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Cactus Alkaloids XVI: Isolation and Identification of Alkaloids in *Coryphantha ramillosa*

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Abstract ☐ The cactus genus *Coryphantha* has been reported to contain certain β-phenethylamine alkaloids. In this investigation, a Texas species, *C. ramillosa* Cutak, yielded five alkaloids which were isolated chromatographically and crystallized as their hydrochloride salts. The isolated compounds were identified as *N*-methyl-4-methoxy-β-phenethylamine hydrochloride, hordenine hydrochloride, *N*-methyltyramine hydrochloride, synephrine hydrochloride, and β-*O*-methylsynephrine hydrochloride, all of which have been previously identified in other *Coryphantha* species.

Keyphrases ☐ Cactus alkaloids—isolation, identification of alkaloids in *Coryphantha ramillosa* ☐ *Coryphantha ramillosa*—isolation, identification of alkaloidal content ☐ Medicinal plants—isolation, identification of alkaloids in *Coryphantha ramillosa* ☐ TLC—isolation, identification, alkaloids in *Coryphantha ramillosa*

Folk medicine of various peoples of the world has, of necessity, included many different plant drugs (1). One such product is the peyote cactus, which is still used as an amulet, hallucinogen, and panacea by the Indians of Mexico and the southwestern United States (2, 3). Phytochemical investigations of the peyote cactus, or *Lophophora williamsii* (Lem.) Coult., have shown the presence of mescaline, mescaline analogs (β-phenethylamines), tetrahydroisoquinolines, and other compounds, the presence of which explains some of the claimed effects of this plant (4–6). The hallucinogen, mescaline, has also been found in some other cactus species, especially in members of the South American genus trichocereus (7–9).

Knowledge of the alkaloid content of various cacti is significant since it can help to explain or disprove the claimed physiological effects of a particular species. Unfortunately, knowledge of the phytochemical distribution of even the various known cactus alkaloids is quite incomplete. The genus *Coryphantha* is a good example. This genus contains approximately 60 species (10, 11). *C. palmeri* Br. and R. has been reported to have folkloric use as a "narcotic" (12), and *C. macromeris* (Engelm.) Br. and R. has ostensibly obtained some stature as a "natural and legal" psychedelic (13). The presence of macromerine and normacromerine in this latter species may explain these reputed effects (14). The screening of seven species of *Coryphantha* previously demonstrated the presence of alkaloids in all seven, and six β-phenethylamines have been isolated and/or identified in *C. cornifera* (DC.) Br. and R. var. *echinus* (Engelm.) L. Benson (15). No information is available in the literature regarding the phytochemistry of *C. ramillosa* Cutak, a species from southern Texas and north-central Mexico. Although it has no recorded folkloric uses, it was selected for study in a search for unusual cactus alkaloids that might have psychotropic potential.

EXPERIMENTAL

Plant Material—Specimens of the cactus were purchased[1], and

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[1] From Homer A. Jones, Southwest Cactus Co., Alpine, Tex.

identification of the plants was made by comparison with the description of Benson (16)[2].

The cacti were sliced and thoroughly dried in a forced air oven at 48° for several days. The dry weight of the plant material was 1.3 kg., representing a weight loss of 3.3 kg. (72% moisture). The dried plant material was then comminuted in a large Wiley mill to obtain a coarse powder.

Preparation of Crude Alkaloid Fractions—The powdered plant material was defatted, basified, and extracted via chloroformic percolation as previously described (17, 18). Condensing the filtered chloroform extract produced a thick syrup, which was extracted with two successive 250-ml. portions of 1 N HCl; emulsions were treated essentially as was previously reported (19). After filtration, the aqueous solutions were combined and extracted with two successive 500-ml. volumes each of chloroform and ethyl ether to remove organic-soluble, nonalkaloidal material. The pH of the aqueous solution was then adjusted to 10.5 (pH meter) with 7.5 N sodium hydroxide, and alkaloids were extracted from the basic aqueous solution with three successive 500-ml. volumes each of chloroform and ethyl ether. These organic extracts were dried over anhydrous sodium sulfate, filtered, combined, and condensed under rotary vacuum to yield a residue (crude alkaloid Fraction A).

In previous studies it had been observed that the organic-extracted, basic, aqueous solution would still retain some water-soluble β-phenethylamines such as tyramine (19). Consequently, this solution was placed under rotary vacuum to remove traces of organic solvents and was then freeze dried. The residue from the lyophilization, largely sodium chloride, was extracted repeatedly with portions of an absolute ethanol–chloroform (1:9) mixture until the filtrates appeared colorless. The combined filtrates were then condensed under rotary vacuum to a small volume (crude alkaloid Fraction B).

Crude alkaloid Fraction A was separated into phenolic and nonphenolic portions by using an anion-exchange resin. The alkaloid fraction, dissolved in ethanol, was passed down a basic ion-exchange[3] column, and the phenolic and nonphenolic portions were obtained as previously described (17).

TLC—Previously described TLC techniques were used analytically to provide a tentative identification of alkaloids in the extracts and preparatively to separate the components (15, 17, 18, 20). Analytical TLC plates were prepared with a 0.25-mm. layer of silica gel G, and preparative plates were prepared with a 1-mm. layer of silica gel PF₂₅₄[4]. Analytical and preparative separations were achieved by the use of the following solvent systems: Solvent A, ethyl ether–methanol–28% ammonium hydroxide (20:2:1); Solvent B, ethyl ether–methanol–28% ammonium hydroxide (17:2:1); and Solvent C, chloroform–methanol–28% ammonium hydroxide (80:20:1). Solvent D, ethyl acetate–methanol–28% ammonium hydroxide (17:2:1), and Solvent E, benzene–chloroform–methanol–28% ammonium hydroxide (8:6:2:1), were used analytically only. The alkaloids were detected using dansyl chloride (0.05% in acetone) and tetrazotized benzidine spray reagents (17). The R_f values are not reported since routine chromatography with reference compounds provided a superior type of presumptive identification.

Resolution of Nonphenolic Alkaloids from Fraction A—Analytical TLC revealed that this fraction contained a single predominant alkaloid with only traces of other compounds. The entire extract, dissolved in ethanol, was streaked as a narrow band (21) onto five preparative TLC plates and developed with Solvent A. The compound was readily detected under UV light, and the appropriate bands were removed. The alkaloid was leached from the combined bands of the five plates by washing with 5 ml. of ammoniacal ethanol (28% ammonium hydroxide–ethanol, 1:19), centrifuging, and rewashing the adsorbent with two additional 5-ml. portions of the basic ethanol.

After filtration, the combined washings were reduced to near dryness under rotary vacuum. The residue was redissolved in a small amount of absolute ethanol. Analytical TLC indicated that

the alkaloid was chromatographically pure. The solution was then acidified (moist pH paper) with anhydrous hydrochloric acid in absolute ethanol (5% w/w). Ethyl ether was slowly added and the solution was refrigerated to cause crystallization of the hydrochloride salt.

Identification of Major Nonphenolic Alkaloid—Analytical TLC in Solvents A, B, D, and E of the major nonphenolic alkaloid and comparison with reference compounds (15) suggested that the alkaloid was N-methyl-4-methoxy-β-phenethylamine. The melting points[5] and mixed melting point were identical to that of authentic N-methyl-4-methoxy-β-phenethylamine hydrochloride (182.5–184°). The IR spectra[6] of the isolated and synthesized compounds were essentially the same, with distinctive absorption peaks noted at 1600, 1510, 1475, and 1095 cm.⁻¹. An interpretation of the NMR spectrum[7] of the isolated material was also consistent with that expected and observed for N-methyl-4-methoxy-β-phenethylamine hydrochloride. A pair of doublets centered at 7.1 δ integrated for four protons (aromatic), a three-proton singlet was noted at 3.8 δ (O-methyl), a diffuse doublet integrating for four protons was centered at 3.1 δ (methylene), and a three-proton singlet was seen at 2.7 δ (N-methyl). The molecular ion (m/e 165) observed upon mass spectrometry[8] of the isolated material was in agreement with the molecular weight of the proposed structure.

Resolution of Phenolic Alkaloids from Fraction A—Analytical TLC of this fraction revealed the presence of four major alkaloids. The extract was streaked as a narrow band onto eight preparative TLC plates. The first plate was developed once with Solvent B, and the remaining seven plates were developed twice with Solvent B, allowing a 15-min. interval of air drying between developments. Visualization under UV light allowed the detection of four major bands, which were removed and eluted with ammoniacal ethanol as already described. The residues of each of the four bands were dissolved in an amount of absolute ethanol suitable for analytical TLC.

Resolution of Alkaloids from Fraction B—Analytical TLC of this fraction indicated that it contained the same major alkaloids as observed in the phenolic portion of crude alkaloid Fraction A. This observation suggested the possibility of obtaining these phenolic alkaloids without passing the fraction through the anion-exchange column.

Upon storage of this concentrated fraction in ethanol and under refrigeration, abundant crystallization occurred. The crystals were filtered, rinsed twice with cold ethanol, and recrystallized from boiling benzene. The crystals were then converted to the hydrochloride salt as already described.

Separation of the alkaloids in the combined mother liquors from the ethanol and benzene crystallizations was achieved by preparative TLC. This material was applied as a narrow band onto 42 preparative plates, which were developed twice with Solvent B. The four major bands (A, B, C, and D, lettering from the top of the plate downward) were recovered, and each was eluted with 30 ml. of the ammoniacal ethanol followed by two elutions of 30 ml. each of ethanol. The eluants for each band were filtered, combined, and concentrated to dryness under rotary vacuum.

Further analytical TLC (appropriate selection of Solvent B, C, D, or E) with portions of these residues and the residues from the four phenolic alkaloid bands of Fraction A, with 10-mcg. quantities of reference compounds, provided tentative identifications of the phenolic alkaloids. Slight contamination of band B was observed; to purify this band, further preparative TLC was employed with Solvent C. Crystalline hydrochloride salts of the four compounds were then prepared as previously described.

Identification of Major Phenolic Alkaloids—The four major phenolic alkaloids, purified from Fractions A and B, had the same chromatographic properties as hordenine, β-O-methylsynephrine, N-methyltyramine, and synephrine. Since the alkaloids from Fraction B and the phenolic portion of Fraction A were identical, studies for verification of identity were carried out only with the crystalline alkaloids obtained from the respective bands of Fraction B.

Cochromatography of authentic hordenine and the crystals that were obtained prior to preparative TLC of Fraction B showed that these two compounds were identical. Analytical TLC (Solvents B

[3] A freeze-dried specimen was sent to Dr. L. Benson, Director, Herbarium of Pomona College, Claremont, Calif., who confirmed the identification and assigned the specimen herbarium No. 317944. In addition, living plants are being maintained for future reference in the greenhouse of the Drug Plant Laboratory, University of Washington.
[3] Amberlite IRA 401S C.P., Mallinckrodt Chemical Works.
[4] Brinkmann Instruments, Inc.

[5] Fisher-Johns melting-point apparatus, uncorrected.
[6] KBr pellets, Beckman IR5A spectrophotometer.
[7] Varian T-60, using 10 mg. of the hydrochloride in tetradeuterated methanol in a microcell.
[8] Performed at Hoffmann-La Roche Laboratories.

and D) further confirmed that band A corresponded to these crystals. Melting points and mixed melting points of authentic hordenine hydrochloride and the hydrochloride of this alkaloid were identical (180.5–181.5°). The IR spectra of hordenine hydrochloride and the isolated compound were also comparable, with distinctive absorption peaks in both spectra noted at 1610, 1512, 1454, and 1348 cm.$^{-1}$.

Reference β-O-methylsynephrine and band B consistently cochromatographed (Solvents B and C); their IR spectra, both as the hydrochlorides, exhibited absorption peaks at 2800, 1610, 1512, 1355, 1265, and 1093 cm.$^{-1}$ and agreed in their characteristic features. Additional analytical TLC revealed the presence of a slight contaminant in the isolated crystals, which was assumed to explain three minor peaks present in the IR spectrum of only the isolated β-O-methylsynephrine hydrochloride. The melting point of the isolated material was 182–184°, and no melting-point depression was noted on admixture with synthetic (racemic) material. The isolated compound was optically inactive.

TLC of band C (Solvents B, C, and D) and reference N-methyltyramine revealed the same chromatographic properties, and melting points of the isolated N-methyltyramine hydrochloride and reference N-methyltyramine hydrochloride were identical (150–151°). The IR spectra of both compounds, as the hydrochloride salts, were also comparable, with major absorption peaks noted at 1635, 1555, 1530, 1368, 1232, and 1191 cm.$^{-1}$.

Cochromatography of synthetic (racemic) synephrine and the alkaloid from band D (Solvents B, D, and E) revealed indistinguishable chromatographic properties for the isolated and reference compounds. The major peaks of the IR spectra of the two as hydrochlorides were very similar, with matching adsorption peaks at 1610, 1512, and 1449 cm.$^{-1}$. As previously noted (22), the IR spectra of salts of (—)- and (±)-synephrine present generally comparable absorption patterns but with some differences. The melting point of the hydrochloride of the isolated material was 166–167°, in contrast to racemic synephrine hydrochloride which melted at 156–158°. The salt of the isolated alkaloid was optically active: $[\alpha]_D^{27}$ —52.0°, c 7.6 mg./ml. in absolute methanol.

Cold Extraction Process—To eliminate the possibilities that the alkaloids might have been enzymatically modified during the slow heat drying process, that some thermolabile alkaloids had been destroyed or altered, or that the small amount of basic methanol involved in the maceration and extraction process might have caused β-O-methylation of syneprine (23), a second cactus sample was examined using a cold extraction process (24) and freeze-dried plant material.

The freeze-dried plant (45.5 g.) was sliced and ground to a powder in a blender at low speed. Cold ethanol was added and the mixture was blended for 25 min. The extract was filtered with the aid of reduced pressure and concentrated to 50 ml. under rotary vacuum (water bath at 36°). About 50 ml. of 5% hydrochloric acid was added and the mixture was shaken vigorously. This acidic ethanolic solution was extracted twice with 50-ml. portions of chloroform and twice with 50-ml. portions of ethyl ether. The pH of the aqueous fraction was then adjusted to 9.5 (pH meter) with 28% ammonium hydroxide. This extract was then run through a basic anion-exchange column, in the manner previously described, to separate phenolic and nonphenolic portions.

Comparison by analytical TLC of the nonphenolic portion obtained from the two different extraction methods revealed the same alkaloid composition. Resolution of the cold-processed nonphenolic extract to the point of crystallization also yielded the same compound as the procedure involving heat.

Comparison of the cold-processed phenolic extract with the previous phenolic extract from Fraction A substantiated the presence of the same alkaloid components in the phenolic extracts prepared by the two procedures.

DISCUSSION AND CONCLUSIONS

Chromatographic procedures have yielded the isolation of one nonphenolic and four phenolic alkaloids from *C. ramillosa*. Using melting points, spectral properties, and chromatographic similarities in comparisons with authentic compounds, identification of the isolated alkaloids was achieved. The isolated nonphenolic alkaloid was established to be N-methyl-4-methoxy-β-phenethylamine, and the identified phenolic alkaloids were hordenine, β-O-methylsynephrine, N-methyltyramine, and synephrine.

Table I—Quantities of Alkaloids Isolated from Soxhlet-Extracted Sample of *C. ramillosa*

	Yield[a], g.	Proportion of Total Alkaloid Fraction, %	Concentration in Cactus[b], %
Hordenine hydrochloride	11.530	91.8	0.73
N-Methyltyramine hydrochloride	0.692	5.5	0.043
β-O-Methylsynephrine hydrochloride	0.241	1.9	0.015
Synephrine hydrochloride	0.090	0.7	0.0057
N-Methyl-4-methoxy-β-phenethylamine hydrochloride	0.015	0.1	0.00092

[a] Reported yields represent the total quantities of alkaloid salts obtained upon processing 1.3 kg. of dried plant material. Phenolic alkaloids were recovered from both Fractions A and B. [b] Calculated as free alkaloid base in dried plant material.

Evidence was also obtained that indicated that the isolated compounds, especially β-O-methylsynephrine which is believed to be formed by β-O-methylation of synephrine during the extraction of tangerine leaves (23), were not artifacts due to the drying and/or extraction processes. These possibilities were discounted when freeze-dried cactus material processed by a cold extraction procedure with ethanol yielded the same alkaloid composition as the initial extracts. Furthermore, no evidence for β-O-methylsynephrine formation was detected when reference synephrine was chromatographed with methanol-containing solvent systems. Presumably, the optical inactivity of the isolated β-O-methylsynephrine hydrochloride indicated the occurrence of racemization of the natural material during either natural methylation or extraction and purification.

Analytical TLC evaluation illustrated that the five isolated alkaloids were present in the cactus in concentrations several times those of some unidentified trace alkaloids. The compound identified as hordenine was the major alkaloid; it was present in concentrations greater than 10 times that of any other single alkaloid (Table I). Such a high concentration of hordenine has not been observed in any of our previous studies of the cactus alkaloids.

N-Methyl-4-methoxy-β-phenethylamine was isolated previously from C. macromeris (Engelm.) Br. and R. var. runyonii L. Benson (24), Ariocarpus retusus Scheid. (25), and C. cornifera (DC.) Br. and R. var. echinus (Engelm.) L. Benson (15). Thus far, the natural occurrence of this compound has only been reported in the Cactaceae. No pharmacological studies concerning any possible psychotropic effects of this compound have been reported.

Hordenine and N-methyltyramine were previously isolated from several cactus species as well as from other plant families (8, 15, 17–20, 24, 26 inter alia). Both are known to have weak sympathomimetic activity (27–29).

β-O-Methylsynephrine was isolated previously from the cactus C. cornifera var. echinus (15). No reported studies concerning its pharmacological activities were detected in the literature; however, a similar compound, β-O-methylepinephrine, produces CNS stimulation (30).

Traces of synephrine itself were detected previously in different coryphantha species, and it was isolated from C. macromeris var. runyonii (24) as well as from tangerine leaves (22). This compound is a known sympathomimetic (29).

The presence of these sympathomimetic β-phenethylamines in C. ramillosa confers physiological activity on the cactus and suggests that consumption of it (minus the abundant spines, of course) might cause some stimulant effects.

SUMMARY

This investigation provides the first reported study of the alkaloid content of the cactus C. ramillosa. The isolated and identified β-phenethylamine alkaloids included N-methyl-4-methoxy-β-phenethylamine, hordenine, β-O-methylsynephrine, N-methyltyramine, and synephrine.

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Simplified NMR Spectra of Bifunctional Tropanes Induced by the Paramagnetic Shift Reagent Tris(dipivalomethanato)europium(III)

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Abstract ☐ Tris(dipivalomethanato)europium(III) has been used as an NMR shift reagent to obtain simplified spectra of tropine, pseudotropine, nortropine, nortropinone, and tropinone. All compounds gave spectra at 60 MHz., which could be interpreted with the aid of spin-spin decoupling. Insofar as the Karplus rule holds for the piperidine ring system, deshielded spectra clearly evidenced a distorted chair form predominating in the conformational equilibrium of α- and β-tropines and tropinones. The results demonstrate the applicability of the shift reagent used with bifunctional systems containing two different heteroatoms. The observed order of coordination was secondary amine > secondary alcohol > tertiary amine ≧ ketone.

Keyphrases ☐ Tropanes, bifunctional—simplified NMR spectra induced by tris(dipivalomethanato)europium(III) ☐ Tris(dipivalomethanato)europium(III)—used as NMR shift reagent to produce simplified spectra for bifunctional tropanes ☐ NMR spectroscopy—tris(dipivalomethanato)europium(III) shift reagent used to produce simplified bifunctional tropane spectra ☐ Paramagnetic shifts induced by tris(dipivalomethanato)europium(III)—simplified spectra of bifunctional tropanes

Tris(dipivalomethanato)europium(III) (I) has been the most extensively studied of the NMR shift reagents now available. This reagent produces paramagnetic shifts that remarkably simplify the NMR spectra of compounds containing heteroatoms for coordinative bonding with the reagent lanthanide.

The europium deshielded NMR represents a time-averaged spectrum between free substrate molecules