CHAPTER 27

Cactus Alkaloids

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I. Introduction

General surveys on cactus alkaloids have been published previously by Späth and Becke (1) and Reti (2, 3, 4). An exhaustive survey on cactus alkaloids and some related compounds has been published recently by Reti (5); see also the book of Hobschette (6) and the chapter on alkaloids of the Cactaceae in Henry's monograph (7); for peyote cf. Ewell (8), Safford (9), Reutter (10), and Amorosa (11).

II. Constitution and Occurrence

The presently known cactus alkaloids are of simple chemical constitution. They are either substituted β-phenethylamines, evidently related to and probably derived from the naturally occurring aromatic amino acids (tyrosine, dihydroxyphenylalanine, *N*-methyltyrosine, etc.), or they are simple tetrahydroisoquinolines that could originate from these bases by condensation and cyclization through the action of organic compounds containing one or two carbon atoms (formaldehyde and acetaldehyde "equivalents").

Obviously, under these conditions, it will be quite possible to find bases of the same type in plants of widely separated botanical families or even in products of animal metabolism. The individual cactus alkaloids will be found, therefore, under the headings β-Phenethylamines (see Vol. III, chap. 22) and Simple Isoquinoline Alkaloids (see Vol. IV, chap. 26), where are also included all other natural bases of similar structure but different origin.

The data in the literature on the alkaloidal composition of cacti are meager and incomplete. Alkaloids have been noted in some thirty species, but in many instances the examined material has been scanty and not well defined. The chemical constitution of the bases is known only with reference to nine species of the 1235 recorded by Britton and Rose (12).

However, the early investigations of Lewin (13–16), Heffter (17–23), and Heyl (24, 25), and the more recent ones of Herrero-Ducloux (26–30), Reti (2–4, 31–36), and others, seem to indicate that the faculty of producing and storing alkaloidal substances should be considered one of the characteristics of this botanical family.

Alkaloids of known structure have been isolated from the following cacti:

1. *Anhalonium lewinii* Hennings, syn. *Lophophora williamsii* (Lemaire) Coulter; Britton and Rose, known as pellote, peyote, peyotl, and challote. The dried slices are called "mescal buttons." Contains: mescaline, *N*-methylmescaline, *N*-acetylmescaline, anhalamine, anhalidine, anhalinine, anhalonidine, pellotine, *O*-methylanhalonidine, anhalonine, and lophophorine (1, 37–59).
2. *Anhalonium fissuratum* Engelmann, syn. *Ariocarpus fissuratus* (Engelmann) Schumann, contains hordenine (anhaline) (17).
3. *Cereus pecten-aboriginum* Engelmann, syn. *Pachycereus pecten-aboriginum* (Engelmann) Britton and Rose, contains pectenine (identical with carnegine) (24).
4. *Carnegiea gigantea* (Engelmann) Britton and Rose, contains carnegine (25).
5. *Trichocereus candicans* (Gillies) Britton and Rose, contains hordenine and candicine (31, 60, 61).
6. *Trichocereus lamprochlorus* (Lemaire) Britton and Rose, contains hordenine and candicine (34).
7. *Trichocereus terscheckii* (Parmentier) Britton and Rose, contains mescaline and trichocereine (32, 36).
8. *Trichocereus spachianus* (Lemaire) Riccobono, contains candicine (62).
9. *Stetsonia coryne* (Salm-Dyck) Britton and Rose, contains coryneine (35).

The presence of alkaloids of undetermined structure has been recorded for the following cacti:

1. *Opuntia vulgaris* Miller (63, 64).
2. *Selenicereus grandiflorus* (L.) Britton and Rose. Sultan (65) isolated from the plant 2 % of an alkaloid and called it cactine.
3. *Neomamillaria magnimamma* (Haworth) Britton and Rose (20).
4. *Epiphyllum ackermannii* (Haworth) Britton and Rose (20).
5. *Schlummbergera russeliana* (Gardner) Britton and Rose (20).
6. *Astrophytum myriostigma* Lemaire (20).
7. *Cereus peruvianus* (L.) Miller (20).
8. *Echinocereus mamillosus* Rümpler (20).
9. *Echinocactus visnaga* Hooker (20).
10. *Ariocarpus retusus* Scheidweiler (17).
11. *Dolichotele uberiformis* (Zuccarini) Britton and Rose (15).
12. *Rhipsalis teres* (Vellozo) Steudel (15).

13. *Lophocereus schottii* (Engelmann) Britton and Rose. Heyl (24) found in this cactus considerable amounts of an amorphous base, m.p. 82–86°, called pilocereine, $C_{30}H_{44}N_2O_4$. Amorphous salts; 13.48 % methoxyl. *Pilocereine*—The amorphous alkaloid found by Heyl (24) in *Lophocereus schottii*—has been recently obtained in crystalline form and investigated by Djerassi, Frick and Geller (72). The major part of the alkaloids resides in the green epidermis, a minor part in the cortex, while the central core is practically devoid of alkaloids. From the crude and complex alkaloid fraction (*ca.* 3.7 % on the dry plant) pure crystalline pilocereine can be separated in an over-all yield, based on dry plant, of 0.5 %.

Pilocereine, $C_{30}\ H_{42}\ O_4\ N_2$, recrystallized from ethyl acetate and from methanol is optically inactive, m.p. 176.5–177°. Pilocereine dihydrochloride, $C_{30}\ H_{42}\ O_4\ N_2 .\ 2\ HCl.\ 2H_2O$, m.p. 228–232° (dec.); diperchlorate, m.p. 214–217° (dec.); dioxalate, forms a dihydrate. The dimethiodide dihydrate decomposes at 230–240°. Acetyl pilocerine, $C_{32}\ H_{44}\ O_5\ N_2$, m.p. 186–186.5°. (All melting points corr.). The pilocereine molecule contains two tertiary nitrogen atoms, one forming part of a heterocyclic ring, while of the four oxygen atoms, two are present as methoxyl groups, one as a phenolic hydroxyl group and the fourth appears to be present in an ether linkage.

14. *Pachycereus marginatus* (DC.) Britton and Rose (66).
15. *Gymnocalycium gibbosum* (Haworth) Pfeiffer (27).
16. *Gymnocalycium multiflorum* (Hook.) Britton and Rose (29).
17. *Echinopsis eyriesii* (Turpin) Zuccarini (26).
18. *Trichocereus* sp. aff. *T. terscheckii* (30).
19. *Trichocereus thelegonoides* (Spegazzini) Britton and Rose (62).
20. *Trichocereus thelegonus* (Weber) Britton and Rose (62).
21. *Trichocereus huascha* (Weber) Britton and Rose (62).

III. Location of the Alkaloids in Tissues of the Cacti

Few observations only are available on this subject. Janot and Bernier (67) found that in pellote the alkaloids are almost exclusively located in the internal cells of the cortical parenchyma at the top of the plant. In *Trichocereus candicans* Niedfeld (60), utilizing microchemical methods, observed that the alkaloids are mostly situated in the chlorophyllaceous cortical parenchyma.

Reti and Castrillón (36) found 0.29 % total alkaloids in the green epidermis of *Trichocereus terscheckii*, while the central parts, including cortical parenchyma, contain 0.45 %.

IV. Extraction of Cactus Alkaloids

Fresh cacti, with a water content of 90–95 %, are difficult to handle; the juice is not easily separated from the fibers, and the presence of mucilagi-

nous substances causes trouble during extraction. Thus, it is preferable to dry the plants immediately after they are collected, in order to avoid losses and deterioration. The plants should be cleaned, the spines extracted with nippers, and the remaining material cut in thin slices and dried in the sun or better in a low-temperature dryer (40–60°). The dried substance is easy to grind, and the powder can be stored if necessary.

The powdered material is extracted following the usual procedure. Extractions of the drug and isolation of the alkaloids from *Anhalonium lewinii* have been described by Heffter (19), Kauder (68), Tomaso (69), and Späth and Becke (1), as well as by Steiner-Bernier (70); and the extraction of alkaloids from *Pilocereus sargentianus* and *Cereus pecten-aboriginum*, by Heyl (24, 25).

The extraction and isolation of the alkaloids of *Trichocereus candicans* (71) will serve as an example of general applicability:

Five hundred grams of dried and powdered material was extracted exhaustively with 95% ethanol acidified with 0.3% of acetic acid. The solvent was removed *in vacuo* and water was added and evaporated again until 500 cc. of ethanol-free solution remained. The solution, decanted from chlorophyll, waxes, etc., was extracted several times with ether in order to eliminate impurities; it was then filtered, made alkaline with excess solid sodium carbonate, the soluble bases extracted exhaustively with ether, and the aqueous solution (A) put aside. The concentrated ether extracts were shaken with strong potassium hydroxide solution, and the ether layer, after washing, was evaporated to dryness thus yielding very small quantities of non-phenolic bases. The alkaline solution was acidified with hydrochloric acid, made alkaline with sodium carbonate, and again extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and after concentration the hordenine (anhaline) crystallized. The mother liquors yielded more, less pure, hordenine. Total yield: 2.5 g. hordenine; 0.5% on the dry plant.

The aqueous solution (A) contained the non-extractable quaternary bases. It was acidified with hydrochloric acid, filtered and precipitated with concentrated Mayer's reagent (50 g. of mercuric chloride, 200 g. of potassium iodide, 400 cc. of water), added with constant stirring. The precipitate was filtered, suspended in hot water, and hydrogen sulfide was bubbled through the suspension until all the mercury was precipitated as sulfide. The hot filtered solution on cooling yielded candicine iodide (hordenine methiodide) in straw-colored needles. The salt was recrystallized from hot water with the aid of charcoal and yielded colorless crystals, which melted at 234°. The mother liquors contained only small amounts of candicine. Total yield: 16.4 g. of candicine iodide; 2% of candicine on the dry plant.

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