Pharmañopo–Psychonautics: Human Intranasal, Sublingual, Intrarectal, Pulmonary and Oral Pharmacology of Bufotenine†

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Abstract—Summarized are *psychonautic bioassays* (human self-experiments) of *pharmañopo*—crystalline bufotenine (5-HO-DMT; 5-hydroxy-N,N-dimethyltryptamine; dimethylserotonine), at times combined with harmaline or harmine—via intranasal, sublingual, intrarectal, pulmonary (inhaled vapor) and oral routes. This is done by way of pharmacological modeling of diverse South American shamanic inebriants, principally the snuffs *ñopo/yopo* and *cebíl/hatáj*, prepared from seeds of *Anadenanthera peregrina* var. *peregrina* and *A. colubrina* var. *Cebil*, respectively. Psychoptic (visionary) activity of bufotenine has been established and the 1967 Holmstedt–Lindgren hypothesis of the *paricá* effect—intranasal potentiation of tryptamines by concomitant administration of monoamine-oxidase-inhibiting (MAOI) β-carbolines from stems of *Banisteriopsis caapi* admixed with the snuffs—has been confirmed by 25 psychonautic bioassays. Salient phytochemical and psychonautic literature is reviewed, and isolation of bufotenine from *Anadenanthera* seeds detailed (with one table and eight references).

Keywords—bufotenine; harmaline; harmine; MAOI; shamanic snuffs; tryptamines

In a previous paper on *pharmahuasca* psychonautics, modeling *ayahuasca* or *Banisteriopsis caapi* (Spr. ex Griseb.) Mort. (Malpighiaceae) potions via self-experiments with pure harmine and DMT or N,N-dimethyltryptamine (Ott 1999; 1994), I noted that Holmstedt and Lindgren had originally proposed in the context of shamanic snuffs what I called the "*ayahuasca* effect"—activation of the orally-inactive (and, presumably, also intranasally-inactive) DMT by concomitant administration of monoamine-oxidase-inhibiting (MAOI) β-carbolines, mainly harmine—later extended to encompass also orally-ingested *ayahuasca* potions in its purview. These chemists found all but one of six South American snuffs to contain tryptamines, whereas a Piaroa *paricá* snuff also contained harmine; a Surára *epéna* snuff only β-carbolines (Holmstedt & Lindgren 1967; Bernauer 1964); likewise a Tucano *paricá* snuff (Biocca et al. 1964). Since snuff tryptamines appeared (erroneously) to be nonpsychoactive intranasally (Turner & Merlis 1959), Holmstedt and Lindgren (1967: 365) conjectured that β-carbolines in the snuffs " . . . could potentiate the action of the simple indoles."

†I am beholden to Dr. C. Manuel Torres for discussions and advice. This article is dedicated to Professor Bo Holmstedt of Karolinska Institutet, in grateful recognition of his pioneering role in elucidating the ethnopharmacognosy of shamanic snuffs.

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In my *pharmahuasca* study, this ingenious theory was effectively confirmed in human beings, with respect to orally-ingested *ayahuasca* potions, and I noted that the snuffs which originally inspired it had been all but forgotten, but were also being studied psychonautically. In this second of four related papers, I report psychonautic bioassays of *pharmañopo*, modeling shamanic snuffs containing principally the recondite tryptamine bufotenine; the third paper will model snuffs based on its O-methyl congener, 5-MeO-DMT (Ott In press); the last *Nicotiana* snuffs containing principally nicotine as psychoactive agent. Despite homology of their active principles, shamanic snuffs containing bufotenine and 5-MeO-DMT constitute distinct topics. The latter are far more restricted geographically and culturally than the former. While there is almost no published human pharmacology on 5-MeO-DMT (albeit it is well established as a psychoptic, or visionary agent), the converse obtains for bufotenine, commonly said to *lack* visionary psychoactivity, although there are five published reports on its human pharmacology. I use the term *shamanic snuffs* because in most cultures they are employed only by shamans, generally as an aid to divination, although in some, such as many Waiká (Yanomamö) tribes of Venezuela and Brazil, they are also used frequently in nonritual contexts by many or most male adults; for other Waikás, shamanic snuffs are also used in hunting, as dart-poisons. Extensive historical, phytochemical and entheobotanical detail on these snuffs can be found in my book *Shamanic Snuffs or Entheogenic Errhines* (Ott 2001).

Ñopo and *yopo* are generic terms mostly applicable scientifically to snuffs derived from ground seeds of *Anadenanthera peregrina* (L.) Speg. var. *peregrina* v. Reis Alt. (Leguminosae), which are of broad historical and contemporary use in Brazil, Venezuela, Colombia, Ecuador and Perú (Torres 1996), and historical use in the Greater Antilles, as *cohoba*. Related snuffs most commonly known as *cebíl* or *vilca*, based on ground seeds of *A. colubrina* (Vel.) Bren. var. *Cebil* (Griseb.) v. Reis Alt., were once common in the Peruvian *montaña* and south Andean region, and are still used in the Chaco of Bolivia/Paraguay/Argentina, where they are best known as *hatáj* (Torres & Repke 1996). There is strong evidence that shamanic snuffs (and enemas) were also prepared from *Anadenanthera* leaves, perhaps an obsolete practice. *Anadenanthera* snuffs are often known as *paricá*, a word I avoid, being a generic term for South American shamanic snuffs, also applied to those derived from barks of diverse *Virola* species (Myristicaceae), which are the subject of my third paper (Ott In press; see also de Smet 1985a, b). *Ñopo* being the best-known term for *Anadenanthera* snuffs, and in keeping with *pharmahuasca* (my neologism for *ayahuasca* analogues using pure alkaloids, which has achieved broad acceptance), I denominate *Anadenanthera* snuff analogues *pharmañopo*.

There are a handful of published reports of psychonautic bioassays of *Anadenanthera* snuffs prepared from both species. Pagés Larraya (1959) made extensive tests of his own powder of crushed, toasted seeds of *A. colubrina* var. *Cebil*, and described depersonalization and experiences of "some mystery surpassing known limits . . . consubstantial with consciousness of the numinous." Snuff expert C.M. Torres and I had tested our own preparations of *cebíl*-seed snuff from material we collected in Argentina; I experienced "sinuous, multihued, arabesque patterns, first viewed behind closed eyes, then on a stuccoed wall in a darkened hallway, at length even on surfaces . . . illuminated *via* a skylight by the crepuscular, desert sun" (Ott 1995). Using the same material, Rätsch (1996) gave a compelling account of his fantastic visionary experience, accompanied by drawings of sinuous, pre-Columbian art motifs from México and Perú which he likened to his *cebíl*-snuff visions. Finally, Castillo (1997) described his insufflation of a *yopo* snuff prepared by a Venezuelan Piaroa shaman (probably from *A. peregrina* var. *peregrina* seeds), after having chewed a piece of *capí* liana (doubtless *Banisteriopsis caapi*). This provoked a bizarre shamanic experience of hyperaesthesia and hallucinations, leading the author to speculate on possible "emergence of a sixth sense."

Considerable chemical work on *Anadenanthera* shows conclusively and consistently that bufotenine is the only significant alkaloid in mature seeds of both species used for snuffs (Torres & Repke 1996; de Smet & Rivier 1987; Sávio Nunes et al. 1987; Rendón 1984; Schultes et al. 1977; Yamasato 1972; Chagnon, Le Quesne & Cook 1971; Fellows & Bell 1971; Holmstedt & Lindgren 1967; Paris, Saint-Firmin & Etchepare 1967; Iacobucci & Rúveda 1964; Giesbrecht 1960; Pachter, Zacharias & Ribeiro 1959; Alvares Pereira 1957; Fish, Johnson & Horning 1955; Stromberg 1954). Up to 7.4% bufotenine has been found in seeds of *A. peregrina* var. *peregrina*, only 0.04% 5-MeO-DMT and 0.16% DMT; 12.4% bufotenine in *A. colubrina* var. *Cebil*, with but 0.06% and traces of both tryptamines, respectively. Seven studies of 15 samples of *Anadenanthera* snuffs likewise showed bufotenine to be the only tryptamine present in significant amounts (up to 2.67%, with only traces of 5-MeO-DMT and DMT) (Torres et al. 1991; de Smet & Rivier 1985; Schultes et al. 1977; De Budowski et al. 1974; Holmstedt & Lindgren 1967; Marini-Bettòlo, Delle Monache & Biocca 1964; Fish, Johnson & Horning 1955). Inasmuch as there is virtually no pharmacological information on bufotenine (or other natural tryptamines) as errhine or snuff, I investigated intranasal pharmacology of this snuff tryptamine. All bioassays were conducted by myself only, outside of the United States, using bufotenine free-base I isolated from *Anadenanthera* seeds I likewise had collected. In spite of bufotenine's Schedule I-status in the United States, *no laws were violated*, neither technically nor *de facto*, in the course of this research—evidently only in the U.S. is bufotenine illicit; all chemical and psychonautic work was conducted in countries in which bufotenine is *not* a controlled substance.

ON ETHICS AND PSYCHONAUTICS

The term *psychonauts* was first coined in German (*Psychonauten*) by Ernst Jünger, in his logbook of pharmacological voyages in inner space—which he named the *psychocosmos* (Jünger 1970). Of late the term *psychonautic bioassay*, to refer to self-experiments with psychotropic drugs, has gained currency, and I here employ the substantive *psychonautics* in characterizing such research. Some might regard this to be a euphemism for *getting stoned*, mayhap with justice in some cases, such as its common use by *basement shamans* (popularized as the name of a botanical supply firm in Illinois) to describe non-novel, unstructured and uncontrolled (and generally unreported) ingestion of psychotropic agents. On the other hand, amateur reports posted on the Internet or in publications like *The Entheogen Review* can be valuable sources of human pharmacological data, albeit requiring winnowing of precious little wheat from abundant chaff.

Moreover, psychonautic bioassays have proven invaluable in phytochemical investigation of visionary compounds. Although alkaloids had first been isolated a decade before from *péyotl*, *Lophophora williamsii* (Lem.) Coult. (Cactaceae), self-experiments by Arthur Heffter in 1897 were required to determine that mescaline was the main visionary agent. Based on animal assays, Sandoz Ltd. pharmacologists had in 1938 rejected LSD as lacking interest, but intuition led Albert Hofmann to resynthesize the compound in 1943, provoking its accidental ingestion and his subsequent psychonautic bioassay, hence the discovery of one of the most potent drugs known. Hofmann later found animal assays useless to guide the isolation of visionary compounds from *Psilocybe mexicana* Heim (Agaricaceae) and *Turbina corymbosa* (L.) Raf. (Convolvukceae). Although in both cases other groups had a head-start, Hofmann alone was successful (finding psilocybine/psilocine and lysergic acid amides, respectively), thanks to his use of psychonautic bioassays. While salvinorin A was isolated pursuant to animal assays, it had previously been found during research on novel terpenoids, and a decade passed before basement shamans demonstrated conclusively it was the visionary agent of *Salvia divinorum* Epl. et Ját. (Labiatae) (Siebert 1994).

Insofar as animal assays have proven ineffective in some areas of research on visionary compounds, the ethics of their use is dubious. This goes double for many types of research on so-called drugs of abuse, given the fact that these are studied owing to their human popularity, *pursuant to their subjective effects*. Some proponents of purportedly objective double-blind animal research dismiss psychonautic bioassays as being subjective, although this is fundamental to scientific interest in many "abused" drugs. As Shulgin and Shulgin (1991) have argued, ethics dictate that the researcher her- or himself be the first to ingest a novel, putative psychotropic drug, and that subsequent human testing be conducted only with fully-informed volunteers—advised as to the identity of the compound, its dose, and the nature of effects already experienced. The Shulgins denominate such secondary testing "double conscious" (after Gordon Alles), and characterize double-blind studies in these cases as "pointless" and "verg[ing] upon the unethical."

In countries where a particular drug is illegal (i.e., bufotenine in the U.S.), it might be argued that any testing of it is unethical absent official authorization, although I would maintain it would still be ethical to test it on oneself (albeit perforce entailing criminal possession). Even in the case of a completely novel compound, whether natural or artificial, *any* human ingestion or ***even its intent***, is illegal in the U.S. under the Controlled Substance Analogue Enforcement Act of 1986. As Shulgin (1992) remarked: "Explicit approval or exemption from the FDA must now precede legal human research with new drugs."

MATERIALS AND METHODS

Bufotenine free-base was isolated and purified as described below, from a mixed collection of *A. colubrina* var. *Cebil* gathered in Salta, Argentina, of which representative specimens were botanically vouchered. Harmine hydrochloride dihydrate and harmaline hydrochloride dihydrate were obtained from Acros Organics of Geel, Belgium. Reagent-grade solvents were utilized in the extraction of bufotenine.

Cebil-seed snuff was prepared by lightly toasting, then triturating to a coarse powder, freshly collected seeds (with addition of reagent-grade sodium bicarbonate as a drying agent to facilitate finer pulverization, and in emulation of shamanic use of ashes or lime in *Anadenanthera* snuffs). Snuff analogues were made by finely pulverizing (and in some cases mixing) the crystalline alkaloids.

In snuff bioassays, I first washed my nose with saline solution, which was exsufflated followed by drying with tissue. Alkaloids were insufflated bilaterally through a short glass tube, after which I reclined until the peak effects were perceived, at times elevating my head to ensure the material did not enter my throat. For sublingual bioassays, the alkaloids were again finely powdered on a glassine weighing paper from which they were dropped under my tongue, which was first lowered to smear them around, after which I would recline with my head propped up, my tongue positioned in the back of my mouth to obviate salivary dilution, again until experiencing peak effects. Oral experiments involved simply swallowing the encapsulated alkaloids. For inhaled-vapor tests, bufotenine was weighed on a square of heavy-gauge aluminum foil subsequently fashioned as a ball, into the opening of which the flared end of a female ball-jointed glass tube would just fit. The material was vaporized over an alcohol lamp, and the vapor retained for 45-60 seconds. Both foil and tube were later weighed to ensure I had absorbed the entire dose. The bufotenine

suppositories (in pharmaceutical cocoa butter) were simply inserted intrarectally.

Careful notes were made of each experiment. At least a full day passed between bioassays. My aim was always to ascertain the threshold dose for unmistakable visionary effects (auditory and visual), so to minimize subjectivity in evaluating the results—the threshold can be noted accurately, whereas comparing stronger effects implies subjective guesswork. Visionary effects of insufflated bufotenine were verified by one colleague well experienced with *Anadenanthera* snuff, those of vaporized bufotenine by several volunteers. As yet, effects of sublingual, oral and intrarectal bufotenine are unreplicated.

SUBJECTIVE EFFECTS OF VISIONARY TRYPTAMINES

Although visionary or psychoptic effects (generally colorful and luminous patterns, either geometric or arabesque; at times also substantive visions) are characteristic of psychoactive tryptamines, for me these are not prominent, in contrast to auditory effects (usually high-pitched tinnitus and a much greater perceptive prominence of the auditory sense) which in turn acquires higher discrimination and resolution of actual sound sources, hence more "depth." Truly physical effects are barely perceptible, although bodily perception may be altered. *Euphoria* is the best word to describe its effect on mood, although some people experience rather anxiety and dysphoria. For me, there are no after-effects; far from a "crash" or depression, I always feel stronger and healthier after (and during) the experience. There is so much variation among individuals in the effects of any given tryptamine that it is futile to generalize further. The pharmacodynamics of bufotenine by distinct routes is discussed below.

ISOLATION AND PURIFICATION OF BUFOTENINE FREE-BASE

Coarse-ground powder of 125 g of seeds of *A. colubrina* var. *Cebil* was stirred twice for eight hours in 500 ml of 96% ethanol 1% tartaric acid, the combined filtrates concentrated to 150 ml and diluted with 200 ml water in a separatory-funnel, causing precipitation of considerable fat. The pH was adjusted to 3–4 with concentrated hydrochloric acid, and the solution defatted by shaking six times with chloroform, which was set aside. The defatted extract was basified to pH 8–9 with ammonium hydroxide, then again extracted eight times with 200 ml chloroform; the combined chloroform extracts were concentrated to a foamy, yellowish oil that dissolved completely in 50 ml hot ethyl acetate, then concentrated to 15 ml and refrigerated overnight. In the morning there were a brace of minuscule rosettes of dark-brownish crystals growing at the base of the flask, which was alternated between periods under refrigeration and standing unstoppered at room temperature during 48 hours, leading to the formation of large masses (some greater than 1 cm) of dark-brownish, prismatic crystals. The mother-liquor was decanted and the crystalline mass rinsed with cold ethyl acetate dried over magnesium sulfate, then dried under reduced pressure to yield 4.1 g of large, free-flowing, sparkling brownish crystals. These were twice recrystallized from dry ethyl acetate, yielding 3.87 g of off-white bufotenine free-base crystals (3.10%), m.p. 125–126° C. Despite loss of chromophores on recrystallizations, the melting-point remained 124–126°. Six reports of isolated bufotenine free-base, from *Amanita citrina* (Schaef.) Gray (Agaricaceae) (Wieland & Motzel 1953) and *Anadenanthera* species (Rendón 1984; Iacobucci & Rúveda 1964; Pachter, Zacharias & Ribeiro 1959; Alvares Pereira 1957; Stromberg 1954—yields reported were from 0.94–7.4% for *A. peregrina* to 0.5–2.1% for *A. colubrina*), disclosed two crystalline isoforms from ethyl acetate, one melting from [123–]124–126[–129]°C, the other 146–147[–150]°C. Two reports of synthetic material disclosed a third isoform, with melting points of 138–140°C (Stoll et al. 1955); and again 146–147°C (Speeter & Anthony 1954). In all cases involving the lower-melting-point isoforms, repeated purification did not alter the melting point, although Iacobucci and Rúveda (1964), upon seeding a recrystallization-solution of their lower-melting-point isoform (123–124°C) with crystals having m.p. 146–147°C, got only crystals of the latter type, which operation was not reversible. By manipulating conditions of recrystallization from ethyl acetate, I was able to generate crystals melting at 145–147°C, and confirmed Iacobucci and Rúveda's observation. DMT free-base from hexane likewise exists as at least three isoforms, melting points from 44–74°C having been reported, and Fish, Johnson and Horning (1956) replicated the irreversible transformation of a lower-melting-point isoform (47–49°C) into a higher-melting-point isoform (71–73°C). Identity and purity of isolated bufotenine were verified by mass-spectral analysis and thin-layer chromatographic comparison with an authentic sample in several solvent systems.

BUFOTENINE-INTRANASAL PSYCHONAUTICS (BN)

Nine bioassays (BN-I through BN-IX, with dosages of 5, 10, 20, 30, 40, 50, 60, 80, and 100 mg, respectively) established the visionary parameters of intranasal bufotenine. Insufflating 40 mg bufotenine free-base in BN-V led me to the visionary threshold, while even 5, 10, 20 and 30 mg (BN-I through BN-IV) were perceptibly psychoactive in every case, with closed-eye luminosity and scintillation commencing at 20 mg (BN-III); whereas 30 mg in BN-IV was barely subthreshold. The following pharmacodynamics are characteristic at 40 mg (0.57 mg/kg): first sign of activity, acouasm (tinnitus) at five minutes; clear tryptaminic body effects at 25 minutes; peak between 35

and 40 minutes; unmistakable diminution by 50 minutes; and evanescent after effects up to 90 minutes. Like *cebíl*-seeds snuffed and smoked, intranasal bufotenine is throughout quite physically relaxing; in no case was there facial rubescence, nor any discomfort nor disesteeming side-effect. BN-VI through BN-VIII (50, 60, 80 mg) gave progressively stronger effects with similar pharmacodynamics. In BN-IX (100 mg; 1.43 mg/kg), colored patterns with eyes closed presented at 15 minutes, much as I had experienced with ground *cebíl*-seed snuff in Chile. Inasmuch as shamanic snuffs are often combined with β-carboline-containing *Banisteriopsis* liana powder (Ott 2001), BN-X through BN-XIII involved combinations of bufotenine free-base with both harmine and harmaline, as hydrochloride dihydrate salts (all β-carboline doses are given as free-base equivalents). Previous research with 5-MeO-DMT *cum* β-carbolines, which will be reported forthwith (Ott In press), had established that even minuscule doses of harmine and harmaline effectively doubled the intranasal potency of this tryptamine, with as little as 3.7 mg (0.05 mg/kg) halving the visionary threshold dose. This proved to be the case for bufotenine as well. In BN-XII, for instance, 50 mg bufotenine (0.71 mg/kg) insufflated with 7.5 mg harmine (0.11 mg/kg) proved to be more potent than 80 mg plain bufotenine (BN-VIII) and roughly commensurate with 100 mg (BN-IX). While bufotenine decidedly has the tryptamine signature, its psychoptic effects are unique and eminently distinguishable from those of DMT or 5-MeO-DMT. In the first place, some are evident only in low-light conditions, and might be missed in darkness, such as a shimmery "magical varnish" (to borrow Baudelaire's *bon mot*) over the world, which seems to breathe, accompanied as this is by susurrant and synaesthetic psithurism, and occasionally a sudden and dramatic dimming of the visual field, as though the starting of a heavy motor had dropped line-voltage and dimmed the lights. On the other hand, at the highest doses tested, there are swirling, colored patterns typical of tryptamines, tending toward the arabesque, whereas for me at very high doses of DMT and 5-MeO-DMT, geometric psychoptic patterns sometimes manifest. With bufotenine there is also an occasional and curious "strobe-effect" in low light, which I have never experienced with either of its visionary congeners.

BUFOTENINE-SUBLINGUAL PSYCHONAUTICS (BS)

Like 5-MeO-DMT, sublingual bufotenine proved to be equipotent with intranasal ingestion, having virtually the same pharmacodynamics, and likewise susceptible to doubling of potency with similar doses of β-carbolines. In BS-II, 50 mg bufotenine (0.71 mg/kg) plus 7.5 mg harmaline (0.11 mg/kg), was considerably stronger than BS-I (50 mg bufotenine neat) and roughly equipotent with BN-XII (50 mg bufotenine plus 7.5 mg harmine, intranasally).

BUFOTENINE-ORAL PSYCHONAUTICS (BO)

There are various reports of oral ingestion of *Anadenanthera* seeds, whether as a simple masticatory or as an additive to alcoholic *chichas*, ranging from the Peruvian *montaña* to central Argentina, and from the epoch of the conquest to the twentieth century. Both Hofmann (1999: 1963) and Isbell (in correspondence to Wassén & Holmstedt 1963) had reported that bufotenine was inactive orally—Hofmann, based on personal bioassays of up to a 50 mg dose (ca. 0.8 mg/kg); Isbell referring vaguely to "doses running up to 100 mg (total dose)," implying that this amount was given fractionally, without specifying individual doses. In BO-I, I ingested 100 mg bufotenine free-base (1.43 mg/kg) encapsulated, to preclude any contact with my buccal mucosa—this dose was most decidedly psychoactive. The first activity, tinnitus, manifested at 20 minutes, developed slowly and lasted some two hours. The peak was attained at one hour 30 minutes with all the classic tryptaminic bodily sensations and mild psychoptic effects, but absent colored patterns. In BO-II, I swallowed a capsule containing 20 mg bufotenine (0.28 mg/kg) plus 40 mg harmaline (0.57 mg/kg—I'd already established per *pharmahuasca* bioassays such quantity orally activated DMT for me, although I am a low-MAO phenotype, and most require about 50% more)—this proved to be nearly as potent as BO-I, with virtually identical pharmacodynamics.

INHALED-VAPOR BUFOTENINE PSYCHONAUTICS (BV)

Both species of *Anadenanthera* used as snuffs have also reportedly been used as fumatories, especially *cebíl* seeds, which presently in the Chaco are more commonly smoked than snuffed (generally with tobacco); shamans assert they are more active thus (Torres & Repke 1996), which I and others in my presence have verified. Tryptamines as a rule are more active via inhalation of free-base vapor than orally or intranasally, and this proved to be the case for bufotenine as well. In five bioassays, I tested increasing doses of inhaled, vaporized bufotenine free-base. BV-II through BV-V involved inhalation of 2, 4, 6 and 8 mg bufotenine (0.03–0.11 mg/kg), respectively. All doses were decidedly psychoactive, increasing in potency proportional to dosage, with roughly the same pharmacodynamics save time of onset, which decreased in proportion to increased dosage (45, 35, 25 and 18 seconds, respectively). The first clear signal (acouasm) was at two minutes; peaks were attained at four to five minutes, unmistakable attenuation by seven to nine minutes, with diminishing effects evident for a full hour. In BV-II through BV-IV, psychoptic effects were limited to that low-light, shimmery "magical varnish" over the world not evident in darkness

and attended by synaesthetic psithurism; while in BV-V (8 mg), at seven to eight minutes there were also ringlike, swirling, colored patterns with eyes closed; visible, albeit fainter, with eyes opened in low light.

BUFOTENINE-INTRARECTAL PSYCHONAUTICS (BR)

De Smet (1985b; 1983) has extensively reviewed the evidence for shamanic enema-injection, which is strong and incontrovertible in the case of infusions of *Anadenanthera* seeds and leaves; accordingly I resolved to bioassay intrarectal bufotenine. De Smet (1983) bioassayed doses as high as 125 mg DMT (as less than 185 mg bioxalate salt in 15 ml water; ca. 2.0 mg/kg) intrarectally, which were "without any discernible effect"—I suspect such high doses of the free-base would have been dramatically active. It's unclear why de Smet chose to bioassay DMT thus, and not bufotenine or 5-MeO-DMT, which would have figured in reported shamanic enemas based on *Anadenanthera* seeds and leaves, respectively. Only in the hypothetical case of shamanic enemas based on *leaves* of *Virola* (Ott 2001)—in which it is the predominant tryptamine—might DMT likely be of importance, but *Virola*-leaf enemas have not been reported (only *Virola* leafen snuffs).

For BR-I, I triturated 30 mg bufotenine (0.43 mg/kg) with 0.25 g sodium bicarbonate into 1.0 g of cocoa butter. Mild physical effects developed quickly and lasted roughly an hour. For BR-II, I inserted an identical suppository with addition of 10 mg harmaline, which proved to have subthreshold effects. Finally, in BR-III, a 50 mg (0.71 mg/kg) bufotenine suppository with 10 mg harmaline, threshold-level psychoptic effects resulted. Initial tinnitus commencing at 15 minutes led to closed-eye scintillation and luminosity at the peak, around 45 minutes, followed by the characteristic, shimmery "magical varnish" over the world.

DISCUSSION AND COMMENTARY

While referring the reader to my comprehensive book (Ott 2001) for fuller details and background on these bioassays, by way of summary I note that at least two species of *Anadenanthera*—*A. peregrina* var. *peregrina* and *A. colubrina* var. *Cebil*—have been used virtually throughout South America and the Caribbean in archaic, historical and contemporary times, as snuffs, fumatories, masticatories, potions and enemas derived from the seeds, and at least as snuffs and enemas made from leaves of the former. Setting aside poorly-documented leafen snuffs/enemas (in which the important tryptamine is probably 5-MeO-DMT), rather extensive phytochemical work points inexorably and consistently to bufotenine as by far the major tryptamine in *Anadenanthera* seeds and snuffs, which may contain only insignificant amounts of secondary compounds such as 5-MeO-DMT and DMT. Nevertheless, thanks to perverse, inconclusive, and frankly unethical experiments on convicts and mental patients in the U.S. and Argentina in the 1950s and 1960s (incarcerated subjects cannot render freely informed consent and may be coerced, while mental patients may not even be asked—many of these experiments provoked circulatory crises, facial lividity described as the color of an eggplant or a plum, and at least one led to cardiac arrest, necessitating resuscitative measures), bufotenine has been dismissed far and wide as a supposititious psychoptic agent in these shamanic inebriants. Indeed, in these very pages, an article outstanding for its repetitive wrong-headedness stated no fewer than 16 times that bufotenine was: "not psychedelic," "not hallucinogenic" and "not psychoactive"—the authors, one of whom is a chemist, eschewing the simple expedient of psychonautic bioassays of bufotenine (which is quite easy to isolate or synthesize, and appears to be a controlled substance only in the United States), which would have saved them this embarrassing error (Lyttle, Goldstein & Gartz 1996). Although they cited Turner & Merlis' (1959) review of Isbell's research, they suppressed the detail that his subjects had experienced: "a play of colors, lights, and patterns" following intramuscular injection of bufotenine; then listed (without citing) the report by Bonhour, Fischer & Melgar (1967), which likewise had referred clearly to "hallucinogenic" effects of intravenously-injected bufotenine.

Others have endeavored to explain away the phytochemical and psychonautic evidence concerning *Anadenanthera* by hypothesizing, absent a shred of proof and again unsupported by bioassays, that human beings must possess in sinuses and lungs an enzyme like O-methyl-transferase, which in only one known species of toad (*Bufo alvarius* Gir.) methylates bufotenine to its O-methyl congener, 5-MeO-DMT, which compound would rather be responsible for the psychoptic effects of *Anadenanthera* preparations. Besides failing the test of scientific parsimony, this notion is as unlikely as it is unsubstantiated. Based on my extensive personal experience with bufotenine, 5-MeO-DMT and their plant-sources, I deem it improbable in the extreme—I would have no trouble distinguishing bufotenine from 5-MeO-DMT by any route of ingestion (indeed, I very much like the latter and dislike the former).

It goes without saying that haphazard human intravenous-bufotenine experiments by Fabing and Hawkins (1956), (Isbell) Turner and Merlis (1959) and Bonhour, Fischer & Melgar (1967) are of scant relevance to *Anadenanthera* pharmacology, besides violating the code of medical ethics adumbrated in the Nürnberg War Crimes Tribunals (which mandates informed consent for human studies). Although Isbell, and Turner and Merlis (1959) conducted some crude and desultory tests involving intranasal bufotenine, the doses employed were too low (no more than 14.3 mg free-base equivalent), they unwisely

TABLE 1
Human Pharmacology of Bufotenine

Route	Dosage [Mg]	Effects	References
Intravenous	1–16	"hallucinogenic"*	Fabing & Hawkins 1956
Intravenous	2.5–20	not psychoactive*	Turner & Merlis 1959
Intravenous	6.4–11.1	"hallucinations"**	Bonhour, Fischer & Melgar 1967
Intravenous	2–8	"psychotomimetic"***	McLeod & Sitaram 1985
Intramuscular	10–12.5	"hallucinations"	Turner & Merlis 1959****
Intranasal	<14.3	not psychoactive*****	Turner & Merlis 1959****
Intranasal	6–10	not psychoactive******	Turner & Merlis 1959
Intranasal	1–16	not psychoactive***	McLeod & Sitaram 1985
Intranasal	40–100	psychoactive	This paper
Sublingual	50	psychoactive	This paper
Oral	100	psychoactive	This paper
Inhaled vapor	2–8	psychoactive	This paper
Intrarectal	50	psychoactive*******	This paper

*As creatinine sulfate salt (expressed as base).
**As 12-16 mg oxalate salt (mono- or bi-oxalate salt not specified)
***As solution of bufotenine oxalate (expressed as base; 2 and 4 mg inactive iv).
****Reporting experiments conducted by H.S. Isbell (pers. com. 4 Oct. 1956).
*****As <40 mg creatinine sulfate salt sprayed in solution.
******Both base and creatinine sulfate salt (apparently expressed as base).
*******With 10 mg harmaline hydrochloride dihydrate salt (30 mg not psychoactive).

used a water-soluble salt, and frankly were quite at sea with this sort of research, which they didn't adequately report, much less follow-up. Similarly, doses employed intranasally of what I call "National Institutes of Health-" or "NIH-snuff" prepared there by Fish (Fish & Horning 1956; Fish, Johnson & Horning 1955) were far too low (no more than 560 mg, containing 6 mg bufotenine). This was also the case for Isbell's and Hofmann's (1963) preliminary oral experiments—I hasten to underscore that Hofmann's involved fully ethical, *personal* psychonautic bioassays, by an eminently qualified expert who knew better than anyone what he was doing.

I think my evidence, although it of course requires further confirmation by others, is conclusive and consistent—there is no reason to look beyond bufotenine, by far their major tryptamine, for the psychoptic agent of shamanic *Anadenanthera* preparations, whether snuffed, smoked, swallowed, sucked or inserted rectally. I very much doubt anyone with a modicum of experience with tryptamines would have difficulty distinguishing bufotenine from other tryptamines, with which it nonetheless shares some commonalities. As inhaled free-base vapor it is roughly equipotent with 5-MeO-DMT, and some four- or five-fold more potent than DMT; as errhine or sublingually it is roughly equipotent with DMT and some several-fold weaker than 5-MeO-DMT. This generally holds for oral ingestion as well, with the proviso that orally, DMT (at least up to a 1.0 g dose) requires activation by MAOI, whereas in sufficient dosage, both bufotenine and 5-MeO-DMT (Ott In press) are impressively active orally by themselves. Given our contemporary fixation on DMT and the so-called "*ayahuasca* effect," mayhap this will surprise many, but it oughtn't. With regard to oral activity, *DMT is the exception, not the rule, among tryptamines*. Of some 30 simple tryptamines reported to be psychoactive by Shulgin and Shulgin (1997), 28 were active orally (correcting for bufotenine and 5-MeO-DMT), and the only other exception simply had not been tried orally.

Nor ought the comparatively high activity of bufotenine as inhaled vapor, and correspondingly low activity by other routes, surprise us (see Table 1). It has been established that bufotenine passes the blood-brain barrier with difficulty, and setting aside intravenous injection of tryptamines (in all events, hardly germane to the pharmacology of shamanic snuffs; *vide* Ott 1999), inhaled vapor effects the most efficient passage of tryptamines through the blood-brain barrier; although at least with respect to psychoptic effects, bufotenine would seem to be more psychoactive as inhaled vapor than via intravenous injection (perhaps due to binding by profuse serotonine receptors in the vascular system and on blood cells). Animal research has shown that once in the brain, bufotenine has more "LSD-like activity" than does 5-MeO-DMT, itself more active than DMT, which is what their chemical structures might lead us to expect (Glennon et al. 1979). Indeed, in rat fundus-strip preparations, bufotenine had twice the serotonine receptor affinity of 5-MeO-DMT (Glennon & Gessner 1975).

As for intranasal activity of other psychoptic tryptamines, Shulgin & Shulgin (1997) reported that N-methyl-N-isopropyltryptamine or MIPT is active intranasally at 20 mg; N,N-diethyltryptamine or DET

likewise at about 100 mg (Gartz 1999); while several reports from basement shamans are consistent regarding intranasal activity of N,N-dipropyltryptamine or DPT from 35–200 mg (Case 1999; Gwyllm 1999; Toad 1999). All three of these compounds remain artificial, and are likewise active orally. As documented in my third paper in this series (Ott In press), the natural snuff-tryptamine 5-MeO-DMT similarly is active intranasally—forthwith I shall document also intranasal activity of DMT.

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