Cactaceae Alkaloids. X[1]. Alkaloids of *Trichocereus* Species and Some Other Cacti

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ABSTRACT.—The alkaloids of 14 species of *Trichocereus* are reported. Eight different previously known phenethylamines *viz.* tyramine, *N*-methyltyramine, hordenine, 3-methoxytyramine, 3,4-dimethoxyphenethylamine, *N*-methyl-3-methoxytyramine, 3-hydroxy-4,5-dimethoxyphenethylamine, and mescaline were identified in these species. Mescaline was found to occur in *T. cuzcoensis, T. fulvilanus, T. taquimbalensis* and *T. validus*. Mescaline was also present in small amounts in *Stetsonia coryne* together with traces of anhalidine and anhalonidine. 3-Hydroxy-4-methoxyphenethylamine is identified in a plant, *Pachycereus pecten-aboriginum*, apparently for the first time. The commonly occurring isomer 3-methoxytyramine was found to be the major alkaloid of *Trichocereus cuzcoensis*. A tetrahydroisoquinoline alkaloid, anhalidine, was isolated from *Pelecyphora aselliformis*.

Results reported in a previous paper, indicated that the occurrence of alkaloids in *Cactaceae* was common (1). The basic alkaloids in 21 species of cacti mainly belonging to the genera *Trichocereus, Helianthocereus* and *Cereus* were reported in part I of this series (1). The structures of those, at that time,

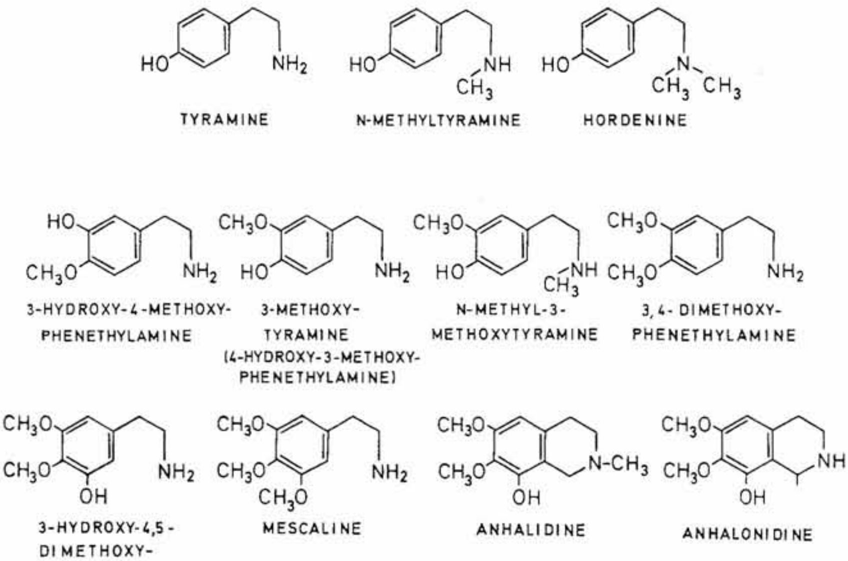

FIG. 1. *Identified alkaloids.*

known basic cactus alkaloids were also reviewed (1). Since then salsoline has been found to occur in *Echinocereus merkeri* Hildm. (2) and *N*-methyl-4-hydroxy-3-methoxyphenethylamine in the peyote cactus (8).

The present report is concerned with the identification of alkaloids of cacti belonging mainly to the genus *Trichocereus* but also alkaloids of *Stetsonia*

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coryne, Pachycereus pecten-aboriginum, Pelecyphora aselliformis and *Echinopsis rhodotricha*.

EXPERIMENTAL

PLANT MATERIAL.—The cacti used in this investigation were obtained from the following sources: *Stetsonia coryne, Pachycereus pecten-aboriginum, Trichocereus cuzcoensis, T. santiaguensis, T. strigosus, T. thelegonoides* and *T. thelegonus* from W. Haage, Erfurt, DDR; *T. courantii, T. knuthianus, T. manguinii, T. pupureopilosus, T. taquimbalensis* and *T. tunariensis* from H. van Donkelaar, Werkendam, The Netherlands; *Pachycereus pecten-aboriginum, Stetsonia coryne, T. santiaguensis, Echinopsis rhodotricha* and *Pelecyphora aselliformis* from K. Edelmann, Reeuwijk, The Netherlands; *T. fulvilanus, T. santiaguensis* and *T. skottsbergii* from *M. Schleipfer, Augsburg,* DBR; *T. validus* and *T. thelegonous* were gifts from Dr. J. P. M. Brenan, Royal Botanic Gardens, Kew, UK.

The nomenclature of species as proposed by Backeberg (4) is used. Plants were checked to conform with the macromorphological descriptions given by Backeberg (4). Reference cacti are maintained in our greenhouse.

ISOLATION AND IDENTIFICATION OF ALKALOIDS.—Methods for isolation and separation of alkaloids have been described earlier (1). The basic technique by which the alkaloids were identified has been fully outlined (1). In essence, the naturally occurring compound was considered as identified, if it showed the same chromatographic behaviour as the reference compound (*i*) on two gas chromatography columns (SE–30, XE–60 or JxR); (*ii*) by tlc [chloroform–ethanol–conc. ammonia (85:15:0.4) or, for phenols, chloroform–ethanol–diethylamine, (85:5:10)] and (*iii*) by gas chromatography–mass spectrometry (glc-ms), giving the same mass spectrum as the reference compound. In addition to the previously used 5% SE–30 and 5% XE–60 columns, a column (6 ft $\times$ 1/8 in.) of 3% JxR on Gas Chrom Q (100–120 mesh) was found to be in some ways superior (Varian model 204 or 2100 Aerograph). Preparative glc was carried out using columns of 5% SE–30 on Gas Chrom P (Varian model 202 Aerograph).

SPECIAL CHROMATOGRAPHIC SYSTEMS.—3-Hydroxy-4-methoxyphenethylamine, the isomeric 4-hydroxy-3-methoxyphenethylamine ("3-methoxytyramine"), and the purified phenolic alkaloid fractions of *T. cuzcoensis* and *Pachycereus pecten-aboriginum* were chromatographed on Whatman no. 1 paper with *n*-butanol–acetic acid–water (4:1:5) as solvent (13). After spraying with Gibbs' reagent, reference 3-hydroxy-4-methoxyphenethylamine (R_F 0.45) and the major phenolic alkaloid of *P. pecten-aboriginum* showed a blue color while the isomer 4-hydroxy-3-methoxyphenethylamine and the major phenolic compound from *T. cuzcoensis* (R_F 0.45) developed a brown color. Gibbs' reagent: 0.1% solution of 2,6-dichloroquinone chlorimide in ethanol followed by 10% sodium carbonate in water.

Reference 4-hydroxy-3-methoxyphenethylamine (R_F 0.60) 3-hydroxy-4-methoxyphenethylamine (R_F 0.45) and the two isomeric compounds isolated from cacti were well separated by tlc on silica gel G plates with chloroform–ethanol–diethylamine (85:5:10) as solvent (10).

The identity of 3-hydroxy-4-methoxyphenethylamine and the major phenolic alkaloid of *P. pecten-aboriginum* was further confirmed by glc using trimethylanilinium hydroxide (5) for on-column methylation of the phenolic groups. In both cases a major compound having the retention time of 3,4-dimethoxyphenethylamine was formed.

TABLE 1. *Occurrence of alkaloids.*[a]

	Lit. ref.	Presence of alkaloids[b]	Amount of alkaloids[c]	Alkaloids[d]
TRICHOCEREUS				
T. courantii (K. Sch.) Backb.	—	++	3	*N*-methyltyramine
			2	*N*-methyl-3-methoxytyramine
			1	tyramine
			1	3-methoxytyramine
			1	3,4-dimethoxyphenethylamine
T. cuzcoensis Br. & R.	—	+++	3	3-methoxytyramine
			1	tyramine
			1	mescaline
			tr.	3-hydroxy-4,5-dimethoxyphenethylamine
T. fulvilanus Ritt.	—	+++	2	tyramine
			2	*N*-methyltyramine
			tr.	mescaline
T. knuthianus Backb.	—	++	2	tyramine
			2	3-methoxytyramine

TABLE 1. *Continued*

	Lit. ref.	Presence of alkaloids[b]	Amount of alkaloids[c]	Alkaloids[d]
T. manguinii Backb.	—	++	2	tyramine
			2	*N*-methyltyramine
			2	hordenine
			1	3-methoxytyramine
T. purpureopilosus Wgt.	—	++	2	tyramine
			2	*N*-methyltyramine
T. santiaguensis (Speg.) Backbg.	—	+	2	hordenine
			2	tyramine
T. skottsbergii Backbg.	—	++	3	hordenine
			1	*N*-methyltyramine
T. strigosus (SD.) Br. & R.	—	++	4	hordenine
T. taquimbalensis Card.	—	++	3	mescaline
			1	hordenine
			tr.	3,4-dimethoxyphen-ethylamine
			tr.	3-methoxytyramine
T. thelegonoides (Speg.) Br. & R.	(15)	—	—	unknown
		++	4	hordenine
T. thelegonus (Web.) Br. & R.	(15)	—	—	unknown
		++	3	hordenine
			tr.	*N*-methyltyramine
T. tunariensis Card.	—	++	2	tyramine
			2	hordenine
T. validus (Monv.) Backb.	—	+++	3	mescaline
ECHINOPSIS				
E. rhodotricha K. Sch.	—	(+)	3	hordenine
			2	tyramine
			1	unknown
PACHYCEREUS				
P. pecten-aboriginum (Eng.) Br. & R.	(14, 15)	—	—	carnegine
		+	1	3-hydroxy-4-methoxyphen-ethylamine[e]
				Other alkaloids to be reported later. See footnote 3.
PELECYPHORA				
P. aselliformis Ehrenbg. (T.)	—	+	2	anhalidine
			2	hordenine
			2	unknown
			tr.	unknown
STETSONIA				
S. coryne (SD.) Br. & R.	(11, 15)	—	—	coryneine
		(+)+	3	3-methoxytyramine
			2	tyramine
			1	*N*-methyltyramine
			1	mescaline
			tr.	3,4-dimethoxyphen-ethylamine
			tr.	anhalonidine
			tr.	anhalidine

[a]Quarternary alkaloids or neutral compounds not included.
[b]Presence of alkaloids: +++ = over 50 mg/100 g; ++ = 10–50 mg/100 g; + = 1–10 mg/100 g; tr. = trace, less than 1 mg/100 g fresh plant.
[c]Per cent of alkaloid fraction: *4* = only alkaloid present; *3* = over 50%; *2* = 10–50%; *1* = 1–10%; tr. = trace, less than 1% of alkaloid fraction.
[d]All alkaloids were identified, as described previously (1), by comparison with reference compounds using thin-layer and gas chromatography and gas chromatography-mass spectrometry.
[e]Additional identification as described in the text.

RESULTS AND DISCUSSION

Our present screening for cactus alkaloids has largely been motivated by the search for biosynthetic intermediates in the formation of mescaline and related tetrahydroisoquinolines. Indeed, three phenolic alkaloids, 3-methoxytyramine (4-hydroxy-3-methoxyphenethylamine), 3-hydroxy-4,5-dimethoxyphenethlamine and 4-hydroxy-3,5-dimethoxyphenethylamine were identified in cacti (3) and were later shown to be true biosynthetic intermediates (9). Still, some plausible progenitors of the tetrahydroisoquinoline skeleton are lacking. Partly, using "mass fragmentography" (7) to simplify the search for likely, presumably phenolic phenethylamine intermediates, a number of the *Trichocereus* species and other cacti listed in table 1 were investigated. Some results with biogenetic implications are reported elsewhere (8). The identification of alkaloids have now been verified mainly by glc-ms and the final results reported here (table 1).

Earlier, we have investigated (1) twelve species of the genus *Trichocereus,* which according to Backeberg comprises in all 38 species. We have now (table 1) examined the alkaloids of 14 more *Trichocereus* species and identified, in all, eight different phenethylamines (table 1). These are previously all known (1) to occur in the genus *Trichocereus,* except *N*-methyl-3-methoxytyramine (*N*-methyl-4-hydroxy-3-methoxyphenethylamine), which is known only from peyote (8). Mescaline, previously isolated from five *Trichocereus* species (1), is now identified also in *T. cuzcoensis, T. fulvilanus, T. taquimbalensis* and *T. validus*. While it occurred as the major alkaloid in *T. taquimbalensis* and *T. validus,* mescaline was only a minor constituent in the two other species. It may also be pointed out that the alkaloid-rich *T. cuzcoensis* contained 3-methoxytyramine as the predominant alkaloid. The macroscopic appearance of the new mescaline-containing species resembled markedly the previously known species and in fact, based on their appearance they were predicted to contain mescaline.

Stetsonia coryne has previously been known (11) to yield the quarternary alkaloid coryneine (*N,N,N*-trimethyldopamine). The occurrence of tyramine and N-methyltyramine, plausible biochemical progenitors of coryneine, was thus to be expected (fig. 2). Furthermore, plants from three different sources of this species, which is a not too distant relative of the *Trichocereus* species, were found to contain beside two other simple phenethylamines small amounts of mescaline. Traces of two phenolic tetrahydroisoquinoline alkaloids, *viz.* anhalonidine and anhalidine were also identified.

Pachycereus pecten-aboriginum was already in 1929 by Späth and Kuffner (14) shown to contain carnegine. This cactus has now been found to contain several alkaloids as will be reported in a later publication[3]. However, the major compound of the phenolic alkaloid fraction turned out to be a hydroxy-methoxyphenethylamine, but surprisingly not the commonly occurring 3-methoxytyramine (4-hydroxy-3-methoxyphenethylamine), but rather the isomeric 3-hydroxy-4-methoxyphenethylamine as described in the experimental section. This latter compound might theoretically be a good precursor of some tetrahydroisoquinoline alkaloids, *e.g.,* carnegine and salsolidine, since it may provide an advantageous *para*-activation for the ring closure. Experiments on the biosynthesis of carnegine and salsolidine in *Carnegiea gigantea* have, however, not entirely supported such assumptions (6).

Pelecyphora aselliformis has been reported[4] to contain alkaloids—probably tetrahydroisoquinoline alkaloids. This is now found to be correct with the identification of anhalidine in addition to the ubiquitous hordenine. The structure of one major alkaloid of this species still awaits elucidation. In this connection, it is known (12) that cacti of several genera of Cactaceae, among them

[3]Unpublished data, Kapadia, G. and S. Agurell.
[4]Private communication, J. McLaughlin, 1969.

Pelecyphora, in Mexico are popularly, although for unknown reasons, classed as "peyote". Possibly, the alkaloids of *P. aselliformis* are responsible for its classification as a "peyote".

Echinopsis rhodotricha was earlier reported (1) not to contain detectable amounts of alkaloids. From a large amount of cacti we have now isolated small amounts of hordenine and tyramine.

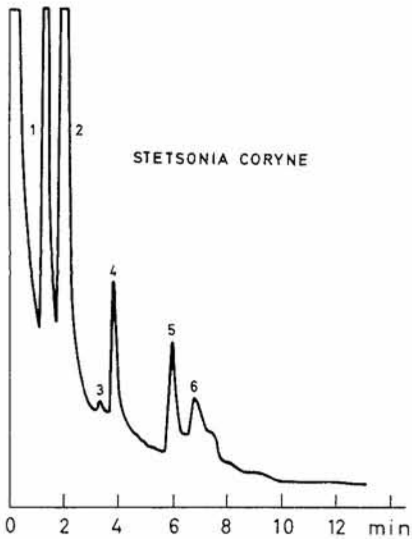

FIG. 2. *Gas chromatogram from glc-ms run of alkaloids of* Stetsonia coryne. 5% SE-30 on Gas Chrom P, 150°. *1* = tyramine and *N*-methyltyramine, *2* = 3-methoxytyramine, *3* = 3,4-dimethoxyphenethylamine, *4* = mescaline, *5* = anhalidine, *6* = anhalonidine.

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LITERATURE CITED

1. AGURELL, S. 1969. Cactaceae alkaloids. I. *Lloydia* **32:** 206–216.
2. AGURELL, S., J. LUNDSTRÖM and A. MASOUD. 1969. Cactaceae alkaloids. VII. Alkaloids from *Echinocereus merkeri* Hildm. *J. Pharm. Sci.* **58:** 1413–1414.
3. AGURELL, S. and J. LUNDSTRÖM. 1968. Apparent intermediates in the biosynthesis of mescaline and related tetrahydroisoquinolines. *Chem. Commun.* **1968:** 1638–1639.
4. BACKEBERG, C. 1959–1961. *Die Cactaceae, vol. I–VI.* Fischer Verlag, Jena.
5. BROCHMANN-HANSSEN, E. and T. O. OKE. 1969. Gas chromatography of barbiturates, phenolic alkaloids and xanthine bases. *J. Pharm. Sci.* **58:** 370–371.
6. BRUHN, J. G., U. SVENSSON and S. AGURELL. 1970. Biosynthesis of tetrahydroisoquinoline alkaloids in *Carnegiea gigantea* Br. & R. *Acta Chem. Scand.* **24:** 3375–3377.
7. HAMMAR, C.-G., B. HOLMSTEDT, J. E. LINDGREN and R. THAM. 1969. The combination of gas chromatography and mass spectrometry in the identification of drugs and metabolites. *Adv. Pharmacol. Chemotherap.* **7:** 53–89.
8. LINDGREN, J. E., S. AGURELL, J. LUNDSTRÖM and U. SVENSSON. 1971. Detection of biochemical intermediates by mass fragmentography. *FEBS Letters* **13:** 21–27.
9. LUNDSTRÖM, J. and S. AGURELL. 1969. A complete biosynthetic sequence to mescaline in two cactus species. *Tetrahedron Letters.* **1969:** 3371–3374.
10. LUNDSTRÖM, J. 1970. Biosynthesis of mescaline and 3,4-dimethoxyphenethylamine in *Trichocereus pachanoi* Br. & R. *Acta Pharm. Suecica* **7:** 651–666.
11. RETI, L. 1950. Cactus alkaloids and some related compounds. *Fortsch. Chem. Organ. Naturstoff.* **6:** 242–289.
12. SCHULTES, R. E. 1967. In *Ethnopharmacologic search for psychoactive drugs.* Public Health Service Publication no. 1645, U. S. Government Printing Office, Washington. pp. 37–39.
13. SENOH, S., J. W. DALY, J. AXELROD and B. WITKOP. 1959. Enzymatic *p-O*-methylation by catechol *O*-methyl transferase. *J. Am. Chem. Soc.* **81:** 6240–6245.
14. SPÄTH, E. and F. KUFFNER. 1929. Die Identität des Pectenins mit dem Carnegin. *Ber. Deut. Chem. Ges.* **62:** 2242–2243.
15. WILLAMAN, J. J. and B. G. SCHUBERT. 1961. *Alkaloid-bearing plants and their contained alkaloids.* U. S. Department of Agriculture, Technical Bulletin no. 1234, Washington.