursors.

Todd seems not to have been aware of the early confusion regarding Anha-lonium lewinii and A. williamsii. In our opinion, however, Heffter's results with A. williamsii can be explained if his plant material had been collected in Querétaro and was in fact Lophophora diffusa. Heffter found 0.75-0.89% pellotine in fresh A. williamsii and only traces of other alkaloids. These re-sults compare favourably with our present study of L. diffusa.

Evidence presented in paper I shows that localities of L. diffusa were known around the turn of the century and that this plant was the object of an extensive trade. After the publication of paper I, the following additional evidence has been found. Two Mexican authors, Altamirano (1900) and Urbina (1912), make independent reference to peyote specimens, collected in Queré-taro. A specimen collected by Altamirano in Querétaro is cited by Anderson (1969) as representative of L. diffusa.

Also, plant material that reached Germany from Mexico in 1896 had morpho-logical characteristics reminiscent of L. diffusa (Vaupel and Fuhrmeister, 1911; cf. Schumann, 1903). No early peyote specimens seem however to have survived in German or Mexican herbaria.

The alkaloid analysis of L. diffusa is interesting from an ethnopharma-cological point of view as well. In contrast to mescaline, pellotine does not give hallucinations but is an active sedative and hypnotic. There is thus a phytochemical basis for a difference in "hallucinogenic value" between L. williamsii and L. diffusa. Whether L. diffusa has been ritually employed or not is still an open question.

As shown in paper I, the alkaloid analysis of L. diffusa also provides an explanation of other controversial points in the history of peyote research.

al. (1971) isolated tyramine, N-methyltyramine and hordenine from Obregonia denegrii Frič. The same alkaloids were identified by us (III), tyramine being the main constituent of the alkaloid fraction. Interestingly, a new compound, 3-hydroxy-4-methoxyphenethylamine was found in Pachycereus pecten-aboriginum (X). The main alkaloid was salsolidine, and traces were also found of 3,4-dimethoxyphenethylamine (XI).

Early in this work, anhalidine and hordenine were identified in Pelecyphora aselliformis Ehrenberg (X). Neal et al. (1972) confirmed these findings and further isolated pellotine and N,N-dimethyl-3-hydroxy-4,5-dimethoxyphenethylamine. Plant material collected by us in San Luis Potosí also contained these alkaloids, but in our cactus sample N,N-dimethyl-3-hydroxy-4,5-dimethoxyphenethylamine, and not hordenine, is the major alkaloid (III).

Neal et al. (1972) also identified trace amounts of mescaline, N-methyl-mescaline, 3,4-dimethoxyphenethylamine and N-methyl-3,4-dimethoxyphenethylamine in Pelecyphora aselliformis. These compounds can not be detected in our extract because of the presence of relatively large amounts of other, as yet unidentified, non-phenolic alkaloids.

Pelecyphora pseudopectinata Backeberg is also called "peyote" (III). The main alkaloid of this cactus is hordenine. In Solisia pectinata Br. & R., hordenine co-occurs with N-methyltyramine (III). Turbinicarpus pseudomacrolele (Backeberg) F. Buxb. & Backebg. could be of interest, since it is found in a place where native informants said there were "peyotillos". Hordenine was the only alkaloid detectable in this species (III). As discussed in paper III, some of these "peyote" cacti seem to have had no aboriginal use as hallucinogens. Nor is there any obvious relationship between the name "peyote" and the alkaloid content.

Hordenine and tyramine are weak sympathomimetics and are inactivated in vivo by monoamine oxidase (MAO). Unless a MAO inhibitor is present, these compounds seldom cause pharmacological effects when taken orally. Tyramine,

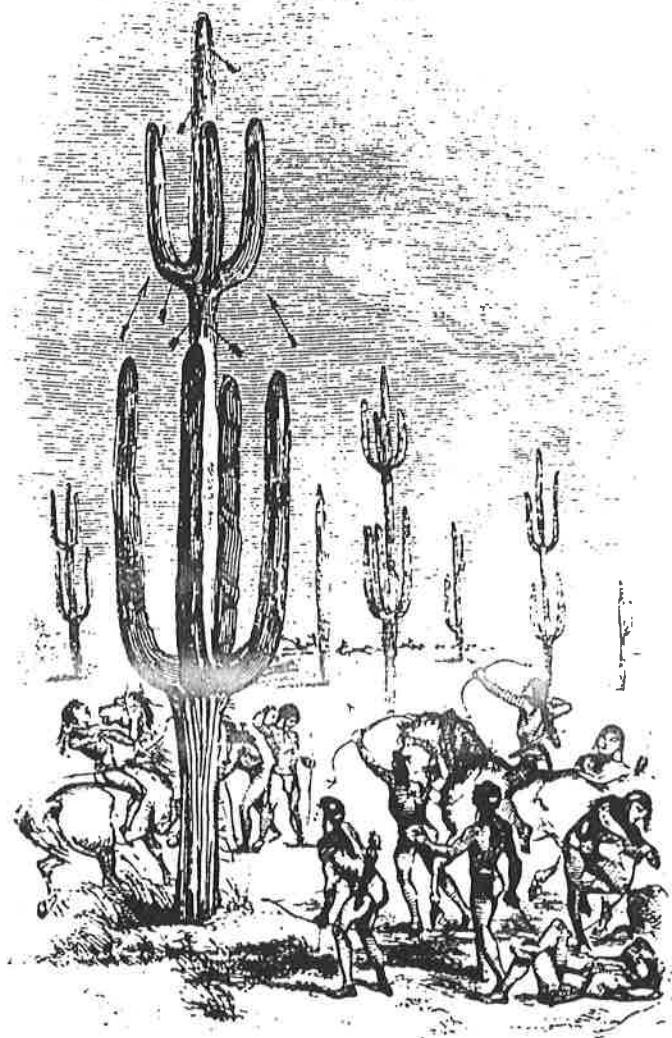


Fig. 4. "Indian amusements. Shooting at the petahaya". Another use of Carnegiea gigantea. From Bartlett (1854).

In our study of Carnegiea gigantea (paper VI), the alkaloid fraction was separated into phenolic and non-phenolic alkaloids with an ion-exchange resin. Column chromatography on aluminum oxide of the non-phenolic fraction yielded carnegine and salsolidine (= norcarnegine). The latter compound is the major alkaloid in our extract and has not earlier been found in cacti. Small amounts of 3,4-dimethoxyphenethylamine were also identified in the non-phenolic fraction by GC-MS.

When the phenolic fraction was subjected to the same column chromatography, gigantine and a new alkaloid were isolated. A trace of 3-methoxytyramine was identified by GC-MS. The structures of the isolated compounds were verified by comparison with authentic samples.

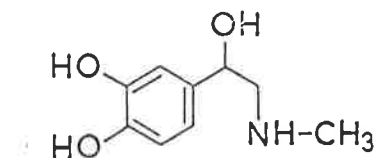
The MS of the new alkaloid was similar to those of salsoline and isosalsoline, but these structures could be ruled out by gas chromatographic comparison. The new alkaloid gave a positive Gibb's test, characteristic of phenols having the para-position unsubstituted. The 100 MHz NMR spectrum favoured structure V (Fig. 5) for the alkaloid, since the aromatic protons appeared as an AB quartet characteristic of two aromatic protons in ortho-position, and one of these protons showed a weak coupling with the $-CH_2-$ (C-4) signal.

Final proof for structure V (Fig. 5) was obtained by total synthesis of this alkaloid. 2-Hydroxy-3-methoxybenzaldehyde (o-vanillin) was benzylated and condensed with aminoacetaldehyde dimethyl acetal, according to the Bobbitt modification of the Pomeranz-Fritsch cyclization (Bobbitt et al., 1969; Shamma, 1972). The Schiff base formed was methylated (Grignard reagent) and the resulting secondary amine cyclized to give 8-hydroxy-7-methoxy-1-methyl-1,2,3,4,-tetrahydroisoquinoline (V, Fig. 5), found to be identical with the isolated alkaloid. To this new alkaloid we have given the trivial name arizonine.

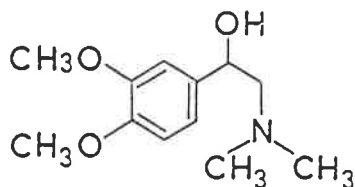
Arizonine is the second known 7,8-disubstituted tetrahydroisoquinoline alkaloid, the first being tepenine (= O,N-dimethylarizonine) (Kapadia et al., 1970). This rare substitution pattern is also found in the benzylisoquinoline

additional β -hydroxylated phenethylamines were found (Keller *et al.*, 1973). In our field screening of cacti in Mexico, *C. calipensis* H. Bravo was found to give a positive alkaloid test. Plants were collected and the alkaloids extracted and fractionated on an aluminum oxide column (paper VIII).

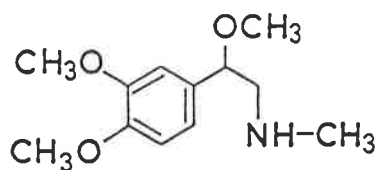
NMR and MS studies of the major alkaloid eluted from the column indicated that the compound was (-)-N-methyl-3,4-dimethoxy- β -methoxyphenethylamine [(-)- β -O-methylnormacromerine] (III, Fig. 6). This structure was confirmed by alkaline permanganate oxidation, which afforded 3,4-dimethoxybenzoic acid, and acid hydrolysis, which gave normacromerine as the major product.



I



II



III



IV

Fig. 6. Structures of epinephrine (I), macromerine (II), and the alkaloids of *Coryphantha calipensis* (III & IV).

and its nor-derivatives are probably not psychoactive. The related 4-methoxy- β -hydroxyphenethylamine and its N-methyl derivatives inhibit monoamine oxidase (MAO) (Ferguson and Keller, 1975), and epinephrine methyl ether (N-methyl-3,4-dihydroxy- β -methoxyphenethylamine) produces significant CNS stimulation (Page and Hoffer, 1964). Alkaloids III and IV (Fig. 6) should consequently be interesting objects for pharmacological study.

7. STUDIES OF MISCELLANEOUS SPECIES

7:1 Alkaloids of Trichocereus species

Peru has long had its counterpart to the Mexican "peyote" in "San Pedro", known to botanists as Trichocereus pachanoi Br. & R. This cactus is the chief ingredient in a mixture of several plants, called "cimora", which is used medicinally and for divination (Schultes and Hofmann, 1973). The main alkaloid of T. pachanoi is mescaline, and this hallucinogen is also found in other Trichocereus species (Aguirell, 1969a; b).

In paper X, and examination of fourteen Trichocereus species for alkaloids is presented. Eight different phenethylamines were identified, all of them known to occur in cacti. Mescaline was found in T. cuzcoensis Br. & R., T. fulvilanus Ritt., T. taquimbalensis Card. and T. validus (Monv.) Backbg. While it occurred as the major alkaloid in T. taquimbalensis and T. validus, mescaline was only a minor constituent in the two other species.

So far it is not known whether T. taquimbalensis and T. validus have been utilized by South American Indians for their hallucinogenic properties. Our limited knowledge of the psychoactive cacti of Peru may indicate that the "San Pedro complex" is less extensive than its Mexican equivalent, but it could also point to the lack of ethnobotanical field studies.

Two species related to Trichocereus, Echinopsis rhodotricha K. Sch. and

peruvianus was included. Only tyramine and hordenine could be detected in the alkaloid extract. It is not unlikely, that reports on the use of C. peruvianus as a hallucinogen, should refer to Trichocereus pachanoi. The latter species has already been misidentified as Opuntia cylindrica (Aguirre, 1969a).

A single report on the occurrence of caffeine in some Brazilian cacti (Freise, 1935) prompted a re-investigation of C. jamacaru DC. (paper XI). Neither the seeds nor the fresh plant could however be shown to contain caffeine. Instead, tyramine was isolated as the only alkaloidal constituent of the cactus stem.

Opuntia species have been used as food for humans and animals. This does not point to the presence of toxic substances. Nevertheless, Opuntia figures (probably erroneously) in a discussion of natural hallucinogens (Gjerstad, 1971). Due to the earlier misidentification of T. pachanoi (see above), Opuntia has entered the literature as containing mescaline. The now studied three species of Opuntia from Uruguay contained only hordenine (paper XII).

A species of Opuntia has also been mentioned as an admixture to "ayahuasca", the South American hallucinogenic drink (Rivier and Lindgren, 1972). So far, Opuntia species would seem to be of doubtful value as hallucinogens, but simple phenethylamines, such as hordenine, which are substrates for monoamine oxidase (MAO), could presumably reinforce the effects of the "ayahuasca" beverage (cf. Schultes and Hofmann, 1973).

ACKNOWLEDGEMENTS

The present work has mainly been carried out at the Department of Pharmacognosy, Faculty of Pharmacy, University of Uppsala. I want to express my sincere thanks to its head Professor Finn Sandberg, for valuable support and encouragement.

I am greatly indebted to Dr. Stig Agurell for introducing me to cactus alkaloid research, for personal guidance and great support including many valuable discussions.

Much of the investigated plant material was collected in Mexico, where I had the pleasure of spending eight months at the Universidad Nacional Autónoma de México, Mexico City. The hospitality and assistance of Dr. Efrén C. del Pozo, Instituto de Investigaciones Biomédicas; Dr. Agustín Ayala Castañares and Dr. Arturo Gómez Pompa, Instituto de Biología; and Dr. Francisco Javier Garfias, Facultad de Química, is gratefully acknowledged.

No words can express my gratitude to Dra. Helia Bravo Hollis and Dr. Hernando Sánchez-Mejorada R., Instituto de Biología. Their help in collecting and identifying cacti was truly invaluable. The many days spent in the field with Dr. Sánchez-Mejorada will never be forgotten.

Part of the study has been carried out in cooperation with the Department of Toxicology, Karolinska Institutet, Stockholm. I am sincerely grateful to its head, Professor Bo Holmstedt, for his constant encouragement and kind interest in this work.

I am further indebted to my collaborators and co-authors, Professor Juan X. de Vries and Drs. Victor Díaz and Patrick Moyna, Universidad de la República, Montevideo, Uruguay, Drs. Jan-Erik Lindgren and Jan Lundström, Mrs. Eva Forsén, Sra. Eréndira Pérez de Gutiérrez and Miss Ulla Svensson.

I particularly want to thank my wife, Catarina Bruhn, not only for her encouragement and patience with my research interests, but also for pleasant

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