Cactus Alkaloids VIII: Isolation of *N*-Methyl-3,4-dimethoxy-β-phenethylamine from *Ariocarpus fissuratus* var. *fissuratus*

D. G. NORQUIST and J. L. McLAUGHLIN

Abstract □ *Ariocarpus fissuratus* var. *fissuratus* (Engelmann) K. Schumann, commonly known as living rock, chaute, peyote, sunami, or dry whiskey, has an interesting history of folkloric medicinal uses. In previous phytochemical studies the alkaloids, hordenine and *N*-methyltyramine, have been identified in both the *fissuratus* and *lloydii* varieties of the species. In the present investigation, a new alkaloid was crystallized from the nonphenolic alkaloid fractions and identified as *N*-methyl-3,4-dimethoxy-β-phenethylamine HCl. This compound has previously been reported in three other cactus species.

Keyphrases □ *N* - Methyl - 3,4-dimethoxy - β - phenethylamine—isolation from *Ariocarpus fissuratus* □ *Ariocarpus fissuratus*—*N*-methyl-3,4-dimethoxy-β-phenethylamine isolation □ Alkaloids, cactus—isolation, identification of constituents

Several authors have reported that the cactus, *Ariocarpus fissuratus* (Engelmann) K. Schumann, has had various folkloric medicinal uses among the Indians of Mexico and the southwestern United States (1–4). Sometimes known as living rock, chaute, sunami, and pezuña de venado, the additional common names of peyote, peyote cimarron, and dry whiskey suggest a use similar to that of *Lophophora* (5, 6). References to the intoxicating and stimulating attributes of the plant are especially interesting (2–4). Heffter (1) in 1894 isolated hordenine from *A. fissuratus* var. *fissuratus*, and McLaughlin (7) recently identified hordenine and *N*-methyltyramine in both the *fissuratus* and *lloydii* varieties of the species.

In the present investigation the nonphenolic alkaloids were resolved from the phenolics, hordenine and *N*-methyltyramine, by use of an anion-exchange resin. TLC analysis of the nonphenolic fraction identified the major constituent as *N*-methyl-3,4-dimethoxy-β-phenethylamine. After acid–base partitioning, this alkaloid was easily crystallized from the nonphenolic fraction as the hydrochloride. Several recrystallizations resulted in a product which gave a comparable melting point and no mixed melting-point depression with synthesized *N*-methyl-3,4-dimethoxy-β-phenethylamine HCl. IR spectra of the isolated and the synthetic compounds were indistinguishable.

Agurell (8) has recently identified traces of this new cactus alkaloid in *Coryphantha macromeris* (Engelmann) Britton and Rose var. *runyonii* L. Benson and has crystallized the compound from extracts of *Echinocereus merkeri* Hildmann (9). Speir *et al.* (10) have also recently crystallized this alkaloid from *Ariocarpus trigonus* (Weber) K. Schumann. A single pharmacological study (11) has indicated that *N*-methyl-3,4-dimethoxy-β-phenethylamine has slight activity in the depletion of cardiac norepinephrine, but the reputed stimulating or intoxicating activities of the plant are not likely attributable to this compound, especially in view of its low concentration in the plant.

EXPERIMENTAL

Living plants of *A. fissuratus* var. *fissuratus* were purchased[1] and matched the latest taxonomic descriptions (12). Sample plants are being maintained as greenhouse specimens.[2] The fresh plants were sliced, dried in a forced-air oven at 48°, and ground through a 6-mm. screen in a Wiley mill.

In a large continuous-extraction apparatus, 5.28 kg. of the plant material was defatted, basified, and extracted with chloroform; the residues from the chloroform extracts were purified, essentially as previously described (13), to produce a mixture of crude alkaloids. This mixture was separated into phenolic and nonphenolic fractions by the use of an anion-exchange resin (14). TLC of the nonphenolic fraction, using methods and solvent systems previously described (10), identified *N*-methyl-3,4-dimethoxy-β-phenethylamine as the major constituent.

The residue of the nonphenolic alkaloid fraction was dissolved in about 20 ml. of 1 *N* HCl, filtered, and extracted twice with equivalent volumes of both chloroform and ethyl ether. After basification of the aqueous solution to pH 9.5 with concentrated ammonium hydroxide, the alkaloids were extracted into chloroform through several partitionings. The chloroform residue was dissolved in absolute ethanol and acidified with 5% HCl (w/w) in absolute ethanol. The acidified solution was condensed under a stream of nitrogen to about 2 ml., ethyl ether was added to produce cloudiness, and the solution was placed in a freezer (−12°) to induce crystallization. The crystals were recovered by vacuum filtration and recrystallized 5 times from absolute ethanol–ethyl ether to a constant melting point (m.p. 139–140°; yield 186 mg., 0.004% of the dried material). A mixed melting point with synthetic *N*-methyl-3,4-dimethoxy-β-phenethylamine HCl (10) was not depressed, and the IR spectra (KBr pellets) of these compounds were essentially identical.

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Effects of Mefruside on Renal Hemodynamics

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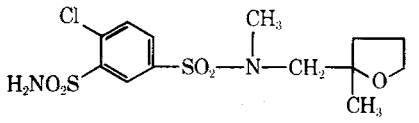
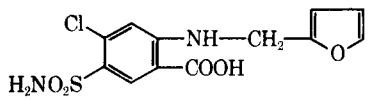
Abstract □ Mefruside, a natriuretic drug similar in structure to furosemide, was examined for activity on renal hemodynamics in the dog. This agent, when administered at 10 mg./kg. i.v., increased renal vascular resistance and decreased renal blood flow. Blood pressure and the rate of glomerular filtration were not affected. Mefruside differs from furosemide in its action on renal hemodynamics, inasmuch as furosemide decreases renal vascular resistance and increases renal blood flow.

Keyphrases □ Mefruside—effects on renal hemodynamics □ Renal dynamics—mefruside, effects

Mefruside {4-chloro-3-sulfonamido-1-[*N*-methyl-*N*-(2′-methyl-2′-tetrahydrofurylmethyl)]-benzenesulfonamide} (I) is a new orally active natriuretic (1). Structurally, this agent is similar to furosemide (II). In



I mefruside



II furosemide

addition to natriuretic activity, furosemide also affects renal hemodynamics to enhance renal blood flow (2–5). The purpose of this study was to determine if mefruside also enhances renal blood flow.

EXPERIMENTAL

Mongrel dogs, weighing 13–16 kg., were anesthetized with sodium pentobarbital, 30 mg./kg. A tracheal cannula was inserted to ensure free passage of air. The kidney to be utilized was exposed by a flank incision, and the renal artery was cleared of the surrounding tissue. A flow transducer (Carolina Medical Electronics model EMP-411, lumen size, 11-mm. circumference) was placed around the exposed renal artery, and renal blood flow was monitored with a square-wave electromagnetic flowmeter (Carolina Medical Electronics model 321). The flowmeter was adjusted to zero flow by briefly occluding the renal artery distal to the flow transducer. Blood pressure was monitored from the carotid artery. Both blood flow and blood pressure were recorded on a Beckman recorder. A solution containing 0.9% NaCl and 0.4% inulin was infused into the right femoral vein at a rate of 0.25 ml./kg./min. for at least 30 min. before and throughout the entire experiment. Mefruside was dissolved in saline using sodium bicarbonate. The drug was given intravenously *via* the right femoral vein.

Urine samples from the exposed kidney were obtained from a renal pelvic catheter introduced into the ureter by way of the retroperitoneal incision. Although urine samples were collected only from the kidney to which blood flow was measured, the other ureter was cannulated *via* a midline incision to ensure free urine flow from the contralateral kidney. Blood samples were obtained from the right femoral artery.

Urine and plasma inulin concentrations were determined by the method of Shreiner (6). Sodium concentrations were determined with a Coleman flame photometer. All data were analyzed with Student's *t* test paired comparisons (7). A *p* value less than 0.05 was used as the level of significance.

Table I—Effect of Mefruside (10 mg./kg.) on Renal Hemodynamics

	Control[a]	Mefruside[b]	Difference[c]
Renal blood flow, ml./min.	174	158	−16 ± 4[d]
Blood pressure, mm. Hg	142	140	−2 ± 2
Renal vascular resistance, mm. Hg/ml./min.	0.84	0.92	0.08 ± 0.02[d]
Sodium excretion, μeq./min.	124	424	300 ± 53[d]
Inulin clearance, ml./min.	30	30	0 ± 3

[a] Control values represent values taken immediately prior to mefruside administration. [b] Mefruside values represent values taken 10 min. after drug administration. [c] Difference from control ± *SE*. [d] Indicates a significant difference, $p < 0.05$, $n = 4$.

RESULTS AND DISCUSSION

Mefruside (10 mg./kg. i.v.) produced a significant decrease in renal blood flow of 16 ml./min. as renal vascular resistance was increased significantly (Table I). These effects were transient. They were maximal about 10 min. after drug administration and returned to control levels by 20 min. after drug administration. Blood pressure was not altered by the drug. Mefruside had no effect on inulin clearance. Sodium excretion was increased from 124 to 424 μeq./min. upon drug administration. The natriuretic action was still present 60 min. after drug administration when the experiments were ended. A lower dose of the drug (2 mg./kg. i.v.) did not produce a significant change in renal vascular resistance or renal blood flow.