Intoxicating Snuffs of the Venezuelan Piaroa Indians

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It is well known that the indigenous peoples and tribes of the Western Hemisphere have used a variety of psychoactive preparations in a ritual context. Major nonoral dosage forms seem to be enemas (de Smet 1983), snuffs (de Smet 1985a) and fumigatories (de Smet 1985b). With respect to snuffs, there can be no doubt that the center of their ritual use lies in South America (see Table I).

One of the numerous South American groups that has been reported to employ intoxicating snuffs is the Venezuelan Piaroa tribe (Wassén 1967). These tropical forest people of the Salivan family are settled along tributaries of the Orinoco in the Guiana Highlands of the Federal Territory of Amazonas (Kaplan 1975). Ethnobotanical sources only stated that the Piaroa Indians prepared snuffs from *Anadenanthera* seeds (von Reis Altschul 1972; Wilbert 1958; Wurdack 1958), but in the 1960's the presence of harmine in a Piaroa snuff was reported (Holmstedt & Lindgren 1967). This compound is not an *Anadenanthera* constituent, but a *Banisteriopsis* alkaloid and its occurrence in South American snuffs is rare.

Consequently, the authors welcomed the opportunity to analyze two different snuffs of the Piaroa Indians that had not been analyzed before. The results of the chemical studies are presented in the second part of this article. This is preceded by an ethnobotanical and chemical overview of Piaroa and related snuffs, and followed by a pharmacological view of the constituents that were isolated.

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ETHNOBOTANY AND CHEMISTRY OF PIAROA AND RELATED SNUFFS

Piaroa Snuffs from *Anadenanthera*

Several sources indicate that the men of the Piaroa tribe use an intoxicating snuff called *yopo*, *niopo* or *niopa* (Kaplan 1975; Wilbert 1958; Wurdack 1958; Gheerbrant 1952; de Wavrin 1948). Gheerbrant stated that this snuff is the crushed black-brown mixture of unidentified ingredients and the fine white ash of certain herbs. The evidence available from other authors suggests that *Anadenanthera* seeds are a common ingredient of Piaroa snuffs. The genus *Anadenanthera*, formerly considered as the section *Niopa* of the genus *Piptadenia*, is the probable source of various South American *yopo* snuffs (von Reis Altschul 1972). According to Wilbert, the Piaroa obtain their *yopo* snuff from the seeds of *Piptadenia* trees. The pulverized seed is passed around in a round tray with a handle in the form of a fish fin, and the snuffing men use Y-shaped tubes of bird bone. Wurdack reported that the Piaroa are avid *yopo* inhalers who annually visit the savannas of the upper Ventuari River and those of the middle Parguaza River to collect mature *Piptadenia* seeds. To prepare the snuff, the bark of *Coco de mono* (a species of the *Lecythidaceae*) is burned and the ashes are added to the pulverized seeds. Von Reis Altschul (1972) identified a *yopo* specimen as *Anadenanthera peregrina* (formerly known as *Piptadenia*

TABLE I

MULTIDISCIPLINARY OVERVIEW OF SOUTH AMERICAN SNUFFS (ADAPTED FROM DE SMET 1985A, 1983)

Scientifc Name	Ethnobotany	Phytochemistry*	Pharmacology	Nasal Efficacy
Anadenanthera species (Leguminosae)	*Anadenanthera* seeds are a common source of South American snuffs	DMT, 5-OH-DMT, 5-MeO-DMT	Established hallucinogenic activity for DMT and 5-MeO-DMT but questionable for 5-OH-DMT	
Banisteriopsis species (Malpighiaceae)	Ethnobotanical evidence is lacking, but *Banisteriopsis* alkaloids are occasionally isolated from South American snuffs	harmine, harmaline, tetrahydroharmine	Established hallucinogenic activity	
Erythroxylum species (Erythroxylaceae)	Coca is reputedly used as a snuff source in the northwest Amazon	cocaine	Established stimulant properties	Well documented
Ilex quayusa (Aquifoliaceae)	Bundled leaves have been found together with snuff trays in a pre-Hispanic Bolivian grave	caffeine	Established mild stimulant properties	Demonstrated in one individual
Justicia pectoralis (Acanthaceae)	Leaves are mostly taken as an admixture to *Virola* bark exudate, but occasionally they are used alone	coumarin, umbelliferone		
Maquira sclerophylla (Moraceae)	There is circumstantial evidence that the fruit was used as a snuff source in the central part of the Brazilian Amazon			
Nicotiana species (Solanaceae)	Tobacco leaves are widely used in South America as a snuff source	nicotine	Established stimulant properties	Well documented
Pagamea macrophylla (Rubiaceae)	Pulverized leaves are used as a snuff among the Colombian Barasana Indians			
Piper interitum (Piperaceae)	Peruvian Kulina Indians are said to prepare a snuff from the dried leaves and roots			
Tanaecium nocturnum (Bignoniaceae)	Brazilian Paumarí Indians use a snuff mixture of the roasted ground leaves with tobacco powder			
Virola species (Myristicaceae)	The bark exudate is a common source of South American snuffs	DMT, 5-MeO-DMT	Established hallucinogenic activity	

*DMT=N,N-dimethyltryptamine; 5-OH-DMT=5-hydroxy-N,N-dimethyltryptamine; 5-MeO-DMT=5-methoxy-N,N-dimethyltryptamine

peregrina), the seeds of which were said to be the source of an intoxicating Piaroa snuff.

Ethnobotany of *Anadenanthera* Snuffs

The ethnological literature on South America includes numerous references on a most interesting, but somewhat enigmatic group of intoxicating snuffs, denoted as *paricá*, *yopo*, *yupa*, *niopo*, *hisioma* and *angico* (von Reis Altschul 1972; Wassén 1972, 1967, 1965; Wassén & Holmstedt 1963). At one time, such snuffs were generally attributed to the seeds of *Piptadenia* spp., in particular *Piptadenia peregrina* (Schultes 1967; Wassén & Holmstedt 1963; Cooper 1949; Lowie 1948; Roth 1924). This leguminous tree has a rather complex nomenclatural history: It has also been known under the binomials *Acacia niopo* and *Mimosa acacioides*. It is now considered to be *Anadenanthera peregrina*, which occurs in northern parts of South America and in the West Indies. From southern Brazil and Paraguay the variety *A. peregrina* var. *falcata* is known (von Reis Altschul 1964). The once common attribution of all *paricá* snuffs and the like to the seeds of *Anadenanthera* spp., such as *A. peregrina*, reflects the general belief in those days that South American snuffs had either *Nicotiana* or *Anadenanthera* as their botanical origin. Since the 1950's, however, it has become increasingly clear that this generalization is a misconception that was kept alive by the uncritical acceptance of infirm or invalid botanical data. Schultes and colleagues have rightly emphasized this fact again and again, thereby pointing at the abundance of *Virola* snuffs in the Amazon basin and at the relatively restricted geographical range of *A. peregrina*. This tree can be expected to occur in open savanna country, but it is not likely to grow spontaneously in the deep and uninterrupted forest areas of Amazonian Brazil (Schultes 1984, 1967, 1954; Schultes & Hofmann 1980; Schultes & Holmstedt 1968). However, the actual use of *A. peregrina* is not necessarily confined to its natural distribution range. A Waiká group of the Brazilian Marauiá River yearly undertakes a long canoe journey to open pastures where they collect the seeds of *A. peregrina* with the purpose of preparing a snuff (Prance 1972). Interestingly, the tree has been observed to occur in the Marauiá area itself, where it is probably cultivated from imported seeds (Schultes & Holmstedt 1968; Wassén 1965).

The domestication of *A. peregrina* and the trade in its seeds have also been reported to occur in the Orinoco basin (Chagnon, Le Quesne & Cook 1971; Granier-Doyeux 1965). From the available botanical evidence it would appear that this territory is the major South American area of *A. peregrina* snuffs, which are principally known there as *yopo*, *yupa*, *niopo* and *hisioma* (Schultes & Hofmann 1980; Schultes et al. 1977; Reichel-Dolmatoff 1975; von Reis Altschul 1972; Chagnon, Le Quesne & Cook 1971; Coppens & Cato-David 1971; Wassén 1967, 1965; Granier-Doyeux 1965; Wurdack 1958). Detailed accounts by early travelers, such as von Humboldt (1958) and Spruce (1908), indicate that the use of such snuffs is not a recent cultural trait of the Orinoco region. Most snuffs are prepared from the roasted and powdered seeds, and in many cases vegetable ash or lime obtained from shells is added (von Reis Altschul 1972; Coppens & Cato-David 1971; Wassén 1967, 1965; Granier-Doyeux 1965).

According to the classic descriptions, the snuffs have a stimulating effect, producing great excitement and the onset of hallucinations. This is followed by sleepiness that often passes to a hypnotic or unconscious state (Granier-Doyeux 1965). Among the Venezuelan Cuiva Indians, who prepare a *yopo* snuff from *A. peregrina* seeds and shell lime, a single dose usually does not exceed five grams and this amount may be taken one to three times a day. One dose was reported to cause an intoxication of one-quarter to two hours (Coppens & Cato-David 1971).

A detailed discussion of all the snuffs, which rightly or wrongly have been associated with *A. peregrina*, is beyond the scope of this article. For overviews of this subject the reader is referred to the meticulous publications of Wassén (1972, 1967, 1965) and von Reis Altschul (1972). Examples of snuffs that probably have been correctly attributed to the seeds of *A. peregrina* are the *paricá* snuffs of the Mura Indians and the other tribes of the Brazilian Madeira region and the famous *cohoba* snuff of the early colonial natives of the West Indies (von Reis Altschul 1972; Schultes 1967; Safford 1916; Barbosa Rodrigues 1875; von Martius 1867).

The genus *Anadenanthera* comprises a second species, *Anadenanthera colubrina*. It occurs in eastern Brazil, and its variety *Anadenanthera* var. *cebil* is known from Argentina, Bolivia, Paraguay, Peru and several localities in southeastern Brazil (von Reis Altschul 1964). The variety *cebil* frequently has been associated with certain early snuffs called *vilca* or *huilca* in southern Peru and Bolivia, and *cébil* or *sébil* in northern Argentina. Although the evidence is circumstantial and sometimes weak, it is quite possible that the association is correct, not in the least because phytochemical studies have revealed the presence of tryptamine alkaloids in the seed of *A. colubrina* var. *cebil* (Schultes & Hofmann 1980; von Reis Altschul 1972, 1967; Schultes 1967; Wassén 1967, 1965; Cooper 1949; Safford 1916).

Chemistry of the Genus *Anadenanthera*

Seeds of *Anadenanthera peregrina* (*Piptadenia peregrina*) were found to contain one or more of the following indole alkaloids (Schultes et al. 1977; Holmstedt & Lindgren 1967): N,N-dimethyltryptamine (DMT); its corresponding N-oxide (DMT-N-oxide); 5-hydroxy-N,N-dimethyltryptamine (5-OH-DMT) or bufotenine; its corresponding N-oxide (5-OH-DMT-N-oxide); and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). During storage, DMT and 5-MeO-DMT may transform into 5-OH-DMT (Schultes et al. 1977).

DMT, 5-OH-DMT and 5-OH-DMT-N-oxide were reported to be present in seeds of *Piptadenia macrocarpa* (Iacobucci & Rúveda 1964), now considered to be *Anadenanthera colubrina* var. *cebil* (von Reis Altschul 1964), whereas 5-OH-DMT has been isolated from seeds of *A. colubrina* (*P. colubrina*) (Holmstedt & Lindgren 1967).

Anadenanthera Alkaloids in South American Snuffs

The occurrence of the *Anadenanthera* alkaloids DMT, 5-MeO-DMT and/or 5-OH-DMT in Venezuelan and Colombian snuffing material has been repeatedly demonstrated (Schultes et al. 1977; De Budowski et al. 1974; Holmstedt and Lindgren 1967; Fish & Horning 1956). Vegetable ashes that are mixed with these snuffs may contain alkaline inorganic substances, such as potassium carbonate (Rivier 1981; Cooper 1949).

Piaroa Snuffs from Other Ingredients

Although the Piaroa appear to be familiar with tobacco (Kaplan 1975; Wurdack 1958; Gheerbrant 1952; Chaffanjon 1889), the consulted literature has not yielded evidence that they ever used tobacco as a snuff source. Yet it would appear that ingredients other than *Anadenanthera* seeds may enter the composition of Piaroa snuffs. There is a vague field report (Wurdack 1958) that the Ventuari Piaroa also employ the vegetative parts of an unidentified bush for preparing a snuff. Much more significantly, Holmstedt and Lindgren (1967) have provided chemical evidence that *Anadenanthera* is not the only snuff source of the Piaroa. They isolated not only *Anadenanthera* tryptamines (DMT, 5-OH-DMT, 5-MeO-DMT), but also harmine from a *paricá* snuff sample of this tribe collected by Bolinder. The β-carboline harmine is not an *Anadenanthera* constituent, but a major *Banisteriopsis* alkaloid.

Ethnobotany of *Banisteriopsis* Snuffs

Intoxicating *Banisteriopsis* drinks are widely employed by the indigenous inhabitants of the South American continent (Schultes 1982; Friedberg 1965; Cooper 1949). There does not appear to be any ethnobotanical evidence for the preparation of snuffs from *Banisteriopsis* (Schultes 1984, 1982; Friedberg 1965). In chemical studies, however, harmine was found in a snuff from the Venezuelan Piaroa Indians, while harmine, harmaline and tetrahydroharmine could be isolated from a snuff of the Surára Indians, a Waiká group of northwestern Brazil. Unfortunately, no botanical material was collected together with the snuffs, so their botanical origin remains uncertain. In South American ethnobotany, the β-carbolines harmine, harmaline and tetrahydroharmine are commonly associated with *Banisteriopsis*, so these chemical findings certainly open up the possibility that *Banisteriopsis* may have been used as a source of snuff (Schultes 1982; Holmstedt & Lindgren 1967). However, the most comprehensive review on the use of *Banisteriopsis* by South American Indians (Friedberg 1965) includes neither the Piaroa nor the Surára as tribes familiar with *Banisteriopsis* drinks.

Chemistry of the Genus *Banisteriopsis*

The principal alkaloids in *Banisteriopsis* spp. used by natives are β-carbolines, particularly harmine, harmaline and (+)-1,2,3,4-tetrahydroharmine (Allen & Holmstedt 1980; Deulofeu 1967). The well-studied species *B. caapi* was found to contain 0.11%–0.83% of alkaloids in the stem, 0.14%–0.37% in the branches, 0.28%–0.70% in the leaves and 0.64%–1.95% in the root. These total percentages consisted primarily of harmine (40%–96%) and, to a lesser extent, tetrahydroharmine (one percent to 44 percent) and harmaline (0%–17%). Small amounts of harmol, 6-methoxytryptamine and an unidentified compound were sometimes also present (Rivier & Lindgren 1972). More recent analytical work on the same species revealed that other β-carbolines may be present as minor components: harmine-N-oxide, harmic acid methyl ester, harmalinic acid, harmic amide, acetyl norharmine, ketotetrahydronorharmine and harmalol (McKenna, Towers & Abbott 1984; Hashimoto & Kawanishi 1976, 1975). In addition, the pyrrolidine bases shihunine and S-(+)dihydroshihunine have been shown to occur in *Banisteriopsis caapi* (Kawanishi, Uhara & Hashimoto 1982).

Banisteriopsis Alkaloids in South American Snuffs

The occurrence of *Banisteriopsis* constituents in South American snuffs has been reviewed by Holmstedt and Lindgren (1967). According to the first table of their review, the presence of one or more *Banisteriopsis* alkaloids has been demonstrated on four different occasions, once by Biocca and colleagues (1964), once by Bernauer (1964) and twice by the authors themselves. On closer

examination, only two actual snuffs seem to be involved.

Biocca and colleagues (1964) did not study a snuff, but the fragment of the stem of a liana from which they isolated harmine, harmaline and tetrahydroharmine. The material was said to serve as a source of *paricá* snuff among the Tukano and Tariana Indians of the Upper Rio Negro area. Biocca (1983) has recently provided a photograph of such a liana. Unfortunately, the collectors have not been able to witness the preparation of the snuff, so it remains uncertain whether the liana actually served as a snuff source and not as an oral ingredient.

Bernauer (1964) analyzed an *epéna* snuff of the Surára Indians of northwestern Brazil. He isolated harmine, (+)-1,2,3,4-tetrahydroharmine and an unidentified amorphous compound, with yields of 1.3% harmine, 0.22% (+)-1,2,3,4-tetrahydroharmine and 0.36% of the amorphous compound before purification, and 0.38% harmine, 0.08% (+)-1,2,3,4-tetrahydroharmine after purification.

Holmstedt and Lindgren (1967) also demonstrated the presence of harmine and tetrahydroharmine in an *epéna* snuff of the Surára Indians, thus duplicating the findings of Bernauer. The gas chromatogram pertinent to the snuff showed a third unidentified peak. The snuff had been collected by Dr. H. Becher, who also supplied the *epéna* sample studied by Bernauer. It seems likely that the same snuff was studied twice and Holmstedt (1983) is inclined to agree with this view. In addition, Holmstedt and Lindgren found harmine together with DMT, 5-OH-DMT and 5-MeO-DMT in a *paricá* snuff of the Venezuelan Piaroa Indians.

Other original publications on *Banisteriopsis* alkaloids in South American snuffs do not seem to be available. Consequently, the authors of the present article welcomed the opportunity to study two different *yopo* samples of the Piaroa Indians.

CHEMISTRY OF TWO *YOPO* SNUFF SAMPLES OF THE PIAROA INDIANS

Material

Sample A, which consisted of dry snuff lumps, was obtained from a European art dealer who had purchased the snuff and some snuff-taking paraphernalia of the Piaroa tribe (Figure 1) from the missionary museum in Puerto Ayacucho, Venezuela. The equipment is now in a private collection.

Sample B, a dry granular powder, was collected by a German named Baumgarter, probably during the 1950's or 1960's. It is presently deposited in the Royal Museum of Central Africa at Tervuren, Belgium. Other than its name would suggest, this museum has a large collection

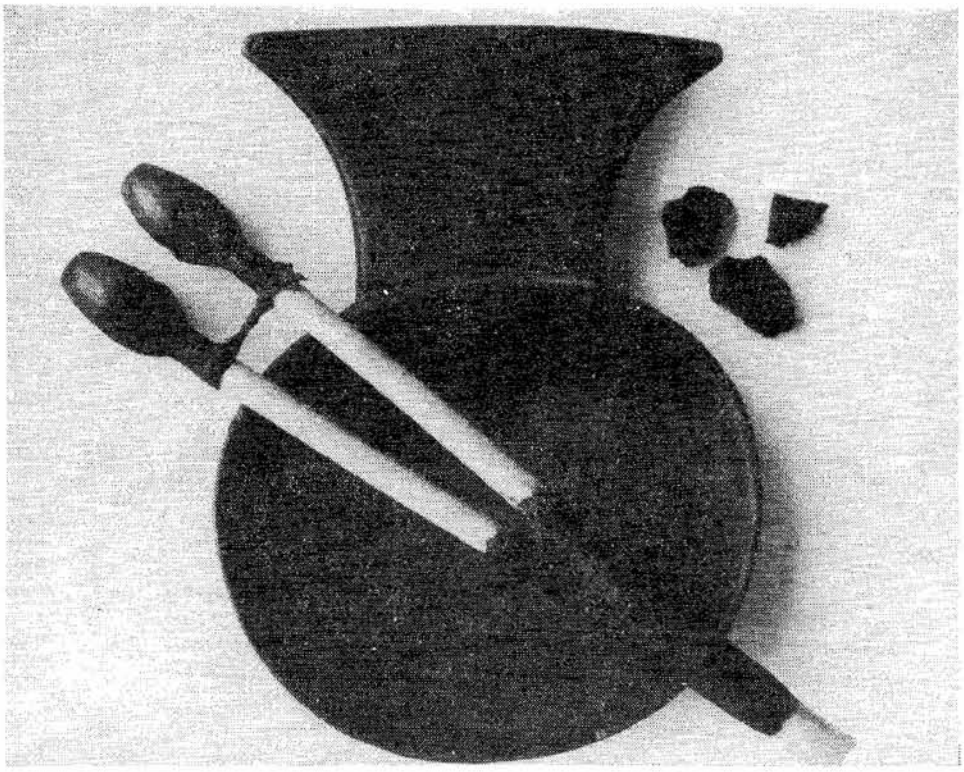


Figure 1. Snuff, tray and tube of the Venezuelan Piaroa tribe (private collection).

of objects from Venezuelan Indians, including various snuff-taking paraphernalia (Figure 2A). Among these items is a Piaroa snuff that is still in its original *kherime* container (Figure 2B; museum number 74.76.594).

Analytical Methods

Isolation of alkaloids: Ground snuff material (100–200 mg) was extracted with ethanol overnight at room temperature. After filtration and evaporation to dryness under nitrogen, the residue was dissolved in a suitable amount of ethanol and submitted to gas chromatographical/mass spectrometric procedures comparable to those described by Schultes and colleagues (1977).

Gas chromatography/mass spectrometry (GC-MS): Analyses were carried out on a combined GC-MS instrument (Hewlett-Packard Model 5985A). Typical GC conditions used throughout were SE-54 WCOT fused silica capillary column (25 m × 0.3 mm i.d.), temperature of the oven isothermal at 100°C for one minute and pro-

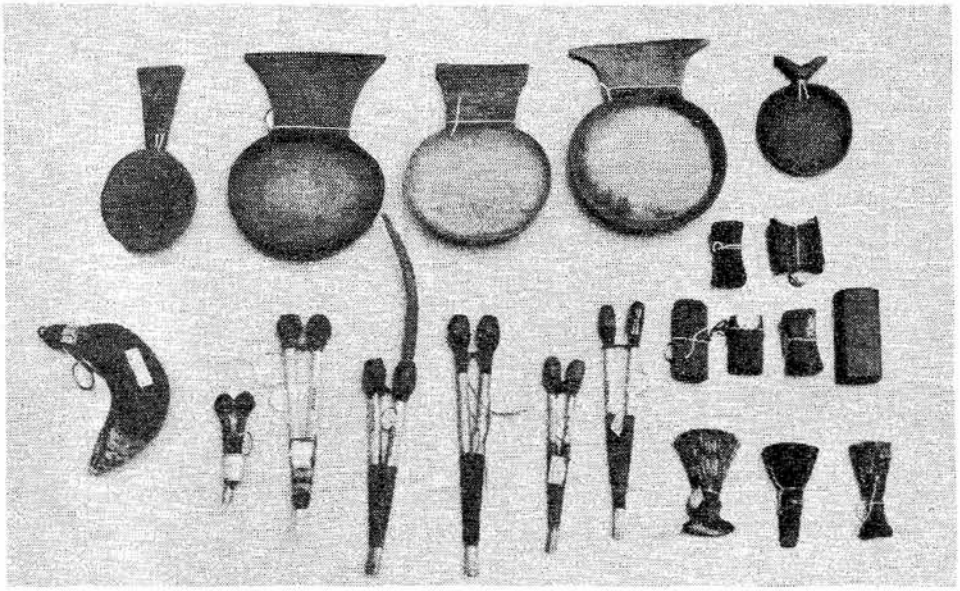


Figure 2A. Snuff-taking paraphernalia of Venezuelan Indians: snuff container, trays, tubes, brushes and pestles (Royal Museum of Central Africa, Tervuren).

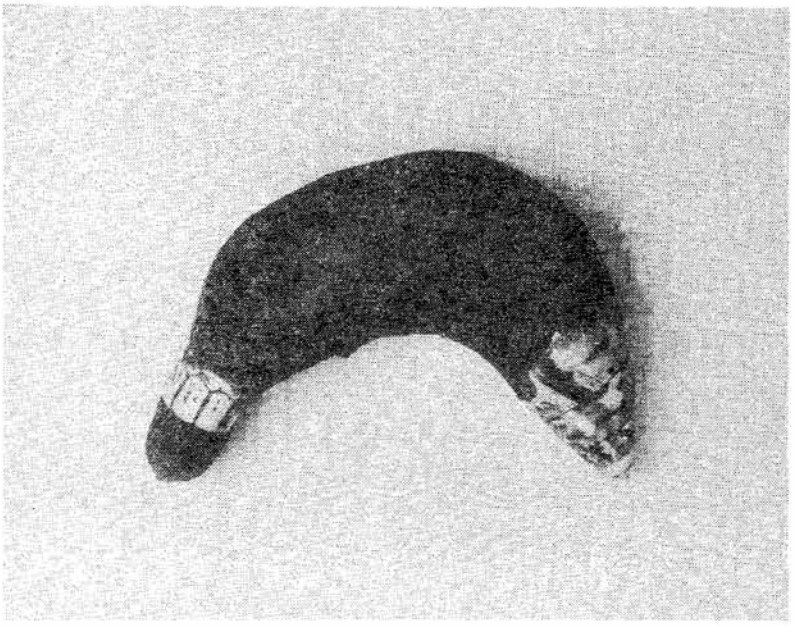


Figure 2B. Snuff container of the Piaroa Indians (Royal Museum of Central Africa, Tervuren).

gramed at 10°C/minute to 240°C. Split mode injections of 1.5 µl were used at a helium pressure of 0.5 kg/cm^2 giving a carrier gas flow of 1.0 ml/minute through the column and a split ratio of 50:1. The capillary column was connected directly to the MS source, which was kept at 200°C. The ion source parameters were set by the Autotune program providing a 70 eV ionization energy and 300 µA emission current. Repetitive scanning from m/z 40 to m/z 340 was performed at one scan per second. The tryptamines and β-carbolines that may occur in South American snuff materials and their source plants were used as reference compounds. Mass spectrometric data for these substances were given by Rivier and Lindgren (1972), Agurell, Holmstedt and Lindgren (1969) and Holmstedt and Lindgren (1967). Both retention time and mass spectrum of authentic reference compounds served as criteria for the identification of the unknown compounds.

Quantitative analyses were performed by using the same analytical conditions. Solutions of known concentrations of reference compounds were injected after each extract sample. Calculation was made by external standardization of the detector response for each detected compound.

In order to check the occurrence of minor alkaloids, a more sensitive setting of the GC-MS was used. By using the selective ion monitoring mode, the detection could be increased twenty- to fiftyfold. Appropriate MS peaks of each compound to be detected were chosen and extracts injected. If the selected peaks emerged at the expected retention time for the reference compound, it was concluded that the substance was present in the extract.

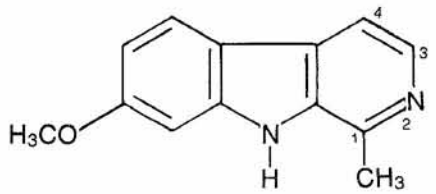
pH determinations: To determine the presence of alkaline substances, 20 mg of ground snuff material was dissolved in 2.0 ml of freshly distilled water by ultrasounds for five minutes. The pH was determined by a combined electrode (Radiometer PHM 83 Autocal pH meter).

Results

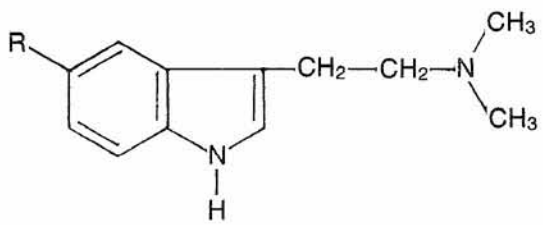
Sample A turned out to contain 10 mg/g of 5-OH-DMT, whereas sample B yielded a trace (<1 mg/g) of 5-OH-DMT. The pH measurements gave values of 9.4 for sample A and 9.2 for sample B. Neither the presence of the *Anadenanthera* alkaloid 5-OH-DMT nor the alkaline reaction of the snuffs is surprising; as the Piaroa Indians are reported to use *Anadenanthera* seeds and plant ashes as snuff ingredients. The substantial difference in quantitative 5-OH-DMT yield might perhaps be related to the condition of the samples: solid lumps (sample A) versus granular powder (sample B).

Sample B also contained a trace of harmine. This finding is quite significant and corroborates the report of Holmstedt and Lindgren (1967), who also found harmine in a Piaroa snuff. Harmine is substituted at C-7, so it could not be produced by ring closure of an *Anadenanthera* tryptamine (Figure 3). In other words, there is at last additional evidence that the Piaroa must have prepared snuffs not only from plants rich in tryptamines, but also from a vegetal source yielding harmine. This conclusion indicates that the tracing of Indian drug materials in European museums and private collections for chemical analyses may lead to interesting results.

Figure 3. Structural formulas of harmine and *Anadenanthera* tryptamines.



Harmine



Anadenanthera tryptamines

R=H: N,N-dimethyltryptamine (DMT)
R=OH: bufotenine (5-OH-DMT)
R=OCH_3: 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)

PHARMACOLOGY OF BUFOTENINE, HARMINE AND PLANT ASH

Clinical Pharmacology of Bufotenine

Isbell, cited by Wassén and Holmstedt (1963) as well as Turner and Merlis (1959), noted that bufotenine (5-OH-DMT) is mostly found to act briefly, altering the perception of colors and sometimes of space when given in intramuscular doses of 10–15 mg. Fabing and Hawkins (1956) had similar findings with intravenous doses of four to 16 mg, as did Bonhour, Fischer and Melgar (1967) with 12–16 mg. In schizophrenics, intravenous amounts up to 20 mg given by bolus injection (e.g., 10 mg within one minute) or by infusion (e.g., 20 mg in 77 minutes) produced neither visual disturbances nor the psychological changes seen after DMT administration (Turner & Merlis 1959). Many secondary sources doubt the hallucinogenic capacity of 5-OH-DMT following peripheral administra-

tion and then point to its poor lipid solubility at physiological pH and its consequent inability to readily enter the central nervous system (Glennon et al. 1979; Luchins, Ban & Lehmann 1978; Holmstedt & Lindgren 1967). Experiments with laboratory animals have demonstrated that 5-OH-DMT does not cross the blood-brain barrier in appreciable amounts (Glennon et al. 1979; Luchins, Ban & Lehmann 1978; Sanders & Bush 1967). This suggests that the reported effects of 5-OH-DMT may well be somatic symptoms of intoxication rather than signs of true hallucinogenic activity. According to Isbell (1967), it is difficult to say whether 5-OH-DMT is a hallucinogen or not because of its powerful cardiovascular effects. For this reason, it is not possible to push the dose in humans and it would be difficult to differentiate whether psychotic reactions were due to central effects or to cardiovascular actions. On the basis of his human studies on bufotenine, Isbell (1984) felt that the cardiovascular danger of bufotenine must be strongly emphasized: "[An injected dose of 10–15 mg] resulted in the development of cardiac arrythmias of the nature of multiple ectopic beats from supraventricular foci. These lasted less than 30 minutes but the arrythmias were sufficiently frightening to cause me to stop the experiments."

Oral experiments with 5-OH-DMT have failed to demonstrate hallucinogen-like effects, although the tested amounts were much higher than parenterally active doses. The alkaloid was without effect when ingested in doses up to 50 mg by a healthy individual (Hofmann 1963) or in "doses up to 100 mg totally"—according to Isbell as cited by Wassén and Holmstedt (1963)—by physically healthy prisoners who had been convicted for narcotics law violations (Isbell 1984). This inefficacy of oral dosing is likely to be principally due to extensive first-pass metabolism by monoamine oxidase (MAO). The structurally related neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) is promptly degraded by intestinal and hepatic MAO when taken orally. The deamination of 5-HT leads mainly to 5-hydroxyindole acetic acid, which is the principal urinary metabolite (Douglas 1980). Although 5-OH-DMT has a dimethylated amino group, there is evidence from rat experiments that it is also deaminated by MAO in vivo (Squires 1975). In humans, 5-OH-DMT is almost completely metabolized: Only one percent to six percent of an intravenous dose can be recovered from the urine in unchanged form and 68%–74% is excreted in the form of 5-hydroxyindole acetic acid (Sanders-Bush, Oates & Bush 1976).

The assertion that 5-OH-DMT undergoes extensive first-pass inactivation by intestinal and hepatic MAO is quite interesting from the ethnopharmacological point of view. Pharmacokinetic studies in rats (Hussain, Kimura & Huang 1984; Hussain, Hirai & Bawarshi 1981) and humans (Hussain et al. 1980) show that first-pass elimination of a high-clearance drug can be adequately avoided by using the nasal route of administration. This may explain why South American natives most often take vegetal sources of 5-OH-DMT in the form of a snuff. So far, however, conclusive clinical support for this assumption has not been published. Human studies on the nasal application of 5-OH-DMT have been conducted in the 1950's, but they have failed to demonstrate hallucinogen-like activity via the nasal route.

Turner and Merlis (1959) have assessed the effects of nasal 5-OH-DMT in schizophrenic subjects. When the alkaloid (as pure base or as creatinine sulfate) was blown into the nares, amounts up to 10 mg merely produced a feeling of fear associated with flushing of the face, lacrimation, tachycardia and tachypnea.

The inhalation of 5-OH-DMT by humans has also been studied by Isbell. In a letter to Turner and Merlis (1959), he stated that "no subjective or objective effects were observed after spraying with as much as 40 mg of bufotenine creatinine sulphate." This compound consists of one part bufotenine base and 1.8 parts creatinine sulfate (Fabing & Hawkins 1956), so 40 mg provides 14.3 mg of bufotenine base. In a letter to Wassén and Holmstedt (1963), Isbell declared that "inhalation of pure bufotenine in aerosol suspension, or oral ingestion of bufotenine in doses running up to 100 mg (total dose) were without effect." Isbell's statements provide insufficient details on the route of inhalation (nasal or tracheal), the test subjects (psychotic patients or not) and the studied doses (100 mg by inhalation or not). Fortunately, Isbell (1984) has recently indicated that the 5-OH-DMT was inhaled nasally and that the subjects were physically healthy male volunteers, aged between 25 and 50, who were imprisoned for narcotics law violations. His communication leaves open, however, whether as much as 100 mg of 5-OH-DMT was inactive by oral ingestion only or also by inhalation.

Isbell's subjects experienced visual disturbances from 10–15 mg of intramuscular 5-OH-DMT, and other investigators have reported visual disturbances from four to 16 mg of intravenous 5-OH-DMT (Bonhour, Fischer & Melgar 1967; Fabing & Hawkins 1956). This would seem to suggest that 5-OH-DMT may induce perceptual changes more readily by injection than by nasal application, which would be consistent with the chemical finding that 5-OH-DMT is poorly lipid soluble at pH 7.4 (Glennon et al. 1979) and thus might not readily diffuse through the lipid nasal membrane. Confirmation of this suggestion is still needed, however, especially in view of recent reports that hydrophilic drugs are absorbed from the nose

gramed at 10°C/minute to 240°C. Split mode injections of 1.5 µl were used at a helium pressure of 0.5 kg/cm^2 giving a carrier gas flow of 1.0 ml/minute through the column and a split ratio of 50:1. The capillary column was connected directly to the MS source, which was kept at 200°C. The ion source parameters were set by the Autotune program providing a 70 eV ionization energy and 300 µA emission current. Repetitive scanning from m/z 40 to m/z 340 was performed at one scan per second. The tryptamines and β-carbolines that may occur in South American snuff materials and their source plants were used as reference compounds. Mass spectrometric data for these substances were given by Rivier and Lindgren (1972), Agurell, Holmstedt and Lindgren (1969) and Holmstedt and Lindgren (1967). Both retention time and mass spectrum of authentic reference compounds served as criteria for the identification of the unknown compounds.

Quantitative analyses were performed by using the same analytical conditions. Solutions of known concentrations of reference compounds were injected after each extract sample. Calculation was made by external standardization of the detector response for each detected compound.

In order to check the occurrence of minor alkaloids, a more sensitive setting of the GC-MS was used. By using the selective ion monitoring mode, the detection could be increased twenty- to fiftyfold. Appropriate MS peaks of each compound to be detected were chosen and extracts injected. If the selected peaks emerged at the expected retention time for the reference compound, it was concluded that the substance was present in the extract.

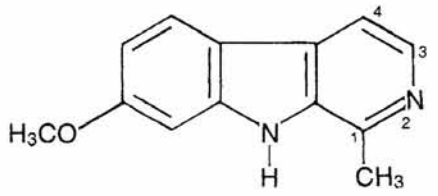
pH determinations: To determine the presence of alkaline substances, 20 mg of ground snuff material was dissolved in 2.0 ml of freshly distilled water by ultrasounds for five minutes. The pH was determined by a combined electrode (Radiometer PHM 83 Autocal pH meter).

Results

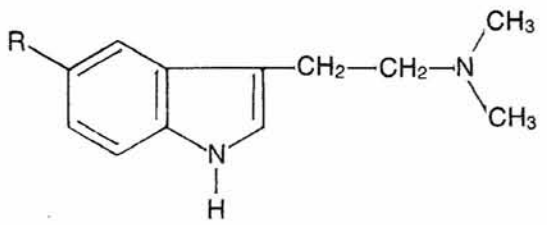
Sample A turned out to contain 10 mg/g of 5-OH-DMT, whereas sample B yielded a trace (<1 mg/g) of 5-OH-DMT. The pH measurements gave values of 9.4 for sample A and 9.2 for sample B. Neither the presence of the *Anadenanthera* alkaloid 5-OH-DMT nor the alkaline reaction of the snuffs is surprising, as the Piaroa Indians are reported to use *Anadenanthera* seeds and plant ashes as snuff ingredients. The substantial difference in quantitative 5-OH-DMT yield might perhaps be related to the condition of the samples: solid lumps (sample A) versus granular powder (sample B).

Sample B also contained a trace of harmine. This finding is quite significant and corroborates the report of Holmstedt and Lindgren (1967), who also found harmine in a Piaroa snuff. Harmine is substituted at C-7, so it could not be produced by ring closure of an *Anadenanthera* tryptamine (Figure 3). In other words, there is at last additional evidence that the Piaroa must have prepared snuffs not only from plants rich in tryptamines, but also from a vegetal source yielding harmine. This conclusion indicates that the tracing of Indian drug materials in European museums and private collections for chemical analyses may lead to interesting results.

Figure 3. Structural formulas of harmine and *Anadenanthera* tryptamines.



Harmine



Anadenanthera tryptamines
R=H: N,N-dimethyltryptamine (DMT)
R=OH: bufotenine (5-OH-DMT)
R=OCH_3: 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT)

PHARMACOLOGY OF BUFOTENINE, HARMINE AND PLANT ASH

Clinical Pharmacology of Bufotenine

Isbell, cited by Wassén and Holmstedt (1963) as well as Turner and Merlis (1959), noted that bufotenine (5-OH-DMT) is mostly found to act briefly, altering the perception of colors and sometimes of space when given in intramuscular doses of 10–15 mg. Fabing and Hawkins (1956) had similar findings with intravenous doses of four to 16 mg, as did Bonhour, Fischer and Melgar (1967) with 12–16 mg. In schizophrenics, intravenous amounts up to 20 mg given by bolus injection (e.g., 10 mg within one minute) or by infusion (e.g., 20 mg in 77 minutes) produced neither visual disturbances nor the psychological changes seen after DMT administration (Turner & Merlis 1959). Many secondary sources doubt the hallucinogenic capacity of 5-OH-DMT following peripheral administra-

in the rat (Su, Campanale & Gries 1984; Hirai et al. 1981).

Not only pure 5-OH-DMT, but also *Anadenanthera* snuffs have been tested nasally in a clinical setting, but unfortunately the studied subjects were not experienced snuff users. Turner and Merlis (1959) were unable to induce an intoxication with snuff prepared from *Piptadenia* seeds. Doses up to 560 mg, containing approximately six milligrams of 5-OH-DMT, were blown forcibly into the nostrils. Subjects could retain the snuff for a few minutes, whereafter violent gagging, coughing and sneezing caused rejection of most of the mass. Cited by Turner and Merlis (1959) as well as Wassén and Holmstedt (1963), Isbell prepared snuffs from a sample of *P. peregrina* in which 5-OH-DMT had been found to be the main component (Holmstedt & Lindgren 1967). He studied untreated snuff as well as roasted, fermented and/or limed snuffs. Inhalation through a straw of amounts up to one gram did not result in subjective or objective effects. In general, subjects discharged most of the snuff by sneezing and coughing.

Clinical Pharmacology of Harmine

In a study by Pennes and Hoch (1957), harmine was hallucinogenic in mental patients at an intravenous threshold dose of 150–200 mg that elicited visual hallucinations in five of 11 patients. Some other effects of these intravenous doses were also produced by oral amounts higher than 300–400 mg, but it is doubtful that indisputable visual hallucinations occurred with oral amounts up to 960 mg.

It has not been unequivocally established why the psychoactivity of harmine is largely route dependent. Substantial hepatic first-pass metabolism certainly cannot be discarded as an unlikely cause. In rodents, harmine is extensively O-demethylated by hepatic microsomal enzymes (Burke & Tweedie 1979).

If harmine indeed undergoes first-pass elimination, nasal application of this alkaloid might be superior to oral ingestion. To test this hypothesis, one of the authors of the present article took the same dose of 0.5 mg/kg of harmine base as a nasal powder and as an oral drink on two different occasions. The dose was derived from a report by Slotkin, DiStefano and Au (1970) that 0.5 mg/kg of harmine HCl intravenously resulted in substantial plasma levels and in transient somatic effects, but not in distinct central stimulation. Plasma samples obtained during the first four hours after administration were assayed by a GC-MS method with a sensitivity down to 2.0 ng/ml. On neither occasion was a notable psychoactive or somatic effect felt and harmine could not be detected in any of the plasma samples. Since Slotkin, DiStefano and Au reported levels in the range of 300–400 ng/ml at 10–60 minutes and 80 ng/ml at 240 minutes after a similar intravenous dose, the latter result was unexpected, especially in the case of the nasal powder. Additional experiments to ascertain why harmine could not be demonstrated in the plasma after nasal application are still needed (de Smet 1985a).

Combination of Bufotenine and Harmine

The joint occurrence of 5-OH-DMT and harmine in Piaroa snuffs deserves a special pharmacological comment as harmine is a potent reversible MAO inhibitor (McKenna, Towers & Abbott 1984; Buckholtz & Boggan 1977; McIsaac & Estevez 1966; Pletscher et al. 1959; Udenfriend et al. 1958), in particular a selective inhibitor of MAO-A (Fowler et al. 1978). As previously mentioned, 5-OH-DMT is inactivated by MAO and it is mainly deaminated in the rat by MAO-A (Squires 1975). These pharmacological data certainly open up the possibility that harmine might enhance the effects of 5-OH-DMT by inhibiting its elimination by MAO-A. There is no clinical evidence in the literature, however, to support this suggestion.

Activity of Plant Ash

Plant ash has no psychoactive effects by itself, but when it is added to a snuff its alkaline reaction may facilitate the diffusion of alkaloids through the nasal mucous membrane (de Smet 1985a). Plant ash might further promote the absorption by helping to prevent agglomeration of the snuff powder (Schultes 1967).

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