Cactus Alkaloids XV: β-Phenethylamine Derivatives from *Coryphantha macromeris* var. *runyonii*

W. J. KELLER, J. L. McLAUGHLIN*, and L. R. BRADY▲

Abstract □ Eleven β-phenethylamine derivatives were isolated and identified from fresh-frozen specimens of *Coryphantha macromeris* var. *runyonii* (Br. and R.) L. Benson. Isolations were accomplished using preparative TLC, and identifications were based on chromatographic properties, IR and NMR spectra, and comparisons with authentic materials. The data provide initial documentation for: the occurrence of *N*-formylnormacromerine in nature; the first recorded detection of metanephrine and *N*-methylmetanephrine in the plant kingdom; the first occurrence of synephrine and *N*-methyltyramine in this cactus; confirmation of earlier GLC–mass spectral data on the presence of *N*-methyl-4-methoxy-β-phenethylamine, *N*-methyl-3,4-dimethoxy-β-phenethylamine, tyramine, and hordenine in the plant; and verification of previous reports on the isolation of macromerine and normacromerine.

Keyphrases □ Cactus alkaloids—isolation, identification of 11 β-phenethylamine derivatives from *Coryphantha macromeris* var. *runyonii* □ *Coryphantha macromeris* var. *runyonii*—isolation and identification of 11 β-phenethylamine derivatives □ *N*-Formylnormacromerine—isolation, identification from *Coryphantha macromeris* □ Metanephrine and *N*-methylmetanephrine—isolation, identification from *Coryphantha macromeris* □ Synephrine—isolation, identification from *Coryphantha macromeris* □ *N*-Methyltyramine—isolation, identification from *Coryphantha macromeris*

Dona Ana [*Coryphantha macromeris* (Engelm.) Br. and R.] is currently being promoted as a "natural and legal" psychedelic agent (1). The hallucinogenic alkaloid, (−)-macromerine (*N*,*N*-dimethyl-3,4-dimethoxy-β-hydroxy-β-phenethylamine), has been isolated from the cactus (2), and *C. runyonii* Br. and R., which is considered currently to be a variety of the former species (3), yielded the same compound (4). *N*-Methyl-4-methoxy-β-phenethylamine, *N*-methyl-3,4-dimethoxy-β-phenethylamine, tyramine, and hordenine (*N*,*N*-dimethyltyramine) were detected as minor alkaloids of *C. macromeris* var. *runyonii* (Br. and R.) L. Benson by combining GLC with mass spectrometry (5, 6). Recently, (−)-normacromerine (*N*-demethylmacromerine) was observed to be a major nonphenolic alkaloid of this variety (7).

The present phytochemical studies of *C. macromeris* var. *runyonii* were undertaken to isolate and confirm the identities of previously detected alkaloids and to continue an examination of the alkaloid fraction of this cactus.

EXPERIMENTAL[1]

Plant Material—Living specimens of *C. macromeris* var. *runyonii*[2] were purchased from two commercial sources[3]. A portion of each shipment was frozen immediately upon receipt, and the remainder was oven dried at 48° and ground to a coarse powder.

Isolation of Crude Alkaloid Fractions—Fresh-frozen plant material (2.54 kg.) was diced and homogenized with 95% ethanol in a large blender[4]. The extraction was carried out before any appreciable thawing had occurred, thereby effectively chilling the extraction mixture. The filtered ethanolic extract was concentrated to approximately one-fourth volume under reduced pressure at 45°. This aqueous solution was acidified by addition of 600 ml. of 25% acetic acid and was extracted with two successive 500-ml. portions each of ether, ethyl acetate, and chloroform to remove the nonpolar, nonalkaloidal material. The resulting aqueous solution was rendered basic with 28% ammonium hydroxide, and the alkaloids were extracted successively with three 500-ml. volumes of chloroform and one 500-ml. volume of ether. Then the combined chloroform–ether extract was filtered through anhydrous sodium sulfate and concentrated to a syrup; this crude alkaloidal mixture was resolved into phenolic and nonphenolic fractions, using an ion-exchange resin as previously described (8).

TLC—A 0.25-mm. layer of silica gel GF_{254} was used for the analytical TLC plates, and the preparative TLC plates were prepared with a 1-mm. layer of silica gel PF_{254}[5]. Five solvent systems were used for the various analytical and preparative separations: A, benzene–chloroform–methanol–28% ammonium hydroxide (8:6:5:1); B, ether–methanol–28% ammonium hydroxide (20:2:1); C, chloroform–*n*-butanol–methanol–28% ammonium hydroxide (145:3:42:10); D, ether–acetone–methanol–28% ammonium hydroxide (9:8:2:1); and E, ethyl acetate–methanol–28% ammonium hydroxide (17:2:1). Alkaloids on the chromatograms were detected under shortwave UV light followed by use of dansyl chloride (0.05% in acetone) and tetrazotized benzidine spray reagents (8).

Synthesis of Reference Nonphenolic Alkaloids—Established synthetic procedures were used to produce racemic macromerine (2) and normacromerine (7). Reference *N*-methyl-3,4-dimethoxy-β-phenethylamine was synthesized by refluxing equimolar quantities of 3,4-dimethoxyphenethylamine[6] and ethyl formate[7] to give an *N*-formyl intermediate, which was subsequently reduced with lithium aluminum hydride to yield the desired product. After purification by preparative TLC with Solvent A, the product was converted to the hydrochloride and then recrystallized from absolute ethanol–ether (49% yield). A similar procedure was employed for the production of reference *N*-methyl-4-methoxy-β-phenethylamine hydrochloride (46% yield), using 4-methoxyphenethylamine[8] as the reactant.

Resolution of Nonphenolic Alkaloids—Analytical TLC using Solvents A, B, and E revealed the presence in this fraction of seven alkaloid-positive substances, two of which were present only in trace amounts. The alkaloid mixture was dissolved in ethanol–chloroform (1:1) and streaked onto 78 preparative TLC plates using

[1] UV spectra were determined in absolute methanol with a Beckman DB spectrophotometer scanning from 340 to 200 nm. IR spectra were obtained neat or using KBr pellets with a Beckman IR5A. NMR spectra were recorded on a Varian T-60 NMR spectrometer using $CDCl_3$ or D_2O solutions. Specific rotations were determined with a Rudolph polarimeter using a sodium lamp and a 2-dcm. tube. Melting points were taken with a Fisher-Johns melting-point apparatus and are uncorrected.

[2] Identification was confirmed by Dr. E. F. Anderson, Department of Biology, Whitman College, Walla Walla, WA 99362. Representative plants are being maintained as greenhouse specimens.

[3] From Sunderland's Cactus Garden, Alamo, TX 78516, and Texas Cactus Gardens, Canutillo, TX 79835

[4] Waring.

[5] Brinkmann Instruments.

[6] Calbiochem.

[7] Aldrich Chemical Co.

[8] Calbiochem.

a previously described technique (9). The alkaloid material was eluted from the silica gel scrapings with three portions of 95% ethanol; the extracts were filtered, combined, and concentrated to near dryness under reduced pressure. The residue in each case was taken up in 40 ml. of 5% HCl, and the solution was rendered distinctly alkaline with 28% ammonium hydroxide and extracted immediately with three 50-ml. portions of chloroform. The chloroform extracts were filtered through sodium sulfate, combined, and reduced to a 5-ml. volume with a rotary evaporator. At this point, each alkaloidal solution was monitored for indication of impurities using TLC, the chloroform was evaporated from the solutions under a stream of nitrogen, and the residues were dissolved in 5 ml. of 95% ethanol and stored under nitrogen in a freezer.

This initial resolution of the nonphenolic alkaloid fraction resulted in two chromatographically pure alkaloids and a ternary mixture. Cochromatography with reference materials suggested that the pure alkaloids were (−)-normacromerine and (−)-macromerine and that the ternary mixture consisted of *N*-methyl-4-methoxy-β-phenethylamine, *N*-methyl-3,4-dimethoxy-β-phenethylamine, and an unidentified compound.

Resolution of Ternary Nonphenolic Mixture—An equal volume of chloroform was added to the ethanolic solution of the ternary alkaloid mixture, and the material was streaked onto 44 preparative TLC plates. Solvent B resolved the mixture into three components, which were removed and processed as already described. The chromatographic evaluations revealed no impurities in the isolated constituents.

Identification of Known Nonphenolic Alkaloids—The ethanolic solutions of the isolated alkaloids were evaporated under a stream of nitrogen, the residues were taken up in 0.7 ml. of deuterochloroform[9], and the NMR spectra were recorded. Deuterium-exchange experiments were carried out in the cases of macromerine and normacromerine. The deuterochloroform solutions were then evaporated to dryness under nitrogen, the residues were dissolved in small volumes of absolute ethanol, the solutions were acidified with anhydrous hydrochloric acid in absolute ethanol (5% w/w), and anhydrous ether was added slowly to effect the crystallization of the hydrochloride salts. One recrystallization from absolute ethanol assured chemical purity. The yields of crystalline hydrochloride salts, the melting points, and the IR spectra (KBr pellet) were recorded. Various properties of the isolated alkaloids corresponded with those reported for normacromerine (7), macromerine (2, 4, 10), *N*-methyl-3,4-dimethoxy-β-phenethylamine (11, 12), and *N*-methyl-4-methoxy-β-phenethylamine (11). Identifications were confirmed by direct comparisons of corresponding IR and NMR spectra of the isolated constituents and synthetic reference compounds.

Characterization of Unknown Nonphenolic Alkaloid—The isolated material was a chromatographically homogeneous (Solvent A, R_f 0.70; Solvent B, R_f 0.42; Solvent E, R_f 0.47), golden-yellow oil which possessed some distinctive properties. The constituent failed to react or to give visible chromophores with the dansyl chloride and tetrazotized benzidine reagents, but it could be detected with Dragendorff's reagent. It also failed to form a crystalline hydrochloride salt. The UV spectrum (0.0066 mg./ml. absolute methanol) showed indication of a λ_{max} at 201 (ε 32,200) and peaks at 229 (ε 6100) and 278 (ε 1800) nm., absorption features indicative of a 3,4-dimethoxy-β-phenethylamine (12). The IR spectrum (neat) exhibited a broad hydroxyl band near 3333 $cm.^{-1}$ and an intense carbonyl stretching vibration at 1642 $cm.^{-1}$. The remainder of the IR spectrum was typical for a phenethylamine derivative. An interpretation of the NMR spectrum (deuterochloroform) was quite informative regarding the structure of the unknown alkaloid. A skewed pair of singlets at 7.95 δ integrating for one proton was attributed to an *N*-formyl proton, peaks at 6.99 and 6.91 δ were indicative of three aromatic protons, and a coalescent doublet centered at 3.88 δ indicated two methoxyl groups. A benzylic hydroxyl proton (4.2 δ) exhibited shifts with concentration differences and disappeared with deuterium exchange. Complex multiplets centered at 4.8 and 3.4 δ indicated a benzylic proton and a methylene group, respectively, while a three-proton singlet at 2.9 δ characterized an *N*-methyl group. On the basis of these data, it appeared that the new alkaloid was the *N*-formyl analog of normacromerine. Synthetic normacromerine was refluxed with an equimolar quantity of ethyl formate to obtain a reference sample of *N*-formylnormacromerine. Comparison of the isolated and synthetic materials revealed indistinguishable UV, IR, and NMR spectra and chromatographic properties.

Resolution of Phenolic Alkaloids—Five major constituents and traces of three other compounds were detected using analytical TLC with Solvents C and D. The phenolic alkaloid fraction was dissolved in an ethanol–chloroform (1:1) mixture and streaked onto 38 preparative TLC plates. After development with Solvent C, the individual plates and resulting silica gel scrapings were processed in the same manner described for the nonphenolic fraction. This separation process resulted in four fractions, three of which were chromatographically pure; the fourth fraction was a binary mixture. Chromatographic comparisons[10] indicated that the pure alkaloids were synephrine, metanephrine, and hordenine and that the binary mixture contained tyramine and *N*-methyltyramine.

Resolution of Binary Phenolic Mixture—The binary fraction was dissolved in a suitable volume of ethanol–chloroform (1:1) and streaked onto nine preparative TLC plates. The plates were developed with Solvent D, and the two desired bands were processed in the usual manner.

Identification of Phenolic Constituents—Characterization of the five isolated constituents proceeded essentially as described for the nonphenolic alkaloids. The observed melting points and IR spectra of the hydrochloride salts corresponding to hordenine and *N*-methyltyramine agreed with reported properties for these substances (8, 12–14). Identifications were confirmed by direct comparisons of IR and NMR spectra of the isolated and reference materials.

The melting points and the IR spectra of the salts from the fractions chromatographically identified as metanephrine, synephrine, and tyramine were consistent with anticipated and reported properties for the corresponding salts (14–16), and no distinctive features were noted upon direct comparisons of the IR spectra of isolated and reference compounds. The small quantities of these three constituents obtained from the cactus (Table I) were insufficient for the determination of NMR spectra. Since tyramine had been detected previously in the plant (5), the chromatographic, melting-point, and IR spectral data were considered adequate to confirm the identity of this constituent. However, NMR spectra or some additional evidence appeared desirable with the other two compounds since the occurrence of metanephrine in the plant kingdom was unknown, since the presence of synephrine in this cactus was unrecorded, and since the IR spectra of the racemate and levorotatory isomer of synephrine were known to exhibit some differences (16).

Preliminary experiments with oven-dried cactus material indicated that the integrity and concentration of both metanephrine and synephrine were unaltered, even though the heat-drying process appeared to produce some artifacts. Thus, an available supply of dried cactus was processed to obtain sufficient quantities of metanephrine and synephrine for further characterization. The coarsely powdered plant material (1.55 kg.) was extracted exhaustively with methanol in a large blender, and the methanolic solution was removed by filtration. The thick syrup, which was obtained upon removal of the methanol under reduced pressure, was acidified with 700 ml. of 5% HCl and filtered. The acidic solution was extracted twice with approximately 700-ml. volumes of a series of organic solvents (petroleum ether, ether, ethyl acetate, and chloroform). This aqueous solution was then adjusted to pH 10.5 (pH meter) with 7.5 *N* NaOH and again subjected to partitioning with the series of organic solvents. The resulting aqueous solution, which contained relatively water-soluble constituents including metanephrine and synephrine, was placed under reduced pressure in a rotary evaporator to remove traces of the organic solvents and was freeze dried. The residue from lyophilization was extracted several times with an ethanol–chloroform (1:9) mixture, and the combined extract was concentrated to a small volume under reduced pressure and examined chromatographically. The concentrated extract, which contained a number of nonalkaloidal substances, was subjected to ion-exchange chromatography[11] and an established method (8) to give an aqueous phenolic fraction rich in metanephrine and synephrine with only traces of other phenolic alkaloids and contaminants. This

[9] Tetramethylsilane from Stohler Isotope Chemicals was used as the internal standard.

[10] Sources of reference phenolic alkaloids: hordenine sulfate and tyramine hydrochloride, Nutritional Biochemicals Corp.; *N*-methyltyramine hydrobromide, courtesy of Hoffmann-La Roche, Inc.; synephrine tartrate, K & K Laboratories, Inc.; and metanephrine hydrochloride, Sigma Chemical Co.

[11] Using Amberlite IRA-401S C.P., Mallinckrodt Chemical Works.

phenolic fraction, dissolved in a small volume of equal parts of ethanol and chloroform, was streaked onto 48 preparative TLC plates. Solvent C was used to achieve separation, and processing of the desired bands gave chromatographically homogeneous, ethanolic extracts of the two phenolic alkaloids.

The ethanolic extract containing synephrine was evaporated to dryness under nitrogen. A portion of the residue was taken up in 4 ml. of absolute methanol, the solution was heated to boiling, and 12 mg. of dry oxalic acid was added. Crystals of synephrine oxalate formed upon cooling, and recrystallization from aqueous methanol gave 13 mg. of material, m.p. 223–224° dec. [lit. (16) m.p. 221–222° dec.]. The remaining portion of the isolated alkaloid was dissolved in a minimum volume of absolute ethanol and converted to the hydrochloride salt; one recrystallization gave a yield of 33 mg., m.p. 166–167°. A portion of the hydrochloride salt (13 mg.) was placed in an NMR tube, 0.7 ml. of D_2O and a small quantity of an internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate[12]) were added, and the NMR spectrum was recorded. The number of exchangeable protons was determined by the integration difference of the sample and a D_2O–internal standard blank of comparable volume run at the same spectrum and integral amplitudes. The observed NMR spectrum of the salt of the isolated alkaloid followed a predictable chemical-shift pattern and proved to be identical to the spectrum obtained with reference material. The hydrochloride salt of the isolated synephrine was levorotatory: $[\alpha]_D^{27}$ −52.5° (c 0.010 g./ml. in absolute methanol).

The ethanolic extract of the isolated metanephrine was evaporated to dryness under nitrogen, and the entire residue was converted to the hydrochloride salt. One recrystallization from absolute ethanol–ether gave 9 mg. of crystalline material, m.p. 158–159°. The NMR spectral studies were carried out with the hydrochloride in D_2O solution as described for synephrine. The predicted NMR spectrum and an excellent NMR spectral correlation between the isolated and reference compounds provided the desired evidence to confirm the presence of metanephrine in the plant extracts. The small quantity of isolated material did not permit determination of optical rotation.

DISCUSSION AND CONCLUSIONS

Five nonphenolic and five phenolic β-phenethylamine derivatives were isolated and identified from *C. macromeris* var. *runyonii* (Table I). Trace quantities of two nonphenolic and three phenolic constituents[13] were also detected, but the minimal amounts of these substances in the quantity of cactus employed in the investigation precluded their purification and characterization. The use of a cold extraction process and fresh-frozen plant material, except for certain studies on metanephrine and synephrine, circumvented the possibility of artifact formation during slow thermal drying. Thus, the 10 isolated compounds, as well as the five unidentified alkaloid-positive substances which were detected, were considered to be metabolic constituents of the cactus.

Identifications of the 10 isolated constituents were based on chromatographic properties, melting points of salts, IR and NMR spectra, and direct comparisons with reference materials. The only exceptions to this protocol involved *N*-formylnormacromerine, which did not form a salt, and the omission of NMR data for tyramine.

N-Formylnormacromerine, metanephrine, and synephrine were the most interesting of the isolated constituents. The natural occurrence of *N*-formylnormacromerine was previously unrecognized. Alkaloids with amide functions are uncommon, and within the Cactaceae, only peyote [*Lophophora williamsii* (Lem.) Coult.] had been shown to possess *N*-formyl derivatives (17). The presence of metanephrine in a biological system was initially demonstrated by Axelrod *et al.* (18), and various chemical and physiological parameters of this metabolite of epinephrine have been studied (19, 20). However, all prior reports directly or indirectly restrict the known occurrence of metanephrine to zoological entities. The natural occurrence of synephrine was first reported from tangerine leaves (16), and until recently it was restricted to the Rutaceae. The known distribution of synephrine has been expanded by its reported presence in genera from the Amaryllidaceae and Moraceae (21), its detection in seven species of coryphantha (22), and its isolation from *C. ramillosa* (15). Identification of synephrine as a constituent of *C. macromeris* var. *runyonii* provides a further expansion of knowledge on the occurrence of this sympathomimetic compound.

The data provided the first evidence for the occurrence of *N*-methyltyramine in *C. macromeris* var. *runyonii;* however, this constituent was known to be distributed widely in the Cactaceae (5, 8, 12–14, 22) and had been detected in other plant families (21). The isolation of hordenine, *N*-methyl-3,4-dimethoxy-β-phenethylamine, *N*-methyl-4-methoxy-β-phenethylamine, and tyramine confirmed earlier GLC–mass spectral data (5, 6) on the presence of these constituents in this cactus. The identification of macromerine and normacromerine from the plant verified previous reports (2, 4, 7).

Macromerine (2), synephrine (23), and the less potent constituents (19, 23–25), hordenine, metanephrine, *N*-methyltyramine, and tyramine, are known to possess sympathomimetic properties. The occurrence of these constituents in the cactus may provide a scientific basis for the purported use of Dona Ana as a CNS stimulant.

Table I—Quantities of β-Phenethylamine Constituents Isolated from Fresh-Frozen *C. macromeris* var. *runyonii*

	Yield[a], g.	Concentration in Cactus[b], %
Nonphenolic constituents:		
Normacromerine hydrochloride	2.133	0.0710
N-Formylnormacromerine (oil)	0.195	0.0077
Macromerine hydrochloride	0.062	0.0021
N-Methyl-3,4-dimethoxy-β-phenylamine hydrochloride	0.019	0.0006
N-Methyl-4-methoxy-β-phenethylamine hydrochloride	0.014	0.0005
Phenolic constituents:		
N-Methyltyramine hydrochloride	0.059	0.0019
Hordenine hydrochloride	0.012	0.0004
Metanephrine hydrochloride	0.006	0.0002
Synephrine hydrochloride	0.003	0.0001
Tyramine hydrochloride	0.002	0.0001

[a] Reported yields represent the total quantities of the constituents or their salts, as indicated, obtained upon processing 2.54 kg. of fresh-frozen plant material. [b] Calculated as free β-phenethylamine in fresh plant material.

REFERENCES

(1) M. J. Superweed, "Herbal Highs," Stone Kingdom Syndicate, San Francisco, Calif., 1970, p. 5.

(2) J. F. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Lett.*, **14**, 1321(1967).

(3) L. Benson, *Cact. Succ. J.*, **41**, 185(1969).

(4) L. E. Below, A. Y. Leung, J. L. McLaughlin, and A. G. Paul, *J. Pharm. Sci.*, **57**, 515(1968).

(5) S. Agurell, *Lloydia*, **32**, 206(1969).

(6) S. Agurell, *Experientia*, **25**, 1132(1969).

(7) W. J. Keller and J. L. McLaughlin, *J. Pharm. Sci.*, **61**, 147 (1972).

(8) J. L. McLaughlin and A. G. Paul, *Lloydia*, **29**, 315(1966).

(9) W. J. Keller and F. R. Cole, *ibid.*, **32**, 498(1969).

(10) A. LaManna, A. Campiglio, and G. Pagani, *Farmaco, Ed. Sci.*, **15**, 9(1960).

(11) J. M. Neal and J. L. McLaughlin, *Lloydia*, **33**, 395(1970).

(12) W. W. Speir, V. Mihranian, and J. L. McLaughlin, *ibid.*, **33**, 15(1970).

[12] Isotopic Products, Merck Sharp and Dohme of Canada, Ltd.

[13] *Note added in proof:* Further observations have provided tentative identification of one of the trace phenolic alkaloids as *N*-methylmetanephrine. The synthesis of reference *N*-methylmetanephrine involved condensation of *O*-acetylvanillin and nitromethane, catalytic reductive methylation with hydrogen and formaldehyde, hydrolysis, and purification by preparative TLC with Solvent C. A six-proton *N*-methyl peak, rather than a three-proton peak, was the only significant NMR spectral difference between the synthetic product and reference metanephrine. The synthetic *N*-methylmetanephrine and one of the bands isolated (yield approximately 1 mg.) during preparative TLC of the phenolic alkaloid fraction were indistinguishable with TLC Solvents A and C, and both the synthetic and isolated materials were extremely labile. This chromatographic detection provides the first evidence for the occurrence of *N*-methylmetanephrine in the plant kingdom.

(13) J. M. Neal, P. T. Sato, C. L. Johnson, and J. L. McLaughlin, *J. Pharm. Sci.*, **60**, 477(1971).
(14) J. M. Neal, P. T. Sato, and J. L. McLaughlin, *Econ. Bot.*, **25**, 382(1971).
(15) P. T. Sato, J. M. Neal, L. R. Brady, and J. L. McLaughlin, *J. Pharm. Sci.*, **62**, 411(1973).
(16) I. Stewart, W. F. Newhall, and G. J. Edwards, *J. Biol. Chem.*, **239**, 930(1964).
(17) G. J. Kapadia and H. M. Fales, *Chem. Commun.*, **1968**, 1688.
(18) J. Axelrod, S. Senoh, and B. Witkop, *J. Biol. Chem.*, **233**, 697(1958).
(19) W. Haefely, A. Huerlimann, and H. Thoenen, *Helv. Physiol. Pharmacol. Acta*, **22**, 125(1964).
(20) P. B. Molinoff and J. Axelrod, *Ann. Rev. Biochem.*, **40**, 465 (1971).
(21) T. A. Wheaton and I. Stewart, *Lloydia*, **33**, 244(1970).
(22) K. M. Kelley Hornemann, J. M. Neal, and J. L. McLaughlin, *J. Pharm. Sci.*, **61**, 41(1972).
(23) D. J. Triggle, in "Medicinal Chemistry," 3rd ed., A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p. 1235.
(24) L. Reti, in "The Alkaloids," vol. 3, R. H. F. Manske and H. L. Holmes, Eds., Academic, New York, N.Y., 1953, p. 330.
(25) B. J. Camp, *Amer. J. Vet. Res.*, **31**, 755(1970).

ACKNOWLEDGMENTS AND ADDRESSES

Received May 12, 1972, from the *Drug Plant Laboratory, School of Pharmacy, University of Washington, Seattle, WA 98105*
Accepted for publication October 10, 1972.
Presented to the Pharmacognosy and Natural Products Section, APhA Academy of Pharmaceutical Sciences, Houston meeting, April 1972.
Supported in part by U. S. Public Health Service Grant MH-17128-03 from the National Institute of Mental Health.
W. J. Keller acknowledges the Sydnor Barksdale Penick Memorial Fellowship from the American Foundation for Pharmaceutical Education and expresses appreciation to Dr. W. L. Nelson, Dr. A. D. Blair, and Mr. A. N. Kotake, University of Washington, for valuable discussions and suggestions.
• Present address: Department of Medicinal Chemistry and Pharmacognosy, Purdue University, Lafayette, IN 47907
▲ To whom inquiries should be directed.

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

P. T. SATO, J. M. NEAL, L. R. BRADY, and J. L. McLAUGHLIN▲

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

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