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CACTUS ALKALOIDS. LIII. CORYPHANTHINE AND *O*-METHYL-CANDICINE, TWO NEW QUATERNARY ALKALOIDS FROM *CORYPHANTHA GREENWOODII*

B.N. MEYER, J.S. HELFRICH, D.E. NICHOLS, J.L. MCLAUGHLIN,

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences

D.V. DAVIS, and R.G. COOKS

Department of Chemistry, School of Science, Purdue University, West Lafayette, IN 47907

ABSTRACT.—Two new quaternary cactus alkaloids were detected in polar extracts of *Coryphantha greenwoodii* by tlc. These alkaloids were crystallized and spectrally identified as *N,N,N*-trimethyl-4-methoxyphenethylamine chloride (*O*-methylcandicine, **1**) and (+)-*N,N,N*-trimethyl-β-methoxyphenethylamine chloride (coryphanthine, **2**). Synthesis of both compounds confirmed the structural identifications. Secondary ion mass spectrometry (sims) was invaluable in determining the molecular weights of these nonvolatile compounds.

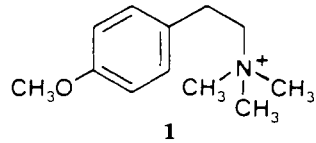
More than 200 alkaloids and related compounds have now been identified in cacti; yet, excluding choline, only five quaternary cactus alkaloids (lophotine, anhalotine, peyotine, coryneine, and candicine) have been reported (1). The first three of these are from peyote, *Lophophora williamsii* (Lem.) Coult. (2,3), while candicine (*N,N,N*-trimethyltyramine) is the most common, having been found in seven of the approximately 180 known alkaloidiferous cactus species (1). Because of the complexity of polar plant extracts, such quaternary compounds are generally difficult to detect, purify, and isolate by classical chromatographic techniques, and the paucity of reported quaternary cactus alkaloids undoubtedly reflects these difficulties.

The direct analysis of plant materials and crude extracts for cactus alkaloids is now possible using mass spectrometry/mass spectrometry (ms/ms), and these techniques can be used to detect new compounds, conduct chemotaxonomic surveys, find suspected biosynthetic intermediates, eliminate extraction artifacts, and map the distribution of alkaloids in plant tissues (4-7). The nonvolatility of quaternary alkaloids precludes their analyses by usual ms/ms techniques. However, we have successfully volatilized candicine by laser desorption (ld) and subsequently detected it by ms/ms; the combined ld/ms/ms method served to detect candicine in the screening of crude ethanolic extracts of cacti (8). We have also found that candicine will volatilize intact using secondary ion ms (sims) procedures, and this technique is, thus, available for detection and molecular weight determination of simple quaternary alkaloids.

In the present study, two new quaternary alkaloids were detected by thin-layer chromatography (tlc) in ethanol extracts of *Coryphantha greenwoodii* H. Bravo. This Mexican species belongs to the alkaloid-rich *Coryphantha* genus, which contains possible psychotropic β-phenethylamines (9,10). Previous phytochemical investigations with *C. greenwoodii* (11,12) have resulted in either the isolation or detection of seven β-phenethylamines: normacromerine, β-*O*-methylnormacromerine [(−)-calipamine], *N*-methyl-3,4-dimethoxyphenethylamine, *N,N*-dimethyl-3,4-dimethoxyphenethylamine, synephrine, β-*O*-methylsynephrine, and hordenine (*N,N*-dimethyltyramine).

A larger amount of plant material (150 g) was extracted with ethanol, and the condensed extract was partitioned between chloroform and basified water. The aqueous fraction was freeze-dried, and addition of Reinecke salt precipitated a mixture of the quaternary alkaloids. Anion exchange chromatography converted the alkaloids to their

chlorides, and cation exchange chromatography resolved the two new compounds. Each, after additional Reinecke precipitation and anion exchange, yielded crystalline chlorides designated as compounds **1** and **2**.



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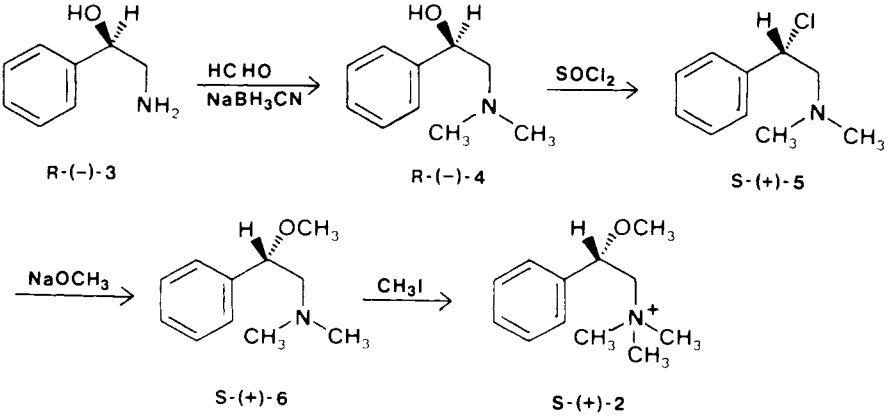
The ^{1}H-nmr spectrum of **1** revealed four aromatic protons in a characteristic *para*-disubstitution pattern (two doublets, J=8.7 Hz), an aromatic *O*-methyl group (s, 4.27 ppm), a complex multiplet at 3.95 ppm, and three *N*-methyl groups (s, 3.62 ppm). These data suggested that **1** was simply *N,N,N*-trimethyl-4-methoxyphenethylamine (trivial name: *O*-methylcandicine). The structural identification was supported by sims data in which the expected peak due to the intact cation was detected at *m/z* 194 as the base peak in the spectrum; the second most abundant ion in the sims spectrum was *m/z* 135 caused by elimination of trimethylamine. Methylation of reference *N,N*-dimethyl-4-methoxyphenethylamine hydrochloride produced the synthetic compound which was identical to **1** (mp, ^{1}H-nmr, ir, sims).

Compound **2** was optically active ([α]D=+87.5°). The ^{1}H-nmr spectrum showed five aromatic protons (s, 7.92 ppm), a doublet of doublets at 5.39 ppm (1H, J=2.4, 9.3 Hz) representative of a single benzylic proton, a two proton multiplet at 4.10 ppm, and a large singlet at 3.72 ppm, which was initially attributed to the protons of three *N*-methyl groups. Consideration of the observed ^{1}H-nmr signals and β-hydroxylation in synephine and normacromerine, prompted the synthesis of *N,N,N*-trimethyl-β-hydroxyphenethylamine (β-phenylcholine). This compound was nonidentical (tlc, ^{1}H-nmr) with **2**. Data from sims (intact cation, C^+, *m/z* 194) and closer examination of the ^{1}H-nmr integrations then suggested the presence of a β-*O*-methyl group whose proton signal was coincident with the *N*-methyl signals. Thus, **2** was proposed to be (+)-*N,N,N*-trimethyl-β-methoxyphenethylamine [trivial name: (+)-coryphanthine]. The main fragmentation observed in the sims spectrum, a low abundance *m/z* 135 ion due to trimethylamine loss, supported this proposal.



SCHEME 1. Synthesis of coryphanthine, (+)-**2**.

Both (+)- and (−)-coryphanthine (**2**) were then synthesized from resolved (±)-β-hydroxyphenethylamine (**3**). The syntheses involved intermediates **4**-**6**, as illustrated in scheme 1, for the synthesis of (+)-**2**. Treatment of **4** with thionyl chloride led to inversion of configuration, probably caused by an intramolecular interaction of the ter-

tiary amine with the intermediate alkyl chlorosulfite; this is the usual role of extramolecular pyridine when it is used to induce inversion in classical examples of this reaction (13). Optically active **6** has been prepared previously by Nishimura (14) by reaction of 2-chloro-1-dimethylamino-1-phenylethane with sodium methoxide; our optically active synthesis involved reaction of **5** with sodium methoxide, forming the identical intermediate aziridinium ion, which opened with a net retention of configuration.

Compound (−)-**6** possesses the same sign of rotation as the known cactus alkaloids that are similarly oxygenated, *e.g.*, (−)-calipamine (15) and, (−)-macromerine (16); the sign of rotation of (−)-**6** remained unchanged upon quaternization with methyl iodide, and (−)-**6** is proposed to have the *D*− or *R*-configuration (17). Natural (+)-coryphanthine, being identical to (+)-**2**, which was synthesized by quaternization of *S*-(+)-**6**, is, therefore, proposed to possess the L or *S* configuration.

Certain pharmacological effects of candicine have been studied (18-20) and include mainly nicotine-like convulsive activity. *O*-Methylcandicine was a partial nicotine agonist in causing frog muscle contraction (19). β-Phenylcholine was an acetylcholine antagonist (21) and caused hypertension and inhibition of peristalsis in dogs, contraction of isolated guinea pig uterus, and a curare-like effect in frogs (22).

When **1, 2,** and related compounds were tested in the brine shrimp assay (23) (table 1), choline and β-phenylcholine were not toxic below 1000 ppm (μg/ml). *O*-Methylcandicine was lethal with an LC_{50} of 425 ppm. For the bioassay, shrimp with highly impaired swimming movements were counted as "dead," and (±)-**2**, (+)-**2**, (−)-**2**, and candicine produced a high number of individuals impaired but not killed after 24 h. This effect was also noticed with strychnine, while nicotine was lethal. Clearly, the natural (+)-coryphanthine is more bioactive than (−)-coryphanthine, with the (±)-mixture intermediate in bioactivity. The utility of this simple and inexpensive bioassay to evaluate relative bioactivity in a series of related compounds is evident.

TABLE 1. Results of the brine shrimp bioassay (23) of **1, 2,** and related compounds

Compound	LC_{50} (95% confidence interval) in ppm (or μg/ml)
Choline chloride	>1000
β-Phenylcholine chloride	>1000
Candicine chloride	923 (667-1484)
O-Methylcandicine chloride	425 (369-480)
(−)-Coryphanthine chloride	494 (448-535)
(±)-Coryphanthine chloride	368 (331-427)
(+)-Coryphanthine chloride	354 (308-395)
Nicotine hydrochloride	158 (136-193)
Strychnine sulfate	164 (144-187)

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined with a Mel-Temp apparatus and are uncorrected. The ir spectra were obtained by use of KBr pellets in a Beckman IR-33 spectrophotometer. ^{1}H-nmr spectra were recorded on a Varian FT-80 in D_2O with TMS as the external standard. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Sims were obtained on the neat samples with a Riber Instrument (Model SQ 156L) employing methods previously described (24). Racemic β-hydroxyphenethylamine hydrochloride was purchased (Sigma), and *N,N*-dimethyl-4-methoxyphenethylamine hydrochloride (mp 173-4°, ^{1}H-nmr) was prepared from 4-methoxyphenylethanol via treatment of the chloride with dimethylamine.

PLANT MATERIAL.—Living plants of *C. greenwoodii* were purchased from Grigsby Cactus Gardens, Vista, CA, and received on June 5, 1975. The plants were identical to those investigated previously (12),

and reference photographs are on file. The plants were sliced, freeze-dried, and ground through a 2-mm screen in a Wiley mill.

EXTRACTION AND ISOLATION OF QUATERNARY ALKALOID MIXTURE.—Plant material (150 g) was extracted twice by shaking for 1 h with 150-ml portions of 95% ethanol. The combined extracts were condensed to a syrup by rotary evaporation and partitioned between 50 ml each of chloroform and water, which was basified to pH 10 with sodium hydroxide. The aqueous layer was freeze-dried, and the residue was heated (steam bath) with 50 ml of ethanol. Insoluble material was removed by filtration. The filtrate residue was dissolved in 50 ml of water and centrifuged to remove a small amount of additional insoluble matter.

The aqueous solution was acidified to pH 2 with hydrochloric acid and filtered again. A 5% solution of ammonium reineckate in acetic acid and water (2:1) was added until precipitation was complete. The filtered precipitate was dissolved in acetone-methanol-water (6:2:1) (20 ml), applied to a column of Amberlite IRA 401S (30 g) in the chloride form, and rinsed with the acetone-methanol-water solution until portions of the eluates no longer reacted with iodoplatinic acid reagent. Under rotary evaporation the eluates were condensed to dryness. Ion pair chromatography on tlc (Silica gel G, 0.5 *M* sodium bromide in methanol) detected two compounds (**1** and **2**) upon visualization with either iodoplatinic acid or Dragendorff's reagents. The alkaloids detected were distinct from choline, candicine, and the seven known alkaloids of *C. greenwoodii* (11,12).

SEPARATION AND ISOLATION OF COMPOUNDS **1** AND **2**.—The mixture of quaternary amine chlorides was dissolved in 1 *N* hydrochloric acid and applied to a 1.5 × 12 cm column of Dowex 50W which had been packed and washed in 1 *N* hydrochloric acid. The column was then eluted, in gradient fashion, with 1 *N* (50 ml), 1.5 *N* (50 ml), 2.0 *N* (50 ml), 2.5 *N* (50 ml), 3.0 *N* (100 ml), 3.5 *N* (300 ml), 4.0 *N* (100 ml), 5.0 *N* (100 ml), and 5.5 *N* (100 ml) hydrochloric acid. Compounds **2** and **1** were eluted, respectively, with 3.5 and 5.5 *N* hydrochloric acid. The eluates containing compounds **1** and **2** were each adjusted to pH 2 with sodium hydroxide and again precipitated with ammonium reineckate. The filtered precipitates were dissolved in acetone-methanol-water (6:2:1) and again converted to the chloride by anion exchange.

Compound **1** chloride crystallized from 95% ethanol-ethyl ether (23 mg, 0.0157% yield) or in low yield from water: mp 200-203°; sims base peak, C^+, *m/z* 194, 135 (minus trimethylamine); ^{1}H-nmr (D_2O), 7.75; (d, *J*=8.7, 2H, =CH), 7.44 (d, *J*=8.9, 2H, =CH), 4.27 (s, 3H, OCH_3, 3.84-4.09 (m, 4H, CH_2CH_2), 3.62 [s, 9H, $N(CH_3)_3$].

Compound **2** chloride was crystallized as hygroscopic needles from methanol-acetone (33 mg, 0.022% yield): mp 159-162° (evacuated sealed tube); sims, base peak, C^+, *m/z* 194, 135 (minus trimethylamine); ^{1}H-nmr (D_2O), 7.92 (s, 5H, C_6H_5), 5.39 (dd, *J*=2.4, 9.3, 1H, βH), 3.96-4.19 (m, 2H, αCH_2), 3.72 [s, 12H, OCH_3 and $N(CH_3)_3$], $[\alpha]_D = +87.5°$ (c=2.9, methanol).

SYNTHESIS OF *O*-METHYLCANDICINE (**1**) AND β-PHENYLCHOLINE.—*N,N*-Dimethyl-4-methoxyphenethylamine and *N,N*-dimethyl-β-hydroxyphenethylamine (ubine) (25) hydrochlorides were dissolved in water, basified with sodium hydroxide, and extracted into chloroform. The residues of the free bases were dissolved in benzene, and a 10 molar excess of methyl iodide was added. The mixture was sealed for 12 h at 4°. The precipitates (85-95% yields) were filtered and recrystallized from 95% ethanol-ethyl ether. Anion exchange on Amberlite IRA 401S, chloride form, in methanol-water (1:1) converted the iodides to the chlorides, which were recrystallized from methanol-acetone-ethyl ether.

O-methylcandicine (**1**); iodide mp 214-215°, Lit. mp 206° (26); chloride mp 206-207°, Lit. mp 206° (27); ^{1}H-nmr, sims and ir spectra matched those from isolated **1**, while *N.N.N*-trimethyl-β-hydroxyphenethylamine iodide was non-identical: mp 229-230°, Lit. mp 223° (22); chloride mp 223-224°, Lit. mp 218° (28); ^{1}H-nmr (D_2O), 7.88 (s, 5H, C_6H_5), 5.79 (dd, *J*=3.0, 8.6, 1H, βH), 3.97-4.11 (m, 2H, CH_2), 3.71 [s, 9H, $N(CH_3)_3$].

RESOLUTION OF β-HYDROXYPHENETHYLAMINE.—Following the procedure of Read and Campbell (28), warm 95% ethanolic solutions of (±)-β-hydroxyphenethylamine (30 g) and (+)-tartaric acid (12 g) were combined. After cooling, the precipitate was filtered, dried thoroughly, and recrystallized from aqueous acetone. Four such recrystallizations yielded (+)-β-hydroxyphenethylamine (+)-tartrate in long silky needles: mp 211-212°, $[\alpha]_D = +43.2°$ (c=1, water). A concentrated solution of the tartrate dissolved in water was basified with sodium hydroxide and extracted ten times with 20-ml portions of chloroform. The chloroform extract crystallized slowly upon removal of the solvent to yield 2.85 g (19% yield) of (+)-β-hydroxypheneylamine: mp 55-56°, $[\alpha]_D = +30.3°$ (c=1, abs. ethanol).

The mother liquor from the first recrystallization of β-hydroxyphenethylamine tartrate was similarily decomposed to obtain the free base; 4.16 g, $[\alpha]_D = -9.6°$ (c=1, abs. ethanol). This material was stirred with 9.84 g of *n*-butanol in 800 ml of petroleum ether (30-60°) for 12 h. The mixture was filtered, and the insoluble material (3.1 g) was optically enriched: $[\alpha]_D = -21.6°$, while the residue (5.27 g) from the solu-

bles had $[\alpha]D=-6.5°$. Repetition with the (−)-enriched material in 275 ml petroleum ether containing 3.36 g of *n*-butanol afforded 2.09 g of (−)-β-hydroxyphenethylamine: mp 54-55°, $[\alpha]D=-31.0°$ and 0.78 g of racemic material: $[\alpha]D=+0.3°$. In the work of Leigh (29), who proposed this dissolution method of enantiomer enrichment, the racemic material remained insoluble, while the enantiomers of several compounds were dissolved.

(−)-*N,N*-DIMETHYL-β-HYDROXYPHENETHYLAMINE (**4**).—(−)-β-Hydroxyphenethylamine (**3**) (1.9 g) was stirred with aqueous formaldehyde (5.6 ml) and sodium cyanoborohydride (1.4 g) in 40 ml of acetonitrile, following the method of Borch and Hassid (30). The free base of (−)-**4** was obtained as a light amber oil: 1.7 g, 74% yield, $[\alpha]D=-43.5°$.

(+)-*N,N*-DIMETHYL-β-CHLOROPHENETHYLAMINE HCL (**5**).—(−)-**4** (1.6 g) was stirred in 20 ml of chloroform, and 10 ml of thionyl chloride, dissolved in 20 ml of chloroform, was added dropwise. After 15 min, the solvent was evaporated, and the residue was recrystallized from methanol-acetone to yield (+)-**5** as shiny white platelets: 1.2 g, 55% yield; mp 201-202°; $[\alpha]D=+68.7°$ (c=1, methanol); ^{1}H-nmr (D_2O), 7.97 (s, 5H, C_6H_5), 5.99 (dd, J=5.0, 10.1, 1H, βH), 4.2-4.4 (m, 2H, CH_2), 3.46 [s, 6H, $N(CH_3)_2$].

(+)-*N,N*-DIMETHYL-β-METHOXYPHENETHYLAMINE (**6**).—(+)-**5** (1.2 g) was refluxed for 1 h with 1 *N* sodium methoxide in methanol. The mixture was then condensed by rotary vacuum evaporation, and the residue was dissolved in 30 ml of water. This solution was extracted six times wih 25 ml portions of ethyl ether; the ether layers were dried over anhydrous sodium sulfate and evaporated to yield (+)-**6** as an amber oil: 0.73 g, 75% yield; $[\alpha]D+6.18°$ (c=1, abs. ethanol); ^{1}H-nmr ($CDCl_3$), 7.31 (s, 5H, C_6H_5), 4.30 (dd, J=3.5, 8.9, βH), 3.23 (s, 3H, OCH_3), 2.38-2.87 (m, 2H, CH_2), 2.31 [s, 6H, $N(CH_3)_3$].

(+)-CORYPHANTHINE (**2**).—(+)-**6** (0.68 g) was dissolved in 60 ml of benzene, and 5.4 g of methyl iodide was added. The flask was sealed and stored for 12 h at 4°. The resulting precipitate (1.2 g, 100% yield) was removed by filtration and recrystallized from 95% ethanol-water to yield thick needles of (+)-**2** iodide: mp 180-181°, Lit. mp 180° (31); $[\alpha]D=+12.2°$ (c=2, water). The chloride was prepared by anion exchange, and hygroscopic needles crystallized from methanol-acetone: mp 161-163° (evacuated sealed tube), $[\alpha]D=+62.0°$, c=2.3, water. ^{1}H-nmr and ir spectra matched those of the isolated (+)-**2**.

(−)-CORYPHANTHINE (**2**).—(−)-**2** was synthesized in an identical way beginning with (+)-**4**: iodide mp 174-175°, $[\alpha]D=-12.2°$ (c=2, water); chloride mp 163-165° (evacuated sealed tube), $[\alpha]D=-65.8°$ (c=3.0, water); ir, sims, and ^{1}H-nmr spectra were identical to those of (+)-**2**.

BRINE SHRIMP ASSAY.—Methods employed were essentially as described previously (23). Compounds were tested at nominal doses of 250, 500, and 750 ppm, except that nicotine and strychnine were also tested at 10, 100, and 1000 ppm and candicine at 1000 ppm. Choline and β-phenylcholine were tested only at 10, 100, and 1000 ppm. Compounds were tested as the chloride or hydrochloride salts (except for strychnine sulfate) because the iodide ion itself is toxic to the shrimp (LC_{50} of sodium iodide is 289 ppm).

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