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Alkaloids of the Cactaceae — The Classics

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Alkaloids of the Cactaceae have been studied for the last 120 years. The first half of that period provided the "classic" compounds, after which a large number of usually very similar analogs were isolated or determined with modern methods. Although some unusual synthetic approaches have been developed, their preparation is generally quite straightforward. Their biosynthesis has been studied but, particularly in the case of the isoquinoline compounds, important aspects have not been addressed. Due to its striking effects, the pharmacology of mescaline has been studied more intensely than that of the other phenethylamines present in cacti, followed only by hordenine. The many 1,2,3,4-tetrahydroisoquinoline alkaloids have attracted much less interest and have often been considered practically inactive. Nevertheless, some recorded activities of this group of compounds suggests a need for additional studies, especially in connection with their co-administration with mescaline, as in dried cacti and in beverages prepared from them.

Keywords: Cactaceae, Alkaloids, Phenethylamines, 1,2,3,4-Tetrahydroisoquinolines, Structures, Synthesis, Pharmacology.

The Cactaceae are exclusively native to the Americas, growing from southern Canada to Patagonia, although *Rhipsalis baccifera* (J.S.Muell) Stearn is also found growing wild in tropical Africa, Madagascar and Sri Lanka and is believed to have been introduced from Brazil or the Caribbean basin, possibly in historical times [1-4]. Four subfamilies are generally recognized: the relatively primitive Pereskioideae, the very small, specialized Maihuenioideae (only two species), and the very numerous Opuntioideae and Cactoideae. Alkaloids (if simple phenethylamines are considered as such) have been found most frequently in the Cactoideae, but there are a few recorded examples from the Opuntioideae and Pereskioideae. The present review will focus on the "classic" cactus alkaloids, discovered up to the middle of the 20th century. The very numerous compounds isolated since then are almost exclusively either simple amines (e.g. phenethylamine, tyramine, dopamine) or commonplace variations on the previous structures. Although valuable reviews on the original compounds were published from 1950 to 1954 by Ladislao Reti [5], modern pharmacology and biochemistry have opened up new vistas, not necessarily connected to the remarkable psychedelic effects of "peyote" (*Lophophora williamsii* (Lem. ex Salm-Dyck) J.M.Coult). This paper attempts to put such knowledge up to date and is a homage to Reti's pioneering work.

The history of Cactaceous alkaloid chemistry begins with Louis Lewin's 1888 study of "peyote", which was then viewed as close to the previously described "*Anhalonium williamsii"* and was designated "*A. lewinii*" in his honor. From this cactus, growing in Northeast Mexico and spreading into Southeast Texas, Lewin, working in Berlin, crystallized a crude sample of anhalonine, the first cactus alkaloid, and showed that it was not responsible for the remarkable psychotropic effects of peyote tops or "mescal buttons" [6(a)]. Up to 1894 he continued studies on cacti that were then classified as "*A. jourdanianum"* and "*A. williamsii*" (now all grouped as *Lophophora williamsii*), as well as four or five *Mammillaria* species and a *Rhipsalis*, but without any clear chemical results [6(b)].

More fruitful early studies were carried out by Arthur Heffter, who isolated and characterized "anhaline" (now known as hordenine) from "*Anhalonium fissuratum*" or "*Mammillaria fissurata*" (now *Ariocarpus fissuratus* (Engelm.) K.Schum.) and pellotine from a "pellote" described as "*Anhalonium williamsii*", plus a small amount of what he later characterized as mescaline from "*A. lewinii"* [7(a)]. In subsequent papers Heffter characterized his pellotine and mescaline more completely, isolated anhalonidine and lophophorine and improved on Lewin's description of anhalonine, all from "*A. lewinii*" [7(b,c)]. In one of his 1898 papers [7(c)] he also demonstrated that mescaline was responsible for peyote's psychedelic properties, while anhalonine and anhalonidine at similar doses were devoid of any effects worthy of note. In contrast, he found that pellotine only made him sleepy, leading to subsequent testing in humans for this purpose. Heffter demonstrated the presence of alkaloids in several other cactus species, but did not describe any chemical details. Shortly thereafter E. Kauder isolated one more alkaloid, anhalamine, from peyote [8]. Stimulated by Heffter and Kauder's work, Georg Heyl published a paper describing the isolation of pilocereine (actually a mixture of alkaloids) from "*Pilocereus sargentianus*" (now *Pachycereus schottii* (Engelm.) D.R.Hunt), and "pectenine" from "*Cereus pecten-aboriginum*" (now *Pachycereus pecten-aboriginum* (Engelm. ex Watson) Britton & Rose) [9]. Many years later Heyl isolated carnegine from *Carnegeia gigantea* (Engelm.) Britton & Rose [10].

This early work included the preparation of various salts of the alkaloids (usually containing metals such as mercury, gold or platinum), elementary analyses and some other chemical tests based on oxidations and the Zeisel quantification of methoxyl groups [11(a,b)], but no convincing structure was determined until 1919, when a young Ernst Späth in the University of Vienna demonstrated the identity of "anhaline" with hordenine and proved the structure of mescaline [12(a)]. In the following decade Späth and his students, particularly Friedrich Becke and Johann Bruck, carried out a number of studies showing the structures of anhalonine and lophophorine [12(b)], carnegine, found to be the same as the "pectenine" of *Pachycereus* species [12(c,d)], pellotine and anhalonidine [12(e)], anhalamine [12(f)], and then of a succession of "new" peyote alkaloids: anhalinine [12(g)], anhalidine [12(h)], *N*-methylmescaline [12(i)], the first non-basic cactus alkaloid *N*-acetylmescaline [12(j)], and *O*-methylanhalonidine [12(k)].

Around the same time as Späth's monumental work on North American cacti was being done in Austria, Enrique Herrero Ducloux determined the presence of alkaloids in a few species from Argentina without establishing any structures. In his study of *Echnopsis eyriesii* (Turpin) Pfeiff. & Otto (or possibly *E. oxygona* (Link) Zucc. ex Pfeiff. & Otto) he found unidentified alkaloids [13(a)] and for *Gymnocalycium gibbosum* (Haw.) Pfeiff. ex Mittler, he mentioned "An α-alkaloid (I) and a β-alkaloid (II) … I, … gave reactions suggestive of anhalonine and lophophorine and is probably a mixture of the two alkaloids. II, … gave the reactions of mescaline" [13b]. The presence of anhalonine and lophophorine, but not mescaline, was only confirmed in *G. gibbosum* in 1997 [14]. In the mid- to late 1930's the Italian Ladislao Reti, who had obtained his PhD in Vienna and is best known for his studies on Leonardo da Vinci, but who was working at the time in Buenos Aires, took up these studies again. In his hands *Trichocereus candicans* (Gill.) Britton & Rose yielded hordenine and the "new" alkaloid candicine, the first quaternary ammonium salt from the Cactaceae [15(a)]. Reti also found both alkaloids in *T. lamprochlorus* (Lem.) Britton & Rose [cited in 15(b)], the "new" trichocereine in *T. terscheckii* (Parm.) Britton & Rose [15(b)], and coryneine, another "new" quaternary base, in *Cereus coryne* (now *Stetsonia coryne* (Salm-Dyck) Britton & Rose [15(c)].

All the isolation work was carried out on dried and ground plant material, extracted with ethanol or methanol with or without addition of acid, followed by partition into chloroform or ethyl ether. Given the presence of phenolic, nonphenolic and quaternary bases, the use of ion exchange resins would seem to be a worthwhile improvement. Nevertheless, the introduction of HPLC-MS/MS mainly in the last decade has made isolation practically obsolete except for the complete identification of new compounds.

The early classic studies of cactus alkaloids revealed seven phenethylamine derivatives (Figure 1):

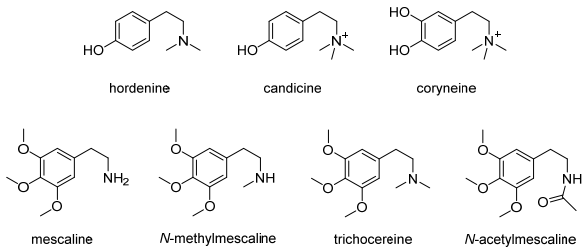


Figure 1: Classic cactus phenethylamines.

and nine simple 1,2,3,4-tetrahydroisoquinolines (Figure 2):

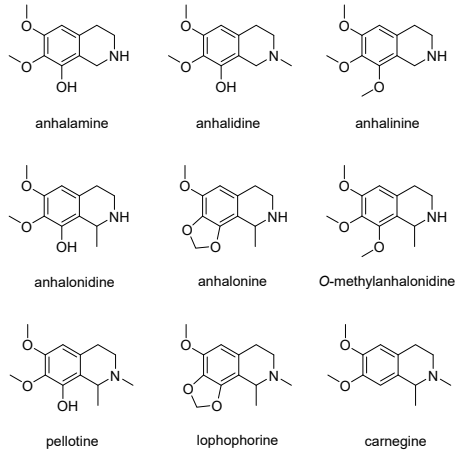


Figure 2: Classic cactus isoquinolines.

To date, a total of fifty phenethylamines (plus fifteen amides, imides and related derivatives, mostly of mescaline), and close to eighty isoquinolines (mostly tetrahydro-, but some 3,4-dihydro- and fully aromatic isoquinolines) have been identified as cactus constituents [3].

Späth synthesized mescaline from 3,4,5-trimethoxybenzaldehyde by condensation with nitromethane to afford the corresponding nitrostyrene, followed by reduction of the latter in two stages [12(a)]. Several other methods were developed with varying success over the following years [16], but the standard procedure now involves lithium aluminum hydride reduction, as pioneered by Erne and Ramírez (1950) [17], and is commonly applied in the synthesis of variously substituted phenethylamines, modified if necessary with appropriate protecting groups. The synthesis of the simple 1,2,3,4-tetrahydroisoquinolines is generally achieved from the corresponding phenethylamines, either by the Pictet-Spengler approach outlined above, which is appropriate when a hydroxyl group is present *ortho*- or *para*- to the desired point of cyclization, or by Bischler-Napieralski reaction of the amides to generate 3,4-dihydroisoquinolines, and subsequent reduction. Both routes lead to mixtures of both *ortho*- and *para*- products that must be separated at some point [18]. An exhaustive review of the syntheses of carnegine, which may serve as a guide to develop improved syntheses of the other cactus tetrahydroisoquinolines, is that of Bracca and Kaufman (2004) [19].

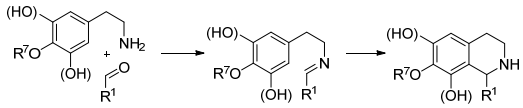
Optical rotations were reported for the 1-methyl-1,2,3,4-tetrahydroisoquinolines anhalonine and lophophorine, but pellotine, anhalonine, carnegine and the related salsoline were apparently isolated in their racemic form in all early attempts. Späth and Kesztler (1936) addressed this problem, synthesizing pellotine and separating its enantiomers. However, they noted that these racemize rapidly on standing in aqueous solution, and that this occurs very much more rapidly in dilute KOH [20]. As anhalonine and lophophorine were always isolated from peyote in their levorotatory forms, the same would reasonably seem to be the case for the other chiral cactus alkaloids. These authors therefore assumed that the 1-methyl-1,2,3,4-tetrahydroisoquinolines are in fact biosynthesized as single enantiomers, and that racemization takes place during their extraction and isolation.

The absolute configurations of the chiral cactus alkaloids were unknown at the time of their original isolation. In 1960 Battersby and Edwards applied the somewhat uncertain comparison of the solvent-related changes in optical rotation with those of related compounds of known configuration to propose that the natural (-)-anhalonine and (-)-lophophorine are both *S* isomers [21]. This was fortunately confirmed a few years later by X-ray crystallography and comparison of ORD and CD spectra and, contrary to expectation, the same configuration was similarly demonstrated for 1*S*-(+)-*O*-methylanhalonidine [22]. Finally, these results were used to develop a general rule that could be applied to determine the absolute configurations of 1-methyl-1,2,3,4-tetrahydroisoquinolines independently of the substitution pattern on the aromatic ring. Surprisingly, assuming that the half-chair dihydropyridine ring adopts the same conformation in all the cactus alkaloids, the *R* configuration was assigned to (-)-anhalonidine and (-)-pellotine [23].

The structural variations of the phenethylamines are biogenetically trivial, starting from the common precursor tyramine or, in very few cases, phenethylamine itself. These have undergone ring oxidation to afford dopamine and its derivatives and 3,4,5-trioxygenated analogs, β-oxygenation, and diverse *N*- and/or *O*-methylations.

Many of these reactions are illustrated in the scheme representing mescaline biosynthesis as studied by Paul's group [24] and by Lundström and Agurell [25], and reproduced in our recent review on mescaline [16]. Finally, in a few cases, amides have been generated with formic or acetic acid or, specifically for mescaline, imides of succinic, malic, maleic, citric or isocitric acids, with occasional minor elaboration. The only outlier is the non-alkaloidal lemairin, the 4-*O*-β-glucoside of 2-(3,4-dihydroxyphenyl)ethanol, that can still be considered a member of this extended family formed by oxidative deamination of dopamine and subsequent (?) glycosylation.

All the isoquinolines are biogenetic derivatives of the phenethylamines, presumably formed by Pictet-Spengler cyclization, usually with formaldehyde or acetaldehyde equivalents to give, respectively, the 1-unsubstituted and the 1-methylated 1,2,3,4-tetrahydroisoquinolines (Scheme 1):



Scheme 1: Biogenesis of tetrahydroisoquinolines from phenethylamines.

Jan Lundström proposed that the coupling moiety is probably glyoxylic or pyruvic acid [26], but modern studies, particularly attempting the isolation and study of the enzymes involved, are lacking. Formation of the tetrahydroisoquinoline skeleton is presumably followed (or possibly preceded) by *N*- and *O*-methylations, ring- or β-hydroxylation, the latter possibly leading to 3,4-dihydroisoquinolines by dehydration which might be otherwise formed by direct dehydrogenation to the 1,2-dihydroisoquinolines. It seems likely that the 7,8-methylenedioxy ring of anhalonine and lophophorine is formed by oxidation of the common 8-hydroxy-7-methoxy pattern.

Regarding the extensively discussed pharmacology of mescaline [16], suffice it to say that its psychedelic action is generally attributed to the activation of serotonin 5-HT_{2A} receptors although, like the other classic hallucinogens, it is also active at the 5-HT_{2C} subtype. It has recently been characterized rather extensively and found to also bind mainly to 5-HT_{1A} and α_{2A} receptors with no other important receptor/transporter interactions [27]. This lack of specificity is reminiscent of LSD's, and may be of relevance to subjective reports of mescaline being somehow "different".

Mescaline is the only cactus alkaloid included in the International Narcotics Control Board's "Green List" in accordance with the United Nations Convention on Psychotropic Substances of 1971. Inclusion in Schedule 1 of this list, as is the case of mescaline, implies that all use of a substance "is prohibited except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them." In practice, this has almost completely stopped research on mescaline and, less directly, on the potentially significant interactions of mescaline with other cactus alkaloids.

The oral ingestion of 550 mg of trichocereine (*N,N*-dimethyl-mescaline) caused no apparent effects in a human subject although it caused excitation in rats according to Ludueña, 1935, cited by Reti [5(a)]. The next study to be published showed that this alkaloid had little effect on several oxidative and hydrolytic brain enzymes [28]. An early behavioral study confirmed the marked excitation ("amphetamine-like") elicited by 25-100 mg/kg intraperitoneal (i.p.) trichocereine in rats while, unlike mescaline, it had negligible effect on the conditioned avoidance response [29]. One might speculate that the excitatory activity noted involves monoamine transporters rather than receptors, but no further studies seem to have been published on this substance. Apparently there are no studies on the pharmacology of *N*-methylmescaline. The i.p. administration of 50 mg/kg *N*-acetylmescaline failed to elicit a mescaline-appropriate response in rats trained to respond to mescaline (10 and 25 mg/kg) [30].

Hordenine is commonly found in grasses, and its name reflects its discovery in barley (*Hordeum vulgare* L.) [31] a few years after Heffter's isolation of "anhaline" [7(a)]. As a consequence its pharmacology has been studied more extensively, not only as a constituent of the racehorse diet, but also as a beer component that is touted for its presumed virtues by the nutritional supplement business. A hypertensive effect due to peripheral vasoconstriction was demonstrated after parenteral administration in the early 1900s and was rapidly attributed to an adrenergic action by Barger and Dale, who considered it too weak to deserve further attention [32]. The fairly numerous early papers on the pharmacology of hordenine were reviewed by Rietschel in 1937, who considered the actions of this alkaloid to resemble both adrenaline and nicotine [33]. Much more recently it was found to be an indirect adrenergic agonist, apparently acting by inhibition of noradrenaline uptake [34]. A later paper, however, suggested that its action was due instead to stimulated noradrenaline release [35].

The intravenous and oral administration of 2.0 mg/kg hordenine was studied in horses. Although the intravenous dose caused a short-lived variety of effects including respiratory distress, none of these effects were seen after oral administration, apparently because of the alkaloid's poor absorption, attaining a peak plasma value of 0.15 μg/mL one hour after dosing [36,37]. However, a significant hypertensive effect was observed in rats after oral administration of 1.0 mg/kg of hordenine and of several of its glycosides [38]. Publications that are not easy to access reported a depressant action on the mouse central nervous system [39] and a bronchodilator action in cats [40].

Hordenine is a substrate for rabbit liver monoamine oxidase (MAO), but it is degraded more slowly than tyramine [41]. These authors noted the large differences among MAO preparations from different organs and animal species. Hordenine is oxidised by pig brain MAO (possibly a mixture of isoforms), with K_m = 2330 μM and V_{max} 6.6 $nmol_{oxygen}$/min [42]. More recent work indicates that it is strongly preferred by rat liver MAO-B, suggesting that it "is unlikely to be deaminated by intestinal MAO" and "is likely to be absorbed and could affect the sympathetic nervous system, by virtue of its action as an inhibitor of noradrenaline uptake" [34]. Nevertheless, regarding the intake of hordenine by humans, these results should be taken with caution in view of the considerable functional differences between rat and human MAOs [43-45].

Very recently, hordenine was shown to be an almost full (76%) D_2 dopamine receptor agonist that signals via G-protein activation, but inhibits β-arrestin recruitment with an EC_{50} value of 37 μM. [46]. Although its functional potency is rather low, and its content in beer is very variable, the authors suggest that its presence might contribute to the mood elevating properties of this beverage. Indeed, hordenine is predicted to pass the blood-brain barrier according to a model study [47]. Clearly, hordenine is a good candidate for future studies.

Barger and Dale examined the effects of intravenously injected candicine (as hordenine methiodide) in 1910, and concluded that its effects resembled those of nicotine [32]. This was confirmed shortly after the isolation of candicine from cacti [48(a,b)], and was analyzed in greater detail in the 1960s when it was shown to be a ganglionic stimulant [49], an effect which may be potentiated by its reversible inhibition of acetylcholinesterase [50]. Injected into the rat brain, it induces epileptic-like electroencephalographic patterns [51]. Unfortunately, the few fairly recent studies on candicine have not addressed its oral administration, which might be of interest considering its likely ingestion in cactus extracts. Surprisingly, the phenolic, charged and generally hydrophilic candicine also penetrates a blood-brain barrier model [47], so the possibility that it might exert some central effects after oral administration cannot be ruled out *a priori*.

Coryneine is a potent and specific ganglionic agonist [52]. Also, in motor nerve terminals it inhibits the nerve-induced release of acetylcholine [53]. Coryneine stimulates adenilyl cyclase in rat brain striatal homogenates and therefore acts like a weak D_1 (or D_1 + D_5) dopamine receptor partial agonist [54]. Its effect on rat fundus ($5\text{-}HT_{2B}$) serotonin receptors was negligible [55]. Nevertheless, the chances of coryneine, with a second hydroxyl group, evidencing any central effects upon oral dosing seem even more remote than with candicine.

In contrast to mescaline and hordenine, the simple isoquinoline alkaloids of cacti have attracted little interest. The late 19th century efforts of Heffter and other authors, who generally observed convulsions in different animal species at high doses, were promptly reviewed by Affanasia Mogilewa (1903) who extended her studies to the isolated frog heart [56]. Some of Heffter's self-experiments revealed nothing of interest and, specifically, no effects remotely resembling those of mescaline. A relatively modern study on anhalamine, anhalidine, racemic anhalonidine and racemic pellotine, testing for muscle relaxation, "tranquilizing" action, sedative activity and anticonvulsant activity in mice, and MAO inhibition *in vitro*, was overall negative [57]. A variety of simple isoquinoline alkaloids were later examined vs. monoamine oxidases (MAOs) [58]. The only cactus alkaloids included were carnegine (both enantiomers), racemic *O*-methylanhalonidine and *O*-methylpellotine, and some members of the newly discovered (since 1985) 5,6,7,8-tetraoxygenated *Pachycereus* alkaloids. *R*-(+)-carnegine proved to be a rather potent competitive MAO-A inhibitor, with a 2 μM K_i value, while its enantiomer was fifty times less potent. *O*-Methylanhalonidine and *O*-methylpellotine were weaker than *S*-(-)carnegine, with K_i values of 160-170 μM, and the 5,6,7,8-tetraoxygenated analogs were several times less potent. None of these showed significant inhibition of MAO-B.

A more recent exploration of mescaline and its 1,2,3,4-tetrahydroisoquinoline analog anhalinine at the neuromuscular junction of the frog and nicotinic receptors in rat brain cortex showed that both alkaloids inhibit neuromuscular transmission by blocking acetylcholine release. In the brain they failed to block [^{125}I]α-bungarotoxin binding to nicotinic receptors [59], but this only reflects their low affinity for homomeric α7 and related receptors, and not for the predominant α4β2 subtype.

Pellotine seems to be exceptional for the attention it has drawn in the last years of the 19th century and the first decades of the 20th. Heffter found that sleep was elicited in rabbits by 50-70 mg doses of pellotine, followed by shaking, chewing and finally rigid paralysis which appeared almost immediately with higher doses. Similar effects were noted in cats, preceded by salivation, pupil dilation and manifestations of excitement. Dogs seemed to be relatively insensitive to pellotine: 50 mg/kg (slightly less than the doses tested in rabbits and cats) had no noticeable effect. Heffter's bold experiments on himself were repeated at higher doses (80-240 mg) and only caused a very tired feeling which left no sequels after a good night's sleep. Then he provided a Dr. Jolly of the Charité Nerve Clinic with a sufficient amount to treat about 40 patients with 40-80 mg, both subcutaneously and orally. The effects were considered similar to those of 1 g trional (methylsulfonal) or 1.5-2.0 g chloral. "Irregular slow pulse, dizziness, a feeling of heat in the head and restlessness before sleep were observed as side effects. Serious effects were not seen in any case". A Dr. Pilcz of the First Viennese Psychiatric Clinic treated 58 patients with insomnia with 40-60 mg pellotine hydrochloride subcutaneously, with complete success in 29 cases, partial success in 17 and none in 12. No unpleasant side effects occurred. More than 100 experiments were carried out by a Dr. Hutchins on 11 mentally ill patients at the St. Lawrence State Hospital (13-30 mg subcutaneously or orally). Ten inmates of the Herrmannstadt (now Sibiu, Romania) Psychiatric Hospital were treated unsuccessfully by Nagy with 20-80 mg, and Langstein reported that a tabetic (tertiary neurosyphilis) patient collapsed after 10 mg. Heffter's conclusion was: "It seems … that although pellotine is not absolutely safe (but what hypnotic is?) it is an innocuous sleeping drug" [6(c)]. Surprisingly (by present-day standards), decades later it was tested orally in schoolchildren (0.05-0.08 g) and in infants (0.01-0.05 g) and found to induce sleep lasting an average of one hour beginning 45-90 minutes after administration. Although it raised the children's glycemia slightly and also decreased heart rate and blood pressure to a minor degree, these values returned to normal after 90 minutes [60].

The pharmacology of the very simple phenethylamines found in cacti, which now include unsubstituted phenethylamine itself, tyramine, dopamine and their *N*-methylated derivatives and, of course, mescaline, seems to be clearly established particularly because tyramine and dopamine are important endogenous human metabolites. In contrast, the simple isoquinoline alkaloids of the Cactaceae are relatively unknown from a pharmacological viewpoint. One might hope for interesting surprises from some of the many analogs isolated after 1950, but the similarity of their structures to those of the "classic" cactus alkaloids makes this seem unlikely.

Although the 1,2,3,4-tetrahydroisoquinolines have generally been considered inactive or nearly so (and certainly non-hallucinogenic), a couple of examples stand out. The proposal that pellotine be used as an innocuous hypnotic seems remarkable from the vantage point of the 21st century, and there are no modern results to validate or explain these early observations. The fairly potent MAO-A inhibitory action of carnegine suggests that this and similar alkaloids, if present in a cactus or one of its extracts, might potentiate the effects of mescaline. Furthermore, nothing is known about other mechanisms through which the mescaline psychedelic experience might be modulated by the co-ingestion of some of these compounds. And what might be the effects of the widespread and sometimes abundant hordenine, when taken together with other alkaloids? Hopefully, this short review will stimulate further studies into these intriguing matters.

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