Cactus Alkaloids. XXXVI. Mescaline and Related Compounds from *Trichocereus peruvianus*

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ABSTRACT.—Agurell has previously detected (tlc, glc-ms) tyramine, 3-methoxytyramine, and two unknown alkaloids in the Peruvian cactus, *Trichocereus peruvianus* Br. and R. The presence of mescaline in other similar *Trichocereus* species prompted us to reinvestigate this species, which is commercially available in the United States. The nonphenolic alkaloid extracts yielded an abundance of crystalline mescaline hydrochloride (0.82% yield) and a trace of 3,4-dimethoxyphenethylamine (tlc-ms). Crystalline tyramine hydrochloride, 3-methoxytyramine hydrochloride, and 3,5-dimethoxy-4-hydroxyphenethylamine hydrochloride were isolated from the phenolic alkaloid extracts; the last compound has not been previously crystallized from nature, although it is the immediate biosynthetic precursor of mescaline. Crystalline 2-chloromescaline hydrochloride was isolated from the nonphenolic extracts; but, as determined by mass-analyzed ion kinetic energy spectrometry, this new compound is an extraction artifact. Both 2-chloromescaline and 2,6-dichloromescaline hydrochlorides were prepared synthetically from mescaline. This cactus species has a mescaline content equal or superior to peyote and should be legally controlled as an item of drug abuse.

The San Pedro cactus, *Trichocereus pachanoi* Br. and R., contains mescaline (3,4,5-trimethoxyphenethylamine) (**1**) and has an ancient history of hallucinogenic usage in Ecuador and Peru (1–4). Potent plants of this species are commercially available in the United States (5) and are often advertised, promoted, and sold as legal psychedelic drugs (6, 7). The mescaline-containing cacti other than *Lophophora williamsii* (Lem.) Coult. (peyote) are not regulated by the Controlled Substances Act of 1970 and subsequent amendments (8). Varying amounts of mescaline have been detected in or isolated from eight additional *Trichocereus* species (9–12). Agurell (11) has observed that the mescaline-producing *Trichocereus* species all have a stem and are candelabra-like, while the *Trichocereus* species that are columnar, creeping, or low contain only the *N*-methylated tyramines and/or the 3,4-disubstituted β-phenethylamines; this observation seems to be quite valid (13).

T. peruvianus Br. and R. is a branching, candelabra-like cactus species originally collected near Matucana in Peru (14–16). Specimens are commercially available in the United States having been grown from seed originally collected in Peru. Agurell (11) has previously detected (tlc, glc-ms) tyramine (**2**), 3-methoxytyramine (**3**), and two unknown alkaloids in this species. The presence of mescaline in other branching species of *Trichocereus* and the commercial availability of *T. peruvianus* prompted us to reinvestigate its alkaloid content. A simple initial screening of alkaloid extracts by tlc revealed the presence of abundant mescaline and traces of additional alkaloids.

A large quantity of plant material was then defatted, basified, percolated with chloroform, and processed to yield fractions A (alkaloids), B (non-alkaloidal materials), and C (water soluble alkaloids), as previously described (17). Fractions A and C were combined and resolved by anion exchange chromatography (18) into phenolic and nonphenolic alkaloid extracts. Analytical tlc with reference compounds and preparative tlc of the phenolic extracts permitted the

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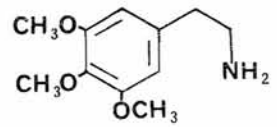
identification, isolation, and crystallization of small quantities of tyramine (**2**), 3-methoxytyramine (**3**), and 3,5-dimethoxy-4-hydroxyphenethylamine (3,5-dimethoxytyramine) (**4**) hydrochlorides. All three of these compounds are on the central pathway in the biosynthesis of mescaline, and **4** appears to be the immediate biosynthetic precursor to mescaline in *L. williamsii* and *T. pachanoi* (19, 20). Tyramine has been previously detected and/or isolated from ten cactus genera including thirteen other species of *Trichocereus* (21); this isolation confirms the previous detection of **2** in *T. peruvianus* (11). 3-Methoxytyramine has been previously detected and/or isolated from four cactus genera including eleven other species of *Trichocereus* (21); this isolation also confirms the previous detection of **3** in *T. peruvianus* (11). 3,5-Dimethoxy-4-hydroxyphenethylamine has been previously detected (glc-ms) in *T. pachanoi* and *T. werdermannianus* Bckgb. (10, 19); this is apparently the first report of the crystallization of **4** from nature although it is likely a mammalian metabolite of mescaline (22). The isolated compound **4** cochromatographed (tlc) and gave comparable physical data (mp, mmp, ms, ir) with reference 3,5-dimethoxy-4-hydroxyphenethylamine hydrochloride (10).



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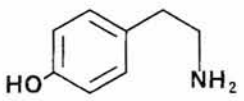

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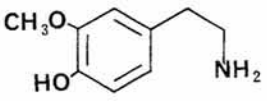

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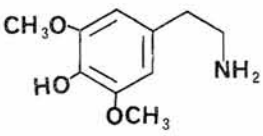

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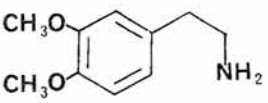

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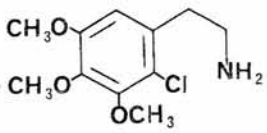

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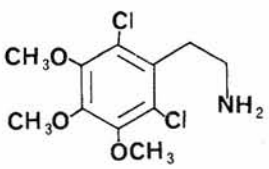

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Analytical tlc of the nonphenolic alkaloid extract detected mescaline (**1**) as, by far, the major alkaloid. The hydrochloride of **1** was crystallized directly from this extract. Analytical tlc of the mother liquors detected a trace of 3,4-dimethoxyphenethylamine (**5**) and another unknown primary amine which was fluorescent with fluorescamine (17). Preparative tlc was used to resolve **1** and the two trace compounds in the mother liquors. The trace of **5** would not crystallize, but cochromatography (tlc in five systems) with reference **5** and ms spectra served to confirm its identification.

The unknown nonphenolic primary amine was chromatographically dissimilar to any of the known cactus alkaloids. The nmr spectrum revealed nine methoxy protons (3 at δ 3.87 and 6 at δ 3.85), amine hydrochloride protons (δ 8.36), four aliphatic protons (δ 3.26), and a single aromatic proton (δ 6.72). Chemical ionization ms spectra revealed protonated molecular ions, m/e 246 and 248 (ratio, 3:1), indicating a single chlorine atom. The single aromatic proton in the nmr suggested that the compound might be 2-chloromescaline (**6**). Mescaline hydrochloride treated with chlorine gas dissolved in chloroform was readily converted to **6** but, primarily, to a compound identified as 2,6-dichloromescaline (**7**). Both of these chlorinated mescaline derivatives were prepared as crystalline hydrochlorides, but preparative tlc was necessary for the isolation of a small amount of **6** from the reaction mixture. Neither of these compounds has been previously isolated, synthesized, or tested for psychoactivity. However, using the principles of additivity, the calculated log P (octanol-water) for 2,6-dichloromescaline is 2.20; this value is well within the range where high psychoactivity would be expected; for example, the log P for the highly potent hallucinogen DOM ("STP") is reported to be 2.08 (23).

Re-extraction of plant material using nonchlorinated solvents failed to yield any **6** in the extracts. Examination of extracts of defatted plant material prepared with four different solvents was performed with the mass-analyzed ion kinetic energy (MIKE) technique of mass spectrometry (24, 25); no **6** was detectable in any of the extracts although **1** was readily detected. The **6** is apparently an extraction artifact formed from the photodecomposition of chloroform to produce chlorine (26).

The mescaline content (0.82% isolated yield) of *T. peruvianus* is equal or superior to the mescaline content of *T. pachanoi* and *L. williamsii*. It would seem advisable to control legally this species, as well as other potent *Trichocereus* species, due to their high potential for use as items of drug abuse.

EXPERIMENTAL[2]

PLANT MATERIAL.—Plants and terminal cuttings were purchased from Abbey Garden, 176 Toro Canyon Road, Carpinteria, CA 93013, and conformed to published descriptions for the species (14). These commercial specimens were grown from seeds collected in the field by Karol Knize (KZ no. 242) and were identified by Robert Foster[3] of Santa Barbara, California. Sample specimens are being maintained in our greenhouse, and reference photographs are on file. The fresh cacti were sliced, frozen, freeze-dried, and pulverized through the 2 mm screen in a Wiley Mill.

THIN LAYER CHROMATOGRAPHY.—Analytical separations and cochromatography were achieved by use of the following solvent systems (17): solvent A, ethyl acetate–methanol–58% ammonium hydroxide (17:2:1); solvent B, chloroform–ethanol–58% ammonium hydroxide (15:20:1); solvent E, diethyl ether–acetone–methanol–58% ammonium hydroxide (9:8:2:1); solvent F, diethyl ether–methanol–58% ammonium hydroxide (17:2:1); and solvent G, chloroform–acetone–58% ammonium hydroxide (10:17:1). Fluorescamine and tetrazotized benzidine (TZB) were used as visualization reagents (17).

Preparative tlc was achieved using solvents A or F, usually with repeated developments. The degree of separation of the various bands on tlc plates was monitored under short wave uv light and by spraying the edge of the plates, when necessary, with the visualization reagents. The appropriate bands were then scraped from the plates, combined, and eluted with 5% ammonium hydroxide in ethanol.

[2]Melting points were determined with a Fisher-Johns or a Mel-Temp apparatus and are uncorrected. Uv spectra were obtained in 95% ethanol on a Perkin-Elmer Coleman-124 spectrophotometer. Ir spectra were obtained using KBr pellets on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Hitachi RMU-6 spectrometer with the sample introduced by the indirect insertion probe; the MIKE spectrometry system was used as previously described (24, 25). Proton nmr spectra were determined on JEOL PFT-100 and XL-100 spectrometers using $CDCl_3$ and CD_3OD as solvents and TMS as internal standard. Analytical tlc plates were 5 x 20 cm or 20 x 20 cm Baker-flex silica gel IB2-F or 5 x 5 cm, Merck silica gel 60 F-254, HP-TLC plates; the HP-TLC plates were developed in circular fashion with a Camag U-chamber system. Preparative tlc plates (20 x 20 cm) were prepared with a 1-mm thickness of silica gel PF-254 (Brinkmann) and streaked with a Kontes Chromoflex apparatus. Reference mescaline HCl was purchased from Sigma Chemical Company, 3,4-dimethoxyphenethylamine hydrochloride and 3-methoxytyramine hydrochloride from Calbiochem, and tyramine hydrochloride from Eastman Kodak Company; and 3,5-dimethoxy-4-tyramine (4) hydrochloride was obtained from the National Institute of Mental Health.

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EXTRACTION AND ISOLATION OF ALKALOID FRACTION.—A total of 400 g of the pulverized *T. peruvianus* was defatted for 48 hr with petroleum ether (30–60°) by Soxhlet extraction (7 g of lipids, 1.75%). The defatted marc was moistened with chloroform–methanol–58% ammonium hydroxide (2:2:1), packed into a percolator, macerated with 1.5 liters of chloroform–methanol–ammonium hydroxide (9:0.9:0.1), and extracted with 18 liters of chloroform. The chloroform extract was condensed under vacuum evaporation and processed, as previously described (17), to yield fractions A (alkaloids), B (nonalkaloidal materials), and C (water soluble alkaloids). Analytical tlc showed similar alkaloids in fractions A and C, so these fractions were combined and resolved into phenolic and non-phenolic fractions using 80 g of Amberlite IRA–401S resin in the hydroxide form (18).

RESOLUTION AND IDENTIFICATION OF PHENOLIC ALKALOIDS.—Spraying of an analytical tlc plate (solvent F) spotted with portions of the phenolic fraction with fluorescamine and T2B detected three primary amines (R_F values at 0.59, 0.50, and 0.33). These were respectively identified by tlc comparison with reference compounds as tyramine, 3-methoxytyramine, and 3,5-dimethoxy-4-hydroxyphenethylamine. Preparative tlc (eight plates, five developments) in solvent F was employed to resolve the three compounds.

ISOLATION OF TYRAMINE HYDROCHLORIDE (2).—The combined eluates from the preparative tlc bands at R_F 0.59 were eluted, concentrated to dryness under rotary vacuum, redissolved in a minimum volume of absolute ethanol, and acidified with 5% (w/w) hydrochloric acid in absolute ethanol. Addition of ethyl ether to induce crystallization resulted in a semi-solid mass. This material was again dissolved in a minimum quantity of ethanol, streaked onto two preparative tlc plates, and developed (twice) in solvent F. Elution and crystallization attempts resulted in the isolation of crystalline **2** hydrochloride. After one recrystallization (absolute ethanol-ethyl ether), the yield was 34 mg (0.0085%). Recrystallization yielded 22 mg (mp 264–266°, mmp 265–266°, reference mp 266–267°). Cochromatography with reference **2** hydrochloride in systems A, B, E, F, and G demonstrated the homogeneity of the isolate. The ir spectra of the isolate and reference **2** hydrochloride were indistinguishable.

ISOLATION OF 3-METHOXYTYRAMINE HYDROCHLORIDE (3).—The hydrochloride of **3** was prepared from the eluates of the phenolic band at R_F 0.50 (40 mg, 0.01% yield). Recrystallization (absolute ethanol-ethyl ether) gave 34 mg (mp 206–209°, mmp 207–209°, reference mp 207–209°). Cochromatography (five systems) and essentially identical ir spectra with reference **3** hydrochloride confirmed the identity of the isolate as **3** hydrochloride.

ISOLATION OF 3,5-DIMETHOXY-4-HYDROXYPHENETHYLAMINE HYDROCHLORIDE (4).—Concentration of the eluates from the phenolic alkaloid band at R_F 0.33 and attempted crystallization of the hydrochloride resulted in a semi-solid mass. After repeated preparative tlc (three plates, three developments in solvent F), crystallization attempts were successful. Recrystallization three times (absolute ethanol-ethyl ether) yielded 14 mg (0.0035% yield) of **4** hydrochloride [mp 242–244°, mmp 243–245°, reference mp 249–251°, lit. mp 258–259° (27)]. Cochromatography with reference **4** hydrochloride in the five tlc systems demonstrated their homogeneity and demonstrated that the isolated compound was not the isomer 3,4-dimethoxy-5-hydroxyphenethylamine. The low resolution mass spectrum of the isolated **4** hydrochloride gave a weak peak at m/e 197 ($C_{10}H_{15}O_3N$, molecular ion), a base peak at m/e 30 ($-CH_2-NH_2)^+$, and an intense peak at m/e 167, 168 (β-cleavage product) as previously noted (10). The ir spectra of the isolated and reference **4** hydrochlorides were superimposable confirming their identity.

ISOLATION OF NONPHENOLIC ALKALOIDS.—Analytical tlc of the nonphenolic alkaloid extract detected mescaline as, by far, the major alkaloid. The non-phenolic extract was dissolved in 50 ml of absolute ethanol and acidified to pH 2 (pH paper) with 5% (w/w) hydrogen chloride in absolute ethanol. Addition of anhydrous ethyl ether to induce cloudiness and subsequent cooling induced crystallization of 2.868 g of mescaline. Analytical tlc (solvent F) of the mother liquor detected additional mescaline as the major band (R_F 0.58), two additional primary amines at R_F 0.66 and 0.89, and a series of trace alkaloids (primary amines) that were only detectable by the superior resolution obtained with the hp-tlc system. The compound at R_F 0.66 was identified as 3,4-dimethoxyphenethylamine by comparison with a series of reference nonphenolic primary amines; the compound at R_F 0.89 was dissimilar to any of the reference compounds.

The mother liquor from the mescaline hydrochloride crystallization was streaked onto eight preparative tlc plates and subjected to seven developments in solvent F. The bands corresponding to mescaline and 3,4-dimethoxyphenethylamine were not sufficiently resolved for their complete separation; therefore, the eluates from these two bands were concentrated, and additional mescaline hydrochloride (400 mg) was crystallized from the mixture. The subsequent crystallization of 3,4-dimethoxyphenethylamine was unsuccessful as it cocrystallized with mescaline hydrochloride. The band at R_F 0.89 was eluted as usual and will be discussed below.

Recrystallization (absolute ethanol-ethyl ether) of the combined mescaline hydrochloride (3.268 g, 0.817% yield) was then performed (mp 183–184°, mmp 183–185°, reference mp 184–185°). The ir spectra of the isolated and reference mescaline hydrochlorides were superimposable. The presence of 3,4-dimethoxyphenethylamine was substantiated by cochromatography

with reference **5** in the five solvent systems. In addition, low resolution mass spectra of the isolated mixture of **1** and **5** hydrochlorides revealed a prominent peak (*m/e*) for the molecular ion of **5**.

ISOLATION OF 2-CHLOROMESCALINE HYDROCHLORIDE (**6**).—Eluates of the non-phenolic primary amine at R_F 0.89 upon crystallization of the hydrochloride yielded 65 mg (0.016% yield). Three recrystallizations (absolute ethanol-ethyl ether) gave 45 mg of purified material (mp 162–164°): uv λ max (ε) 282 (615) and 210 (23,000); ^{1}H nmr (deuterochloroform) δ ppm 3.26 (4*H*, s, broad, $-CH_2CH_2-$), 3.85 (6*H*, s, two CH_3O- at 4 and 5), 3.87 (3*H*, s, CH_3O- at 3), 6.76 (1*H*, s, aromatic proton at 6), 8.36 (s, broad, $-NH_3^+$); mw (high resolutions ms) calcd for $C_{11}H_{16}O_3NCl$, 245.080, found 245.080. The low resolution ms (CI, isobutane) showed essentially only the protonated molecular ions at *m/e* 246 and 248 (ratio 3:1). The ir spectrum showed strong absorptions at 3410, 2980, 1580, and 1480 cm^{-1}.

PREPARATION OF 2-CHLOROMESCALINE (**6**) AND 2,6-DICHLOROMESCALINE (**7**) HYDROCHLORIDES.—Chlorine gas was generated from potassium permanganate and hydrochloric acid (28), and a 5% (w/v) solution was prepared in chloroform. A total of 150 mg of mescaline hydrochloride was dissolved in 100 ml of chloroform to which 1 ml of the chlorine solution was added. After the mixture was kept at room temperature for 2 hr, the solvent was removed under rotary vacuum (only **7** was formed if the mixture was kept for longer periods of time). The residue was treated in the usual manner to crystallize 120 mg of hydrochloride (shiny plates, mp 218–22°). Recrystallization (absolute ethanol-ethyl ether) purified this material, which was identified as 2,6-dichloromescaline hydrochloride (**7**): mp 225–227°, uv λ max (ε) 210 (27,460); ^{1}H nmr (deuterated methanol) δ ppm 3.33 (4*H*, m, $-CH_2-CH_2-$), 3.87 (6*H*, s, two CH_3O-), 3.90 (3*H*, s, CH_3O-), 4.90 (2*H*, s, broad, $-NH_2$); low resolution mass spectrum (CI iosbutane) *m/e* 280, 282, and 284 (ratio, 9:6:1) (MH^+); ir 3400, 2950, 1570, and 1480 cm^{-1}. The mother liquor from the crystallization of **7** hydrochloride showed three spots upon analytical tlc in solvent A (R_F 0.36, 0.55, and 0.77). Poor resolution was obtained in solvent F.

The mixture (90 mg) from similar mother liquors was subjected to preparative tlc (three plates, two developments) in solvent A. The band at R_F 0.36 yielded 26 mg of recovered **1** hydrochloride (mp 182–183°); the band at 0.77 gave 36 mg of additional **7** hydrochloride identical (tlc, mp, mmp) to that obtained previously. The band at R_F 0.55 yielded 15 mg of **6** hydrochloride (mp 169–170°). A mixture melting point with isolated **6** hydrochloride showed no depression; and cochromatography (five systems) showed the synthetic and isolated **6** to have identical mobilities. Uv, ms, ir, and nmr data for the synthetic and reference **6** hydrochlorides were indistinguishable.

ABSENCE OF 2-CHLOROMESCALINE IN ORIGINAL PLANT MATERIAL.—Re-extraction of a 10 g portion of plant material with ethanol and subsequent purification of the extract to yield fraction A failed to yield detectable **6** upon tlc analysis of the nonphenolic extract. However, the abundance of mescaline could have obscured the detection. Consequently, the very sensitive procedure of mass-analyzed ion kinetic energy (MIKE) spectrometry was employed (24, 25) to determine the natural occurrence of **6**. A total of 8 g of plant material was defatted with hexane by overnight Soxhlet extraction. Two g portions of the defatted material were extracted respectively with ethanol and ethyl ether–methanol–58% ammonium hydroxide (9:0.9:0.1). Two additional 2 g portions were basified with methanol–58% ammonium hydroxide (9:1) and extracted respectively with benzene and ethyl acetate. The residues from the four extracts were carefully examined using the MIKE spectrometry system. In no case did the peak at *m/e* 246 corresponding to protonated **6** increase relative to background, nor could fragmentations characteristic of **6** be observed in the kinetic energy spectrum taken at this mass. By contrast, protonated mescaline was readily detected (*m/e* 212) and identified by its characteristic fragments by loss of 15 and 17 mass units. It is noteworthy that the amount of mescaline in the benzene extract could be estimated from the MIKE spectrum to have two orders of magnitude more than that in the ethanol extract. The ethyl acetate gave an intermediate yield. The miniscale benzene extraction combined with MIKE spectrometry thus serves as a rapid and sensitive qualitative assay for mescaline in plant material.

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