

CHAPTER TWO

A MULTIDISCIPLINARY OVERVIEW OF INTOXICATING SNUFF RITUALS  
IN THE WESTERN HEMISPHERE

## CHAPTER TWO PART ONE

### THE ETHNOBOTANY, CHEMISTRY AND PSYCHOPHARMACOLOGY OF RITUAL SNUFFS IN THE WESTERN HEMISPHERE

#### 2.1.1. Acorus calamus

Araceae

Acorus calamus L.

##### 2.1.1.1. Ethnobotany

Acorus calamus, commonly known as rat root or sweet flag, is often included in reviews on ritual botanical intoxicants (Farnsworth 1972; Emboden 1979a; Schultes and Hofmann 1980a,b). Therefore its nasal use by North American tribes should not go unrecorded here. The Chippewa Indians snuffed pulverized rat root to treat colds (Densmore 1928), and the Omaha gave the plant as a snuff to horses to make them spirited and run faster (Morgan 1980). These data confirm the general impression that North American Indians valued the rhizomes of sweet flag as a medicine and stimulant rather than as a true ceremonial intoxicant (Morgan 1980).

##### 2.1.1.2. Chemistry and psychopharmacology

Most publications on the phytochemistry of Acorus calamus concern the rhizomes, which may contain 0.4 to 10.8 % of essential oil (Hegnauer 1963; Röst 1979; Stahl and Keller 1981). It is often stated that this oil has sedative effects, which are thought to be due to its constituents alpha-asarone and beta-asarone (Hoffer and Osmond 1967; Brown and Malone 1978; Schultes and Hofmann 1980a,b). Such statements are based on phytochemical and pharmacological studies with Old World samples, in particular with samples from India (Baxter et al. 1960; Dandiya and Menon 1965; Dhalla and Bhattacharya 1968). There is now considerable evidence, however, that a substantial asarone fraction can only be expected in triploid and tetraploid plants from the Old World, and not in diploid plants from the New World (Hegnauer 1963; Röst and Bos 1979; Stahl and Keller 1981, 1983).

Calamus oil from rhizomes of the North American diploid variety americanus contains acoragermacron, acorone, acorenone, preisocalamendiol, and hydrocarbons as its main constituents, when the oil is extracted with supercritical carbon dioxide

(Stahl and Keller 1983). When it is obtained by water distillation, the thermolabile compound acoragermacron is no longer present, and the major principles are shyobunone derivatives, acorone, acorenone, preisocalamendiol, and hydrocarbons (Röst and Bos 1979; Keller and Stahl 1983).

An unspecified type of Acorus calamus is said to have produced an LSD-like response in two sophisticated subjects who had both taken 10 inches of rat root 5 times (Hoffer and Osmond 1967). This report should not be viewed without caution, for the subjects had taken LSD several times under controlled conditions, so perhaps they were preconditioned to have a similar experience (Morgan 1980).

### 2.1.2. Anadenanthera species

Leguminosae

Anadenanthera colubrina (Vell.) Brenan

var. cebil (Griseb.) Altschul

Anadenanthera peregrina (L.) Speg.

var. falcata (Benth.) Altschul

#### 2.1.2.1. Ethnobotany

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 (Wassén and Holmstedt 1963; Wassén 1965, 1967, 1972a; von Reis Altschul 1972). At one time, such snuffs were generally attributed to the seeds of Piptadenia species, in particular Piptadenia peregrina (Roth 1924; Lowie 1948; Cooper 1949; Wassén and Holmstedt 1963; Schultes 1967b). This leguminous tree has a rather complex nomenclatural history, for 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 species like A.peregrina reflects the general belief in those days that South American snuffs had either Nicotiana or Anadenanthera as their botanical origin. Since the fifties, however, it has become increasingly clear that this generalization is a misconception, kept alive by the uncritical acceptance of infirm or invalid botanical data. Schultes and co-workers 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 savannah country, but it is not likely to grow spontaneously in the deep forest areas of Amazonian Brazil (Schultes 1954, 1967b, 1984; Schultes and Holmstedt 1968; Schultes and Hofmann 1980b). However, the actual use of A.peregrina is not necessarily confined to its natural distribution range. A Waiká group of the Brazilian Marauíá 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 in the Marauíá area itself, where it is probably cultivated from imported seeds (Wassén 1965; Schultes and Holmstedt 1968).

The domestication of A.peregrina and the trade in its seeds have also been reported in the Orinoco basin (Granier-Doyeux 1965; Chagnon et al. 1971). From the available botanical evidence it would appear that this territory is the major South American area of A.peregrina snuffs, principally known there as yopo, yupa, niopo, and hisioma (Wurdack 1958; Granier-Doyeux 1965; Wassén 1965, 1967; Chagnon et al. 1971; Coppens and Cato-David 1971; von Reis Altschul 1972; Reichel-Dolmatoff 1975; Schultes et al. 1977; Schultes and Hofmann 1980a,b). Detailed accounts by early travellers like von Humboldt (1958) and Spruce (1908) indicate that the use of such snuffs is not a recent culture 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 (Granier-Doyeux 1965; Wassén 1965, 1967; Coppens and Cato-David 1971; von Reis Altschul 1972). There is some evidence to suggest that the Yecuaná-Makiritare Indians of southern Venezuela may employ the bark (Fuchs, quoted by Wassén and Holmstedt 1963).

According to the classical descriptions, the snuffs have a stimulating effect, producing great excitement and the onset of hallucinations. This is followed by sleepiness, which 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 does usually not exceed 5 grams, and this amount may be taken one to three times a day. One dose is said to cause an intoxication of 1/4 to 2 hours (Coppens and 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 section. For good overviews of this subject, the reader is referred to the meticulous publications of Wassén (1965, 1967,

1972a) and von Reis Altschul (1972). Examples of snuffs, which have probably correctly been attributed to the seeds of A.peregrina, are the paricá snuffs of the Mura Indians and other tribes of the Brazilian Madeira region (Martius 1867; Barbosa Rodrigues 1875; Schultes 1967b; von Reis Altschul 1972). The recent isolation of 1.5% of the Anadenanthera alkaloid bufotenin from 19th century paricá seeds of the Maué Indians supports this botanical assertion (vide 1.3). The famous cohoba snuff of the early colonial natives of the West Indies is also said to have had A.peregrina as its probable source (Safford 1916; Schultes 1967b; von Reis Altschul 1972).

There is evidence to suggest that snuffing was not the only method of using A.peregrina. Various South American tribes have been reported as having taken paricá as an enema (vide 1.1.2.1). Schomburgk (1848) describes the occurrence of A.peregrina in British Guiana and gives paricá and paricarama as vernacular names. According to this 19th century traveller, the natives of this region burnt the pulverized beans and inhaled the smoke.

The genus Anadenanthera comprises a second species, A.colubrina. It occurs in eastern Brazil, and its variety cebil is known in Argentina, Bolivia, Paraguay, Peru, and several localities in southeastern Brazil (von Reis Altschul 1964). The variety cebil has been frequently 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 (Safford 1916; Cooper 1949; Wassén 1965, 1967; Schultes 1967b; von Reis Altschul 1967, 1972; Schultes and Hofmann 1980b). There is a recent report that a mixture of tobacco and cebil (or jatá) is smoked by Argentinian aboriginals (Califano 1975). According to the 18th century missionary Dobrizhoffer (1822), Indians of the Paraguay region inhaled the smoke of burnt œvil pods.

#### 2.1.2.2. Chemistry and psychopharmacology

Chemical data on the seeds of Anadenanthera species and the psychopharmacology of Anadenanthera tryptamines with a dimethylated aminogroup are summarized in section 1.1.2.2.

The occurrence of the Anadenanthera alkaloids DMT, 5-MeO-DMT and/or 5-OH-DMT (=bufotenin) in Venezuelan and Colombian snuffing material has been repeatedly demonstrated (Fish and Horning 1956; Holmstedt and Lindgren 1967; De Budowski et al. 1974; Schultes et

al. 1977; vide also section 2.3).

The bark of A.peregrina has been shown to contain N-monomethyl-tryptamine (=MMT), 5-methoxy-N-monomethyltryptamine (=5-MeO-MMT), N,N-dimethyltryptamine (=DMT), and 5-methoxy-N,N-dimethyltryptamine (=5-MeO-DMT) (Legler and Tschesche 1963; Holmstedt and Lindgren 1967; Schultes et al. 1977). Besides these tryptamine alkaloids, small amounts of 6-methoxy-2-methyl-1,2,3,4-tetrahydro-beta-carboline (=6-MeO-MTHC) and 6-methoxy-1,2-dimethyl-1,2,3,4-tetrahydro-beta-carboline (=6-MeO-DMTHC) are occasionally found in the bark (Schultes et al. 1977). Such compounds might be expected from the point of view of biosynthesis and workup procedure (Holmstedt et al. 1980).

The pharmacological effects of the beta-carbolines and the monomethylated tryptamines found in the bark of A.peregrina are discussed in section 2.1.15.2.

### 2.1.3. Banisteriopsis species Malpighiaceae

#### 2.1.3.1. Ethnobotany

Banisteriopsis preparations are widely employed by the indigenous inhabitants of the South American continent (Cooper 1949; Friedberg 1965; Schultes 1982). Most reports concern the use of Banisteriopsis as an ingredient of intoxicating drinks, but it has also been reported that Indians of the upper Orinoco area chew the dried stem (Spruce 1908; Roth 1924). There does not appear to be any ethnobotanical evidence for the preparation of snuffs from Banisteriopsis (Friedberg 1965; Schultes 1982, 1984). In chemical studies, however, harmine was found in snuffs 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 (vide 2.1.3.2). Unfortunately, no botanical material was collected together with the snuffs, so their botanical origin remains uncertain. In South American ethnobotany, the beta-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 (Holmstedt and Lindgren 1967; Schultes 1982). 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.

### 2.1.3.2. Chemistry and psychopharmacology

The chemistry and psychopharmacology of Banisteriopsis and its native beverage ayahuasca are discussed in section 1.1.3.2.

The presence of Banisteriopsis constituents in South American snuffs has been reviewed by Holmstedt and Lindgren (1967). According to table I of their review, the presence of one or more Banisteriopsis alkaloids has been demonstrated on four different occasions, once by Biocca et al. (1964), once by Bernauer (1964), and twice by the authors themselves. On closer examination, only two actual snuffs seem to be involved.

Biocca et al. (1964) did not study a snuff, but the fragment of the stem of a liane, 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 liane. Unfortunately, the collectors have not been able to witness the preparation of the snuff, so it remains uncertain whether the liane actually served as a snuff source and not as an oral ingredient.

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

Holmstedt and Lindgren (1967) have also demonstrated the presence of harmine and tetrahydroharmine in an epéna snuff of the Surára Indians, thus duplicating the findings of Bernauer (1964). The gaschromatogram pertinent to the second snuff shows a third unidentified peak (fig. 9 of the original publication), and the snuff was collected by Dr. H. Becher, who also supplied the epéna sample studied by Bernauer (1964). It seems likely that the same snuff was studied twice, and Holmstedt (pers. commun. 1983) is inclined to agree with this view. In addition, Holmstedt and Lindgren (1967) have 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. Section 2.3 of this thesis, however, reports on the isolation of harmine and bufotenin from a yopo snuff of the Piaroa Indians, which result corroborates the unusual findings in the sixties.

#### 2.1.4. Cannabis species Cannabaceae

##### 2.1.4.1. Ethnobotany

Although Cannabis is smoked among the Brazilian Tenetehara Indians (Wagley and Galvão 1949), and eaten among Mexican aboriginals like the Tepehua Indians (Heffern 1974; Williams-Garcia 1975), it is not a major intoxicant in native rituals of the western hemisphere. Plausible explanations might perhaps be that Cannabis was introduced after the conquest and had to compete with the numerous psychoactive plants already available (Partridge 1975), and that nowadays it is an illegal intoxicant in many countries.

Substantial data on the snuffing of Cannabis by American aboriginals appear to be lacking. A 19th century Portuguese catalogue of objects from Amazonian tribes states that 'parica tobacco' was much used as a snuff and that 'pango, an African tobacco', served as a substitute for parica (Teixeira de Aragão 1892). Since the word pango is a vernacular name for Cannabis, the question arises as to whether the catalogue may possibly indicate the snuffing of hashish (Wassén 1972a). However, there are no additional data whatsoever to support this suggestion.

##### 2.1.4.2. Chemistry and psychopharmacology

Since hemp has become a major recreational drug in western society, more chemical and pharmacological research has been directed to this plant than to any other natural hallucinogen (van Praag 1972; Miller 1974; Braude and Szára 1976; Schultes and Hofmann 1980b; Turner et al. 1980). In view of its minor role in native American practices, the complex chemistry and pharmacology of Cannabis are not discussed in detail here.

The most important constituents of Cannabis are cannabinoids. Up to now, more than sixty cannabinoids have been detected in hemp or in crude drugs prepared from hemp. Most of these are trace components, and some are considered to be artificial (Schultes and Hofmann 1980b; Turner et al. 1980).  $\Delta^9$ -tetrahydrocannabinol (THC) is by far the most psychoactive one. In seized samples from various countries, THC concentrations were in the range of 0.4-5.0% in unspecified Cannabis parts and 1.1-8.7% in Cannabis resin (Baker et al. 1981).

Acute intoxication with a Cannabis product appears to be a reasonably benign experience. To elicit LSD-like activity, high doses of THC are needed; modest doses merely induce

depersonalization and mild hallucinogenic effects (Meyer 1972). Although neither smoking nor oral ingestion of hemp results in a high bioavailability of THC, both methods of application can produce a subjective response (Ohlsson et al. 1980).

#### 2.1.5. Capsicum species Solanaceae

##### 2.1.5.1. Ethnobotany

Some reviews on South American 'narcotics and stimulants' have included Capsicum, because the Makusi of the Rupununi used peppers as a stimulant and excitant (Roth 1924; Cooper 1949). The Makusi poured a liquid preparation from crushed peppers and water into the nostrils of patients with a headache (Roth 1924). More recently, Uscátegui Mendoza (1965) reported the nasal use of a Capsicum preparation among a Tukano group of the Colombian Vaupés region. After they have danced and drunk alcoholic beverages the night before, they pour a mixture of crushed pepper and water into the nose to drive away the effects of the festivities. The Tukano also practise this administration during their initiation period. Occasionally, the initiates cleanse themselves by taking drops prepared from fresh chili peppers through the nose, using for this a small funnel made of a leaf (Reichel-Dolmatoff 1975).

When the consulted literature speaks about pepper, it either identifies pepper as Capsicum or fails to offer a botanical name. In the last case, it should be borne in mind that pepper is a vernacular term which might also refer to a Piper species (Hegnauer, pers. commun. 1983).

##### 2.1.5.2. Chemistry and psychopharmacology

The chemistry and psychopharmacology of Capsicum fruits are discussed in section 1.1.5.2.

#### 2.1.6. Datura species Solanaceae Datura innoxia Mill.

##### 2.1.6.1. Ethnobotany

From pre-Hispanic times until the present day, Mexican Indians have known the hallucinogenic properties of oral Datura

preparations (Safford 1922; Guerra 1967; Dfaz 1979). According to a journalistic rather than scientific source, the dust of dry toloachi leaves was taken in the Mexican town of Guanajuato as a snuff (Reko 1949). Toloachi, more often denoted as toloache, is a vernacular name used for various Datura species, such as D.innoxia (Dfiaz 1979; Schultes and Hofmann 1980b).

Although tree Daturas, now treated as the genus Brugmansia, are common intoxicants in South American rituals (Cooper 1949; Plowman 1981a), there does not seem to be evidence that they have served as a source of snuffs (Schultes 1967b).

#### 2.1.6.2. Chemistry and psychopharmacology

The chemistry and psychopharmacology of Datura species are discussed in sections 1.1.4.2 and 1.1.6.2.

#### 2.1.7. Erythroxyllum species

Erythroxyllaceae

Erythroxyllum coca Lam.

var. ipadu Plowman

Erythroxyllum fimbriatum Peyr.

Erythroxyllum macrophyllum Cav.

Erythroxyllum novogranatense (Morris) Hieron.

var. truxillense (Rusby) Plowman

##### 2.1.7.1. Ethnobotany

The widespread use of coca among the Indians of western South America is well established (Bühler 1948; Cooper 1949; Schultes 1957, 1981b; Antonil 1978; Plowman 1979, 1981b; Wiedemann 1979; Scheffer 1981). Its role as a true ceremonial drug seems to be of minor importance, at least in present times (Cooper 1949; Wiedemann 1979). The principal Indian way of taking coca is usually designated as chewing. A common method consists of placing coca leaves in the mouth and rolling them around or chewing them briefly until a wad has formed. The wad is held reasonably still between cheek and gums, and lime or ash is added periodically. The juice is swallowed and some of the leaf material may occasionally be ingested (Bühler 1948; Cooper 1949; Antonil 1978; Holmstedt et al. 1979). Another common method, sometimes denoted as eating, consists of taking coca powder prepared from pounded coca leaves and alkaline plant ash. Moistening of the powder with saliva results in a pasty quid which is held between the cheek and gums, and the juice is

swallowed. In contrast with a quid from whole leaves, which cannot be totally swallowed, most and occasionally all of the coca powder will pass to the stomach (Schultes 1957, 1981b; Holmstedt et al. 1979; Plowman 1981b; Scheffer 1981).

Exceptional ways to utilize coca include the drinking of an infusion from the leaves — among the Peruvian Pánobo Indians (Tessmann 1930; Schultes 1981b). And, the injection of coca powder into the mouth by means of a bag with a bone tube — by certain tribes in the Vaupés region (Plowman 1981b; Schultes 1981b). It is said that the Omaguas of northeastern Peru have smoked coca leaves (Bühler 1948), but this claim is not supported by a primary reference. In recent years, the urban youth of Peru has developed the practice of smoking cigarettes containing coca paste mixed with tobacco or marihuana; coca paste is a crude extract from coca leaves (Jeri et al. 1978).

There are various undetailed statements on the Indian use of coca snuffs (Hartmann 1890, Bühler 1948; Wilbert 1975; Plowman 1981b; Scheffer 1981), in particular by certain tribes of the northwest Amazon (Schultes and Hofmann 1980b). Schultes (1967b) mentions the addition of powdered coca to tobacco snuff among the Colombian Witoto and Yukuna Indians. In later publications he reports, on the basis of reliable hearsay, that the Yukunas as well as the Tanimukas may have utilized coca-ash powder as a snuff in certain annual ceremonies (Schultes 1981b, 1984). The use of coca powder as a snuff by the Witotos has also been reported by Wavrin (1948). Such use would seem a considerably rare practice, since the Witotos are a relatively well-known tribe, and most field workers fail to describe this method of administration (Plowman 1981b).

The genus Erythroxylum includes perhaps as many as 250 species, but only E.coca and E.novogranatense are cultivated in South America. Both species include two varieties. E.coca var. coca (Bolivian or Huánuco coca) occurs throughout the wet tropical valleys of the eastern Andes from Ecuador south to Bolivia, whereas E.coca var. ipadu is cultivated in many parts of the Amazon Basin. E.novogranatense var. novogranatense (Colombian coca) is grown in drier regions of Colombia and Venezuela, whereas its variety truxillense (Trujillo coca) is cultivated in the dry Marañón valley and on the desert coast of northern Peru (Holmstedt et al. 1977; Plowman 1979, 1981b; Plowman and Rivier 1983). The type of coca cultivated in the northwest Amazon, where coca snuffs are said to occur, is E.coca var. ipadu, but it should be added that the Witotos and other tribes in this area may also employ the wild species E.fimbriatum and E.macrophyllum (Schultes 1981b).

### 2.1.7.2. Chemistry and psychopharmacology

Dried leaves from the two main cultivated Erythroxylum species are stated as having a total alkaloid content of about 0.5–2 % (Hegnauer 1966; Grinspoon and Bakalar 1976). Their principal alkaloid is undoubtedly cocaine (=benzoylmethylecgonine). It is often claimed that the Trujillo leaf has a higher total alkaloid content than the Bolivian leaf, but that the latter has a greater proportion of cocaine to other alkaloids (Grinspoon and Bakalar 1976; Reynolds 1982; Novák et al. 1984). Recent studies on dried South American coca leaves have revealed cocaine percentages of 0.13–0.96% in E.coca var. coca, 0.11–0.41% in E.coca var. ipadu, 0.17–0.93% in E.novogranatense var. novogranatense, and 0.42–1.02% in E.novogranatense var. truxillense (Holmstedt et al. 1977; Plowman 1981b; Plowman and Rivier 1983). In other words, the highest percentage of cocaine was found in the last variety, which contradicts the belief that Trujillo coca is lower in cocaine content than other varieties (Plowman and Rivier 1983). There is some evidence to suggest a distinct phytochemical difference between E.coca var. coca (Andean coca) and the variety ipadu (Amazonian coca). After Amazonian and Andean coca plants had been grown in the greenhouse under the same uniform conditions, the dried leaves of the former yielded only 0.34–0.41% of cocaine, whereas the latter showed consistently higher percentages of 0.51–0.81%. If this finding can be confirmed, it might explain why Indians of the Amazon Basin pulverize the coca leaf before use (Plowman 1981b; Plowman and Rivier 1983).

Apparently no or very little cocaine is present in most wild Erythroxylum species like E.fimbriatum and E.macrophyllum (Hegnauer 1966; Holmstedt et al. 1977; Plowman 1981b; Plowman and Rivier 1983). In a recent study of 29 different species, a cocaine percentage of 0.1% or more could only be demonstrated in E.recurrens and E.steyermarkii (Plowman and Rivier 1983).

Reviews of the minor alkaloids, claimed as occurring in the two main cultivated Erythroxylum species (Hegnauer 1966, 1981; Evans 1981; Novák et al. 1984), show the following picture:

- 11 ecgonine alkaloids (cis-cinnamoylcocaine, trans-cinnamoylcocaine, ecgonine, norecgonine, norformylecgonine, methyl-ecgonine, benzoylecgonine, cinnamoylecgonine, methylecgonidine, alpha-truxilline, beta-truxilline);
- 5 tropine alkaloids (tropine, pseudotropine, dihydroxytropine, tropacocaine, benzoyltropine);
- 4 pyrrolidine alkaloids (hygroline, hygrine, cuscohygrine, dihydrocuscohygrine);
- 2 other alkaloids (choline, nicotine).

The question arises as to how many of these reported minor constituents are artifacts instead of naturally occurring substances in living material. Rivier (1981) examined crude ethanolic extracts of E.coca leaves without any further purification by a GC-MS method, and could only demonstrate cocaine, cis-cinnamoylcocaine and trans-cinnamoylcocaine as endogenous alkaloids.

Depending on leaf age, species and variety, the cinnamoylcocaines may represent 2-60% of the total alkaloid content (Rivier 1981; Turner et al. 1981).

The acute and chronic toxicity of cocaine is discussed at length by Grinspoon and Bakalar (1976). The most striking acute systemic effect is stimulation of the central nervous system, which can result not only from intravenous injection, but also from oral ingestion (Van Dyke et al. 1978; Wilkinson et al. 1980), nasal application (vide 2.2.2.4), and smoking (Perez-Reyes et al. 1982; Siegel 1982). The central stimulation manifests itself as a feeling of well-being and euphoria, although sometimes dysphoria occurs. These effects may be accompanied by garrulousness, restlessness, excitement, confusion, apprehension, and anxiety (Ritchie and Greene 1980; Oderda and Klein-Schwartz 1982). When used for a long time or in high doses, cocaine may provoke a psychosis; an iatrogenous case has been recently observed in a patient with oral stomatitis, who had been given 3 ml of a 10 % solution every 4 hours for more than two weeks (Lesko et al. 1982).

Over the last few years, growing attention has been paid to the metabolism of cocaine in man (Lindgren 1981; Oderda and Klein-Schwartz 1982), and to the plasma levels of this alkaloid (Barnett et al. 1981; Javaid et al. 1983).

Only a small portion of cocaine is excreted unchanged in the urine. Major metabolites in human urine are the hydrolysis products benzoylecgonine (Fish and Wilson 1969; Jindal and Vestergaard 1978) and ecgonine methylester (Inaba et al. 1978; Ambre et al. 1983). There is evidence to suggest that the latter compound is formed largely by esterases, and that the former one results from spontaneous, nonenzymatic hydrolysis in the body (Stewart et al. 1979). A minor metabolic pathway in man is N-demethylation of cocaine to norcocaine (Inaba et al. 1978), which in its turn might undergo hydrolysis (Stewart et al. 1979; Lindgren 1981). Other minor metabolites, such as ecgonine, have been demonstrated in multiple intoxication and overdose cases (Lindgren 1981).

The pharmacological effects of cocaine and its metabolites, after intravenous dosing, have been studied in the rat. No

observable effects were noted with benzoylecgonine after doses of 250 mg/kg and with ecgonine methylester or ecgonine after doses of 200 mg/kg. Cocaine and norcocaine caused excessively rapid heart beat, convulsions and death after injection of 20 mg/kg, and lower doses of 5-10 mg/kg produced similar results without mortality (Misra et al. 1975). In monkeys, norcocaine is effective in maintaining intravenous self-administration, although it is less potent than cocaine itself (Bedford et al. 1980; Spealman and Kelleher 1981). In contrast to cocaine, however, norcocaine does not stimulate locomotor activity or fixed-interval feeding behaviour of rats, which suggests that the two compounds do not have the same behavioural profile (Bedford et al. 1980).

These data indicate that only norcocaine is a pharmacologically active metabolite of cocaine. Norcocaine seems to be a minor metabolite in man, however, accounting only for 2.4% and 6.2% of an oral dose in two subjects (Inaba et al. 1978). Consequently it would appear that the activity of cocaine in man is not principally due to metabolites, but to the alkaloid itself.

Studies on nasal application do not show a close correlation between the time course of effects and the curve of the plasma level. Maximal central effects tend to occur prior to peak plasma levels, and a certain level during the increasing phase of the curve is associated with a more intense 'high' than the same level during the decreasing phase (Van Dyke et al. 1978, 1982). This phenomenon, which is known as acute tolerance, has also been observed with central depressants like alcohol (Jaffe 1980).

In a study on the chewing of coca powder and coca leaves, material containing 16.8-48 mg of cocaine produced maximal cocaine plasma levels of 11-149 ng/ml after about 1-2 hours. Only one of the studied subjects was an Indian, and the highest level of 149 ng/ml after 1 hour was obtained when this subject chewed leaves containing 21 mg of cocaine. Just as is the case with pure cocaine, the subjects felt stimulated during the rising phase of the plasma curve, and they reported no more stimulation during the falling phase, when the quid was still in the mouth. These results suggest that central stimulation by coca leaves or powder is primarily due to cocaine (Holmstedt et al. 1979).

This view is supported by a recent survey on the pharmacology of minor Erythroxylum alkaloids. With respect to cinnamoylcocaines, apparently the most important alkaloids besides cocaine, the survey claims a lack of pharmacological activity. Unfortunately, no discrimination is made between the cis- and trans-form (Novák et al. 1984). Furthermore, there is a recent report that water-soluble alkaloid-free fractions of coca leaves

are not centrally active in the mouse (Harland et al. 1982).

Significant plasma levels of cocaine from coca chewing have also been demonstrated by Paly et al. (1980). One of their test groups included pure Indians and subjects of mixed ancestry who were experienced in the use of coca. They received 50 g of coca leaves containing 0.65% of cocaine. Single blood samples drawn during the chewing yielded plasma levels ranging from 130 to 859 ng/ml with a mean value of 249 ng/ml.

Until recently, it was commonly felt that cocaine is ineffective after oral administration because of poor bioavailability.

However, in recent human studies on the oral and nasal application of 2 mg/kg cocaine HCl, oral administration did not result in less euphoria or in lower bioavailability than nasal dosing. In the oral experiments, cocaine was given in a gelatine capsule, and plasma levels could not be detected until half an hour after administration. This finding suggests that orally ingested cocaine is not well absorbed until it reaches the small intestine (Van Dyke et al. 1978; Wilkinson et al. 1980). Such a time lag is not observed in coca chewers, who show measurable plasma levels of cocaine after only 5 minutes of chewing (Holmstedt et al. 1979). This implies that there is a significant buccal absorption in coca chewers. Intestinal absorption will occur as well, since coca chewers swallow the juice and may also swallow plant material (vide 2.1.7.1). Since coca chewing involves significant buccal absorption, it is somewhat a misnomer from the pharmaceutical point of view to denote this practice as oral administration.

The literature is not unanimous about the reason why coca chewers add alkaline material like lime or plant ash to their coca quid (Rivier 1981). Some authors express the view that these admixtures produce an alkaline environment, in which cocaine is hydrolyzed into benzoylecgonine and ecgonine before it is absorbed. According to this supposition, not cocaine itself, but metabolites like ecgonine have a central place in the pharmacology of coca chewing (Nieschulz 1971; Burchard 1975). This hypothesis does not appear to be acceptable. Firstly, recent *in vitro* experiments simulating natural conditions do not show an immediate extensive hydrolysis of cocaine in an alkaline environment (Rivier 1981). Secondly, experienced coca chewers report local anaesthesia in the mouth, and this effect is considered as an indication of the yield of alkaloid extracted from the coca quid (Antonil 1978). Cocaine is known to be a potent local anaesthetic (Ritchie and Green 1980), whereas neither benzoylecgonine nor ecgonine have appreciable local anaesthetic properties (Novák et al. 1984). Thirdly, the

metabolite hypothesis fails to explain why coca chewers show substantial plasma levels of cocaine and why they report central stimulation (Antonil 1978; Holmstedt et al. 1979; Paly et al. 1980). Another, much more acceptable explanation is, of course, that the alkaline material facilitates the cocaine absorption through the buccal mucosa (Antonil 1978; Holmstedt et al. 1979; Rivier 1981; Siegel 1982). Furthermore, the addition of lime is reported to transform the bitter and unpleasant flavour of coca leaves into a more sweet and agreeable taste (Antonil 1978; Siegel 1982).

Principal effects of coca chewing by South American Indians are said to be a reduction of hunger, cold and fatigue (Hanna and Hornick 1977). Considerable controversy still exists as to whether the practice is detrimental or not (Holmstedt et al. 1979). Cases of acute overdosage or obvious chronic toxicity seem to be uncommon among South American coca chewers (Grinspoon and Bakalar 1976; Hanna and Hornick 1977; Antonil 1978). In contrast, the heavy use of coca paste is strongly associated with a variety of psychopathological states, including full-blown psychoses (Jeri et al. 1978; Siegel 1982). Coca paste is a concentrated extract from coca leaves, reported to contain 40-85% of cocaine sulphate (Siegel 1982). Recently, coca paste cigarettes, each containing 75 mg of cocaine, have been tested in regular users. The smoking of one cigarette in 3 minutes produced cocaine plasma levels of 91-462 ng/ml, and ad libitum smoking of five cigarettes resulted in levels of 266-882 ng/ml after only 25-47 minutes (Paly et al. 1982).

#### 2.1.8. Ilex guayusa

Aquifoliaceae

Ilex guayusa Loes.

##### 2.1.8.1. Ethnobotany

The use of Ilex guayusa as a ritual stimulant and emetic by natives of the South American Montaña area is well established (Cooper 1949; Patiño 1968; Schultes 1972a). Bundled leaves of I. guayusa have been found, together with several snuff trays, in a pre-Hispanic medicine-man's tomb of Highland Bolivia. This joint occurrence in an archaeological context raises the possibility that guayusa leaves may have once served as a source of snuff, but there is no direct evidence for this supposition (Schultes 1972a, 1984; Wassén 1972b).

#### 2.1.8.2. Chemistry and psychopharmacology

The chemistry of I.guayusa and the psychopharmacology of its principal alkaloid caffeine are discussed in section 1.1.7.2.

#### 2.1.9. Justicia pectoralis

Acanthaceae

Justicia pectoralis Jacq.

##### 2.1.9.1. Ethnobotany

Several groups of Waiká Indians prepare a snuff from Virola exudate, the dried leaves of mashihiri, and vegetable ashes. Technically, these Indians are known as the Yanomamö or Yanonami Indians (Schultes and Holmstedt 1968; Prance 1972). The mashihiri plant, which is cultivated for this purpose, has been identified as Justicia pectoralis var. stenophylla (Seitz 1965, 1967; Schultes and Holmstedt 1968; Brewer-Carias and Steyermark 1976; Schultes 1978). Chagnon et al. (1971) report that different types of Justicia are cultivated, all of which they tentatively classify as different varieties of Justicia pectoralis or as different forms of Justicia pectoralis var. stenophylla. Schultes (pers. commun. to MacRae and Towers 1984b) feels that the variety stenophylla is a growth form of J.pectoralis rather than a genetic variant. In keeping with this suggestion, the varietal epithet is left out of the following discussion.

In some Waiká villages of the Brazilian Roraima territory, the dried leaves of Justicia pectoralis are commonly added to Virola snuffs, apparently without adding vegetable ashes (Prance 1972). A Waiká name for this plant is paxararok (Schultes 1978). The Waikás of the Brazilian Tototobí River likewise prepare Virola snuffs without ashes, and J.pectoralis (known as masha-hára-hanak or boo-haná) is added very occasionally (Schultes and Holmstedt 1968).

According to various field reports, Indians themselves consider Justicia leaves an aromatic admixture, which has no intoxicating effect, but merely improves the aroma of the Virola snuff (Seitz 1965, 1967; Schultes and Holmstedt 1968; Prance 1972). Yet here is evidence that the Waikás may use Justicia as the sole source of a snuff (Schultes 1967b; Chagnon et al. 1971; Schultes and Hofmann 1980b; McKenna et al. 1984b). The Caburiwe-Teri group, living in the border region of Venezuela and Brazil, uses mashihiri powder mostly to strengthen their more powerful Virola snuff, but mashihiri can also be used alone. Since the powder is

too fine by itself, it is generally mixed with plant ashes before use (Brewer-Carias and Steyermark 1976). Prance (pers. commun. 1984) has observed Waiká Indians at the Tototobí River 'taking pre-Justicia snuff without Virola; after the shaman took this he was apparently in a trance'.

#### 2.1.9.2. Chemistry and psychopharmacology

Many reviews on botanical hallucinogens have included J.pectoralis, stating that tryptamines (in particular dimethyl-tryptamine) might be present, but that the preliminary indications for this suspicion should be verified (Furst 1976a; Emboden 1979a; Schultes and Farnsworth 1980; Schultes and Hofmann 1980a,b). These statements go back to the end of the sixties, when preliminary chemical indications for the presence of alkaloidal principles were reported (Schultes and Holmstedt 1968). At that time, a small amount of an indole alkaloid had been isolated from J.pectoralis, but the material had been harvested by Indians with Virola exudate on their hands, so it may well have been contaminated (Holmstedt, pers. commun. 1984). Additional studies by Holmstedt failed to detect an hallucinogenic alkaloid in the dried leaves of J.pectoralis, used as an admixture in the Roraima territory (Prance 1972). This negative chemical result corresponds with ethnological reports that natives do not attribute hallucinogenic properties to the aromatic herb.

Recently, coumarin and its 7-hydroxyderivative umbelliferone have been found in Peruvian J.pectoralis (MacRae and Towers 1984b). These non-alkaloidal benzopyran compounds could also be isolated from two Venezuelan Yanomamö snuffs, labeled as mashahari and as buhenak + mashahara (McKenna et al. 1984b).

Coumarin is a fragrant principle, which has been used in cosmetics and detergents (Opdyke 1974). According to toxicological text books, it may produce nausea, vomiting, headache, dizziness, and loss of consciousness (Lewin 1962; Braun and Dönhardt 1975). Its pharmacokinetics in man have been studied by Ritschel et al. (1977, 1979). After oral ingestion, the compound is absorbed completely, but only 2-6% reaches the systemic circulation in intact form because of extensive first-pass metabolism. The major metabolite is 7-hydroxycoumarin, which in its turn undergoes glucuronidation. In a recent study in gerbils, intraperitoneally administered coumarin distributed rapidly into the cerebral tissue, whereas its metabolites 7-hydroxycoumarin and 7-hydroxycoumarin glucuronide entered the brain only to a small extent, if at all. The tested dose of 40

mg/kg produced transient sedation, and this effect corresponded rather well with the time of maximal coumarin brain concentration and with the subsequent rapid removal of coumarin from the brain (Ritschel and Hardt 1983). The same intraperitoneal dose of 40 mg/kg of coumarin was found to cause a longer and deeper level of sedation in the rat, but this species is a poor 7-hydroxylator of coumarin (Hardt and Ritschel 1983).

All in all, 7-hydroxycoumarin (=umbelliferone) is unlikely to have any central effect, and coumarin will thus not readily show psychoactive symptoms when taken orally. Whether coumarin might be centrally active in man via other routes of administration, is still far from clear.

As Justicia pectoralis is mostly used as an admixture to Virola, the question arises if this plant could modulate the activity of Virola. To test this possibility, MacRae and Towers (1984b) examined the influence of J.pectoralis extracts on the effects of the Virola alkaloid 5-methoxy-dimethyltryptamine (5-MeO-DMT) in the mouse. None of the aqueous, ethyl acetate and ethyl ether extracts tested had any significant effect upon the changes in behaviour and in locomotor activity induced by 5-MeO-DMT.

Hegnauer (1964, pers. commun. 1985) points out that many acanthaceous plants have cells enclosing calcium carbonate (cystoliths). If such cells would occur in J.pectoralis, this admixture to Virola snuffs might give an alkaline reaction, which might facilitate the absorption of the Virola alkaloids (vide 2.2.1). This could be of importance when the snuff is prepared from Virola and Justicia without the addition of alkaline plant ash.

#### 2.1.10. Maquira sclerophylla

Moraceae

Maquira sclerophylla (Ducke) C.C. Berg

##### 2.1.10.1. Ethnobotany

An enigmatic snuff, known only by the general Portuguese term rapé dos indios, is said to have been formerly employed in the central part of the Brazilian Amazon, especially in the Pariana region. Direct observation of its preparation and use has never been possible. The source of the snuff is reputed to be the fruit of Maquira sclerophylla, which was first known as Olmedioperebea sclerophylla (Schultes 1967b, 1984; Schultes and Farnsworth 1980; Schultes and Hofmann 1980b). According to von Reis Altschul

(1972), the seeds of this gigantic forest tree are said to be a traditional snuff source of the Mundurucú Indians.

#### 2.1.10.2. Chemistry and psychopharmacology

Chemical and pharmacological data on Maquira sclerophylla have apparently not been reported in the literature (Schultes and Hofmann 1980b). According to Carlini and Gagliardi (1970), water and ethanol extracts from wood of the related Maquira calophylla are devoid of Cannabis-like activity in animal experiments, even at doses ten times those required for Cannabis sativa to demonstrate such effects. These investigators announced that their studies would be continued with extracts from leaves and flowers of M.calophylla and M.sclerophylla, but results have not as yet been published (Schultes and Farnsworth 1980). Recently, another research group has reported the isolation of the coumarin derivatives marmesin, oxypeucedanin hydrate and pranferol from the stem bark of Maquira calophylla (Rovinski and Sneden 1984).

#### 2.1.11. Nicotiana species

Solanaceae

Nicotiana rustica L.

Nicotiana tabacum L.

Nicotiana thyrsoiflora Bitter ex Goodsp.

##### 2.1.11.1. Ethnobotany

South American Indians are known to have used tobacco since their earliest contacts with Europeans, and these practices undoubtedly go back to pre-colonial times (Stahl 1925; Castiglioni 1943; Cooper 1949; Bondeson 1972; Elferink 1983). Most South American tribes of the twentieth century take tobacco in one form or another for magico-religious, medicinal and/or recreational purposes. The major South American method of using tobacco is smoking, but chewing, drinking, eating, licking and snuffing are also well documented (Stahl 1925; Cooper 1949; Zerries 1964; Wilbert 1972, 1975). Snuffing is said to be the most widespread method of tobacco use in certain parts of South America, especially in the wet, tropical lowland areas like the Amazon valley (Schultes 1967b; Schultes and Hofmann 1980b). According to Cooper (1949), the three main regions for which tobacco snuffs have been recorded, are the Orinoco territory, the Montaña region, with an extension down the Purús river, and early colonial Peru. This author rightly cautions that, in the

literature, tobacco snuffs are not always clearly distinguishable from truly hallucinogenic snuffs. Consequently, the actual use of tobacco snuffs may have been somewhat less widespread than generalizing statements would suggest (Schultes 1967b).

The Peruvians of the early colonial days have been reported as taking a snuff prepared from tobacco root for medicinal reasons (Cobo 1964), but most tobacco snuffs were and still are prepared from the dried leaves (Cooper 1949; Schultes 1967b).

The mixing of tobacco powder with plant ashes has been recorded for Arawak groups of the Purús river (Cooper 1949), such as the Dení, Jarawara, and Jamamadí Indians (Prance 1972, 1978). Tribes of the Brazilian Guaporé River are said to have mixed tobacco powder with vegetable ash and crushed angico seeds (Snethlage 1937). Angico may well refer to Anadenanthera (Schultes 1967b), but also to other genera (von Reis Altschul 1972). Other reported admixtures include Tanaecium (Prance et al. 1977) and Erythroxylum (Schultes 1967b).

Not only tobacco snuff, but also tobacco juice has been used nasally. This practice has been documented for several tribes of northeast Peru (Tessmann 1930), the famous Jivaro Indians (Karsten 1935), and the Bush negroes of the Guiana region (Roth 1929). Recently, it has been reported that the Creoles of French Guiana and the Bush negroes of Surinam inhale a liquid through the nostrils, which is prepared from tobacco leaves and plant ash, for recreational purposes (Plotkin et al. 1980).

Of the 36 Nicotiana species occurring in South America (Goodspeed 1954), Nicotiana tabacum is undoubtedly the principal source of South American tobacco preparations (Schultes 1967b). In his elaborate monograph on the genus, Goodspeed (1954) even goes so far as to state that no other species can be shown to have been, or, with the possible exception of N.rustica, to be today a source of tobacco in South America. This statement would not seem entirely correct, however, as a herbarium annotation on Peruvian N.thyrsoflora explicitly mentions the use of its leaves for smoking (von Reis and Lipp Jr. 1982).

Harrington (1932) reports that the Karuk Indians of California use the expression imcakare.he.raha to designate the snuffing of tobacco, and the Nootka Indians of the northwest coast are said to have snuffed tobacco (von Welck 1981). The snuffing of tobacco powder in ancient Mexico has been recorded by the early authors Hernández (1959) and Clavijero (1970). There appear to be few references of this kind, so the practice is not believed to have been widespread in North and Middle America (Wilbert 1975; Elferink 1983).

#### 2.1.11.2. Chemistry and psychopharmacology

The chemistry and psychopharmacology of tobacco are discussed in section 1.1.9.2.

#### 2.1.12. Pagamea macrophylla

Rubiaceae

Pagamea macrophylla Spr. ex Benth.

##### 2.1.12.1. Ethnobotany

Among the Colombian Barasana Indians, the pulverized leaves of Pagamea macrophylla are aspirated by medicine men, in the form of a snuff, during ceremonies of divination. The Barasana name for the plant is ma-nu-su-ka-ta (Schultes 1980a).

##### 2.1.12.2. Chemistry and psychopharmacology

The chemistry and psychopharmacology of Pagamea macrophylla appear to be unknown (Schultes 1980a, 1984).

#### 2.1.13. Piper interitum

Piperaceae

Piper interitum Treal. ex Macbr.

##### 2.1.13.1. Ethnobotany

Among the Kulina Indians of eastern Peru, Piper interitum is known as tetsi. These Indians are said to prepare a snuff from the dried leaves and roots, which is used as a substitute for tobacco (Schultes 1980b).

##### 2.1.13.2. Chemistry and psychopharmacology

I am not aware of phytochemical or pharmacological research on Piper interitum.

#### 2.1.14. Tanaecium nocturnum

Bignoniaceae

Tanaecium nocturnum (Barb.-Rodr.) Bur. et K. Schum.

##### 2.1.14.1. Ethnobotany

The Paumarí Indians of the Brazilian Rio Purús region prepare a ritual snuff by mixing tobacco powder with the roasted, grounded leaves of a vine called koribó. This vine has been botanically identified as Tanaecium nocturnum. According to the Indians, the snuff has the same effect as another snuff, which they prepare from the bark of Virola elongata. Paumarí women do not usually take the snuff, but they drink an aqueous brew from the root bark of koribó. This brew is said to produce drowsiness, inability to concentrate, and reduced awareness (Prance et al. 1977).

##### 2.1.14.2. Chemistry and psychopharmacology

The fresh leaves of Tanaecium nocturnum have been reported as containing a very high concentration of hydrogen cyanide (Grajales Diaz 1967). Field investigators found the fumes from freshly collected material poisonous, causing dizziness and headache in one of them. When the snuff is prepared, however, the leaves are toasted and this probably removes the cyanide (Prance et al. 1977). Which compounds are formed or left intact during the preparation of the snuff is still unclear. In 1978, chemical and pharmacological studies were announced (Prance 1978), but to my knowledge, the results of these investigations have not yet been published.

The stem of Tanaecium nocturnum contains an essential oil consisting almost exclusively of benzaldehyde (Gottlieb et al. 1981). Animal experiments have shown that this compound has antispasmodic, local anaesthetic and antibacterial properties (Macht 1923). According to toxicological textbooks, it is also capable of producing central nervous depression (Gleason et al. 1969; Braun and Dönhardt 1975; Dreisbach 1977).

### 2.1.15. Virola species

Myristicaceae

Virola calophylla Warb.

Virola calophylloidea Markgr.

Virola cuspidata (Spr. ex Benth.) Warb.

Virola elongata (Spr. ex Benth.) Warb.

Virola rufula Warb.

Virola sebifera Aubl.

Virola theiodora (Spr. ex Benth.) Warb.

#### 2.1.15.1. Ethnobotany

Many South American Indian tribes prepare potent psychoactive snuffs from Virola species for ceremonial and recreational uses (Schultes 1954, 1967b, 1984; Uscátegui Mendoza 1959; Seitz 1965, 1967; Wassén 1965, 1967; Schultes and Holmstedt 1968; Prance 1970, 1972; Chagnon et al. 1971; Reichel-Dolmatoff 1975; Brewer-Carias and Steyermark 1976; Prance et al. 1977; Schultes and Hofmann 1980a,b). All important ethnobotanical references to these snuffs appear to be comparatively recent. Older reviews on the botanical sources of South American snuffs tend to focus on Nicotiana and Anadenanthera, and fail to pay any attention to Virola (Cooper 1949). This raises the question as to whether this merely reflects the insufficiency of certain early ethnobotanical investigations, or whether it may also indicate a difference between past centuries and the present. Whatever the answer may be, it has become more and more clear that Virola is one of the major sources of psychoactive South American snuffs, and that the use of Anadenanthera snuffs is less widespread than was once believed (Schultes 1954, 1967b; Schultes and Holmstedt 1968).

The principal native users of Virola snuffs are tribes in the Colombian Vaupés region, and the Waiká Indians inhabiting the upper Orinoco area in Venezuela and the Brazilian territory north of the Rio Negro (Schultes and Holmstedt 1968; Schultes and Hofmann 1980b). Depending on tribe and locality, the snuffs are known under different native names, such as yá-kee, yá-to and paricá in Colombia, and epéna, ebene, paricá and nyakwána in Brazil (Seitz 1967; Schultes and Holmstedt 1968; Schultes and Hofmann 1980b). It should not be forgotten that these indigenous names have no distinctive botanical value. Paricá may also refer to Anadenanthera (vide 1.1.2.1) and epéna or ebene tends to be a general term designating snuffs, regardless of their exact botanical origin (Chagnon et al. 1971; Brewer-Carias and Steyermark 1976).

The preparation of Virola snuffs is described in detail by

field workers like Schultes (1954), Seitz (1967), Schultes and Holmstedt (1968), Prance (1970, 1972), Brewer-Carias and Steyermark (1976), and Prance et al. (1977). Most snuffs appear to be based on the powdered blood-red exudate from the inner bark of Virola species (Schultes and Holmstedt 1968; Schultes and Hofmann 1980b), but the Paumarí Indians of central Amazonia use the entire bark and not merely its exudate (Prance et al. 1977). Seitz (1967) did not observe an admixture to Virola among the Tukano Indians, but several Colombian tribes are reported as mixing the Virola dust with plant ashes (Schultes 1954). Some Waiká groups use the dusted exudate without an admixture, whereas other groups add aromatic Justicia leaves and/or vegetable ashes (Schultes and Holmstedt 1968; Prance 1970, 1972; Brewer-Carias and Steyermark 1976). Other admixtures have been reported as well, but unfortunately botanical identifications are not available (Seitz 1967; Chagnon et al. 1971). The addition of ashes is thought to serve as a means of drying, to free the alkaloids more easily from the exudate, to keep the snuff from rapid deterioration during storage, or merely for mechanical purposes (Schultes and Holmstedt 1968). The addition of Justicia is discussed in the section on this genus.

The effects of Virola snuffs seem to vary, but in Indians they often include initial excitability, beginning within several minutes of the first snuffing. This is followed by numbness of the limbs, twitching of the facial muscles, inability to coordinate muscular activity, nausea, visual hallucinations with frequent macropsia, and afterwards, a deep, disturbed sleep (Schultes and Hofmann 1980b). The Indians themselves acknowledge that it can be a dangerous practice to use large doses of a Virola snuff. An informant illustrated this with the death of a medicine-man, from the Colombian Puinave tribe, during a yá-kee intoxication (Schultes 1954, 1967b). The Waiká Indians visited by Seitz (1965, 1967) usually inhale two coffee-spoons full, one in each nostril, which results in a short intoxication of approximately one hour.

While snuffing is the most common way to administer Virola, it is certainly not the only method employed by South American natives. Venezuelan witch doctors are said to smoke the dried bark of V. sebifera to cure fevers (von Reis Altschul 1967; Schultes and Hofmann 1980b), and Brazilian witch doctors reportedly smoke the bark of an indeterminate Virola species as an additive to tobacco (McKenna et al. 1984b). In the past decade, the oral ingestion of Virola preparations by the Witoto and Bora Indians of Amazonian Colombia and adjacent Peru has become well documented (Schultes 1969; Schultes and Swain 1976;

Schultes et al. 1978). A recent publication describes the effect of such oral preparations in a field investigator, who tested four different samples in amounts exceeding those recommended by native informants. Two of the samples exhibited oral activity, but no strictly hallucinogenic response could be observed. The most potent sample had the effect of a pressor amine or general anaesthetic rather than the effect of an hallucinogen (McKenna et al. 1984b).

Principal Virola species utilized to prepare snuffs are V.calophylla and V.calophylloidea in the Colombian region, and V.theiodora in the Waiká area (Schultes 1954; Schultes and Holmstedt 1968; Prance 1970, 1972; Holmstedt et al. 1980). Another important Virola species appears to be V.elongata. This plant is used as a snuff source by certain Waikás (Brewer-Carias and Steyermark 1976), by the Paumarí Indians in central Amazonia (Prance et al. 1977), and possibly by the Taiwanos in Amazonian Colombia (Schultes 1954). In a recent taxonomic monograph on Virola, Rodrigues (1980) treats V.theiodora as equivalent to V.elongata, but Schultes (1982) prefers to consider the two as separate species, since they look very different in the field and are widely recognized as distinct by Indians who use them.

Other species of which the nasal use has been suggested in the literature, include V.cuspidata and V.rufula (Biocca 1968). Unfortunately, these suggestions are not supported by herbarium voucher specimens (Schultes, 1982). Rodrigues (1980) considers both binomials as synonyms of V.elongata, but the different phytochemistry of V.cuspidata casts doubt on its disposition under V.elongata (Schultes 1982).

#### 2.1.15.2. Chemistry and psychopharmacology

The chemistry of Virola species has been studied by Agurell et al. (1969), Holmstedt et al. (1980), and McKenna et al. (1984b). These studies have shown that the following tryptamine alkaloids can be present in the Virola genus: tryptamine (=T), N-mono-methyltryptamine (=MMT), 5-methoxy-N-monomethyltryptamine (=5-MeO-MMT), N,N-dimethyltryptamine (=DMT), and 5-methoxy-N,N-dimethyltryptamine (=5-MeO-DMT). Although the Indians usually employ only the bark and especially its exudate, tryptamines have not only been demonstrated in bark samples, but also in samples of leaves, flowering shoots, and roots. In addition to tryptamine derivatives, beta-carbolines could be isolated as minor components: 2-methyl-1,2,3,4-tetrahydro-beta-carboline (=MTHC), 6-methoxy-2-methyl-1,2,3,4-tetrahydro-beta-carboline (=6-MeO-MTHC), and 6-methoxy-1,2-dimethyl-1,2,3,4-tetrahydro-beta-carboline

(=6-MeO-DMTHC). Such compounds might be expected from the point of view of biosynthesis and workup procedure (Holmstedt et al. 1980).

Bark samples of V.calophylla, V.calophylloidea, V.rufula and V.theiodora were found to have DMT and 5-MeO-DMT as their main alkaloids (Aguirell et al. 1969; Holmstedt et al. 1980). An exudate sample of V.elongata contained T, MMT, DMT and MTHC; a bark sample of this species yielded MMT and DMT as principal alkaloids (Holmstedt et al. 1980). The bark of V.sebifera may contain DMT, 5-MeO-DMT and MMT (Corothie and Nakano 1969; McKenna et al. 1984b), whereas 6-methoxy-harman, 6-methoxy-harmalan, and 6-methoxy-tetrahydroharman are present in V.cuspidata (Cassady et al. 1971).

When these chemical data on Virola species are considered, the possibility must be kept in mind that a natural alkaloid composition might alter during the preparation and the storage of a snuff (Holmstedt et al. 1980). For instance, one step in the preparation of Virola snuffs involves concentration of the exudate to a thick syrup. The effect of such a treatment on 6-methoxy-tetrahydroharman, the major component in V.cuspidata, was determined in the laboratory. Refluxing in water for eight hours resulted in partial aromatization to 6-methoxy-harmalan and 6-methoxy-harman (Cassady et al. 1971). However, snuffs from tribes familiar with Virola contain the same simple tryptamine alkaloids which are also found in Virola plant material (Holmstedt and Lindgren 1967; Agurell et al. 1969; McKenna et al. 1984b). A nyakwána snuff, which had been prepared solely from the exudate of V.theiodora by the Waiká Indians of the Brazilian Rio Tototobí, yielded an unusually high total alkaloid content of 11%, consisting mainly of 5-MeO-DMT and DMT (Aguirell et al. 1969). The Anadenanthera alkaloid bufotenin, which apparently does not occur in Virola plants, is also absent in Virola snuffs (Holmstedt et al. 1980).

Pharmacological data on DMT and 5-MeO-DMT, the major alkaloids in utilized Virola species, are summarized in section 1.1.2.2. The pronounced hallucinogenic activity of these N,N-dimethylated tryptamine derivatives is probably not seen with T, MMT and 5-MeO-MMT (Brimblecombe and Pinder 1975). T was reported as producing changes in perception and sensation in patients by intravenous infusion of 0.025-0.364 mg/kg/min for a total dose of 23-277 mg during an experimental day (Martin and Sloan 1970). There is little doubt, however, that the observed effects were largely autonomic in nature (Brimblecombe and Pinder 1975; Kantor et al. 1979). In an earlier study, intravenous infusion of 1 mg/min for a total dose of 10-40 mg, did not change the

subjective state or the blood pressure and pulse of depressed patients pretreated with a MAO-inhibitor (Coppen et al. 1965). Human studies on the activity of MMT and 5-MeO-MMT seem to be lacking (Kantor et al. 1979). Behavioural studies in animals suggest that these compounds are probably not hallucinogenic (Brimblecombe and Pinder 1975; Gillin and Wyatt 1977). In the rat, 5-MeO-MMT was found to cross the blood-brain barrier only to an extremely small extent, whereas a rapid crossing of 5-MeO-DMT could be shown (Vogel 1969). Consequently 5-MeO-MMT is not likely to exert profound central effects.

Animal experiments show that T, MMT and 5-MeO-MMT are rapidly and extensively metabolized into their corresponding indoleacetic acids. Since T and its N-monomethylated congeners are good substrates for monoamine oxidases, these enzymes are held responsible for the conversion (Vogel 1969; Brimblecombe and Pinder 1975).

Besides the tryptamines, the commonly utilized Virola species may contain small amounts of the beta-carbolines MTHC, 6-MeO-MTHC and 6-MeO-DMTHC (Holmstedt et al. 1980). One of the best studied pharmacological properties of such simple beta-carbolines is their MAO-inhibiting activity. Over the years it has been demonstrated that series of beta-carbolines have this effect in vitro (Udenfriend et al. 1958; Pletscher et al. 1959; McIsaac and Estevez 1966; Buckholtz and Boggan 1977; McKenna et al. 1984a). Experimental data on MTHC and 6-MeO-DMTHC are still awaited, but a recent study has compared 6-MeO-MTHC with various common beta-carbolines. On a molar base, the Banisteriopsis constituents harmine and harmaline were the most potent MAO-inhibitors, and the Virola alkaloid 6-MeO-MTHC was found to be in the same intermediate range of potency as harman and harmol (McKenna et al. 1984a). It should be noted, however, that studies on the relative potency of beta-carbolines have used different methods of assessing MAO-inhibition, and that their results are partly conflicting (McIsaac and Estevez 1966; Buckholtz and Boggan 1977; McKenna et al. 1984a). Since the tryptamine alkaloids in Virola species serve as substrates for MAO (vide 1.1.2.2), it is sometimes speculated that 6-MeO-MTHC and its congeners may modify the activity of the Virola tryptamines by acting as MAO-inhibitors (Furst 1976a; Schultes and Hofmann 1980b). However, these beta-carbolines usually occur in Virola in trace amounts, unlikely to be of pharmacological importance (Holmstedt et al. 1980; McKenna et al. 1984b). In other words, unlike the DMT in ayahuasca beverages (vide 1.1.3.2), the tryptamines in oral Virola preparations stand little or no chance of being protected from first-pass metabolism by beta-carbolines.

Recently, various lignans have been isolated from the bark of Virola elongata, and some of these non-alkaloidal constituents, when given intraperitoneally to mice, could be shown as reducing isolation induced aggression and spontaneous locomotor activity (MacRae and Towers 1984a). It is not yet clear, however, whether the reported oral activity of native Virola drugs should be attributed to these lignan derivatives (McKenna et al. 1984b).

The MAO-inhibiting activity of 6-methoxy-harman, 6-methoxy-harmalan and 6-methoxy-tetrahydroharman, the alkaloids in V.cuspidata, is well documented (McIsaac and Estevez 1966; Buckholtz and Boggan 1977; McKenna et al. 1984a). Interestingly, 6-methoxy-harmalan and 6-methoxy-tetrahydroharman have been found to be psychoactive in man. They appear to produce a state of inspiration and heightened introspection rather than an hallucinogenic experience in the strict sense. In the case of 6-methoxy-harmalan, subjective effects become apparent with approximate oral dosages of 1.5 mg/kg (Naranjo 1967).

#### 2.1.16. Conclusion

From the ethnobotanical, chemical and psychopharmacological approach to intoxicating snuff rituals in the western hemisphere, the following categories of ritual snuff ingredients arise:

- 1) It is well established that the plant contains one or more psychoactive principles and the Indian use of the plant as a ritual snuff ingredient is confirmed or is quite probable: Anadenanthera, Erythroxylum, Nicotiana, Virola.
- 2) It is well established that the plant contains one or more psychoactive principles, but the Indian use of the plant as a ritual snuff ingredient is not well recorded or is even unlikely: Banisteriopsis, Cannabis, Datura, Ilex guayusa.
- 3) The Indian use of the plant as a ritual snuff ingredient is confirmed or is quite probable, but it is not well established that the plant contains one or more psychoactive principles: Justicia pectoralis, Pagamea macrophylla, Tanaecium nocturnum.
- 4) The Indian use of the plant as a ritual snuff ingredient is not well recorded, and it is not well established that the plant contains one or more psychoactive principles: Acorus calamus, Capsicum, Maquira sclerophylla, Piper interitum.

## CHAPTER TWO PART TWO

### NASAL PHARMACOKINETICS AND EFFICACY OF POSSIBLE RITUAL SNUFF CONSTITUENTS

#### 2.2.1. General introduction

Since the 1920s, medical practitioners have treated diabetes insipidus with the nasal insufflation of posterior pituitary powder (Choay and Choay 1946; Carter and Shorr 1947). In the last two decades, this treatment has been superseded by the application of synthetic substances like lypressin and desmopressin. Just like the pituitary snuff, these pure compounds show substantial antidiuretic activity when applied to the nasal mucosa (Dashe et al. 1964; Kosman 1978). Despite this long-standing evidence, nasal administration has never been adopted in the medical profession as a generally useful method of systemic delivery of drugs. Until recently, the nasal route has been employed almost exclusively for local treatment. Common examples are the topical use of corticosteroids, sympathicomimetics and antihistamines for perennial rhinitis and the like (Empey and Medder 1981). Such topical drugs are not intended, of course, to be absorbed into the general circulation from the nose, but the occasional systemic side-effects of nasal sympathicomimetics and antihistamines indicate that systemic availability is not always negligible (Parr 1983). Recent case reports associate nasal sympathicomimetic preparations with the development of a psychotic syndrome after long-term abuse (Snow et al. 1980; Escobar and Karno 1982), and with central excitation or depression in small children after apparently normal dosing (Söderman et al. 1984).

Before the seventies, human studies on the systemic efficacy of nasal preparations were limited to a handful of therapeutic drugs besides pituitary snuff and synthetic antidiuretic compounds (Riegelman and Sorby 1971; Gorman and Hall 1973; Ritschel 1973). In the last few years, the interest in nasal administration as a convenient way to introduce drugs into the body has revived. Recent research has especially confirmed the potential usefulness of nasal application for drugs, which show a very poor effect in man after oral administration, such as: insulin (Hirai 1982; Pontiroli et al. 1982), buserilin (Bergquist et al. 1979; Koch 1981), testosterone (Danner and Frick 1980), nitroglycerin (Hill et al. 1981), glucagon (Pontiroli et al. 1983), and protireline (Borkenstein 1983). The advantage which the nasal route appears

to have for certain drugs over the oral route, can be easily explained. Drugs which are absorbed through the nasal mucosa, immediately enter the general circulation, and thus evade any form of presystemic degradation by the acid gastric juice and first-pass elimination by intestinal and hepatic enzymes. Among the various drugs of which the oral efficacy is greatly reduced by first-pass metabolism, are the sex hormones progesterone and testosterone. In recent studies on the kinetics of these hormones in the rat, nasal and intravenous administration resulted in practically similar systemic availability, whereas the availability following duodenal administration was approximately 1% that of intravenous dosing (Hussain et al. 1981, 1984). With respect to humans, the most striking data have been obtained for the beta-receptorblocking agent propranolol HCl, which is known to suffer from an extensive first-pass effect when taken orally. Intravenous and nasal doses of 10 mg produced practically identical serum levels; an oral amount of 80 mg produced relatively low serum levels and, after adjustment for the dose difference, the oral availability was only 25% of the intravenous availability (Hussain et al. 1980).

Nasal application does not only prevent presystemic elimination, it is also a rapid way of drug delivery. Most of the recent human studies mentioned above show peak levels and/or maximal activity within half an hour after nasal dosing. It is not difficult to understand such findings, when the anatomy and physiology of the nose are taken into consideration. The nasal cavity comprises an olfactory region in its extreme upper area and a respiratory region in its lower and greatest part. In the different regions, the nasal mucous membrane varies in its thickness and its vascularity. It is thick and most vascular in the upper area and over the septum, but on the floor of the nasal cavity and in the sinuses the membrane is very thin. The surface area is enlarged by the subdivision into sinuses, and it is further increased by the presence of microvilli comparable to those in the small intestine. In addition, the vascular bed of the respiratory mucosa within the nose appears to be designed for the rapid passage of fluid and dissolved materials from the blood vessels to the tissues and vice versa. All in all, the nose is a suitable site for drug absorption, and this seems to be particularly true for the respiratory region (Parr 1983).

The use of nasal dosage forms for systemic therapy may have its drawbacks. A large variability in systemic effects, resulting in an erratic response, has been strongly emphasized by some early investigators (Talledo et al. 1964; Hankiss 1982). In the case of cocaine, the rate of absorption from the nasal mucosa appears to

be highly variable, and as this alkaloid is a potent vasoconstrictor, this might be due to a fluctuating degree of local vasoconstriction (Wilkinson et al. 1980). A recent major concern is the ciliotoxicity of active constituents and additives (van de Donk and Merkus 1981).

Clinical studies on the nasal application of psychoactive alkaloids are summarized below. Wherever possible, the relationship between dose and activity is indicated. Field investigators report that an Indian snuff dose usually does not exceed 5 g (Coppens and Cato-David 1971) or about one to two teaspoons full, which would be equal to some 5-10 g (Schultes 1954; Turner and Merlis 1959). It seems difficult, if not impossible, to retain such large doses completely. In other words, when a snuff contains 1 % of a psychoactive alkaloid, the nasal threshold level of this alkaloid should be less than 50-100 mg to get an effect from one dose, and when only 0.1 % is present, a threshold level lower than 5-10 mg will be required. It must be emphasized, however, that the pertinence of clinical results to snuffing rituals may be somewhat limited. Nasal absorption does not only depend on the physicochemical properties of the active compound (pKa, partition coefficient, molecular size), but it is also governed by other factors. Potentially influential differences between experimental and native practices include:

- characteristics of the drug product

In situ recirculation tests with the nasal cavity of the rat have shown that the absorption rate of weak electrolytes is pH-dependent. In the case of aminopyrine (=aminophenazone), the absorption behaviour even closely followed the rules of the pH-partition theory, which assumes that only unionized drug molecules are capable of passive diffusion across a mucous membrane (Hirai et al. 1981). It would thus appear that the common addition of alkaline plant ashes or lime to South American snuffs may be significant. Up to half of a snuff can consist of plant ash (Seitz 1967; Schultes and Holmstedt 1968; Prance 1972). Just as is the case in coca chewing practices, the addition of such alkaline material may facilitate the diffusion of the alkaloids through the mucous membrane. Vegetable ash might further promote absorption by helping to prevent agglomeration of the snuff powder (Schultes 1967b).

Clinical studies on insulin (Hirai 1982), gentamicin (Rubinstein 1983), and scopolamine (Tonndorf et al. 1953) have demonstrated that surfactants have a great potential for enhancing nasal drug absorption. Consequently it would be interesting to ascertain, whether South American snuffs contain

surface-active compounds like saponins (Hegnauer, pers. commun. 1984), and if so, whether these compounds improve the absorption of the alkaloidal constituents.

- characteristics of the user

A potential difference between western individuals and South American Indians is that the western subjects may be less able to retain a nasal powder. In clinical studies on Piptadenia snuffs, most of the dose was discharged by sneezing and coughing, because of the inexperience of the test subjects (Turner and Merlis 1959).

Another potential difference may be the condition of the nasal mucosa. British tobacco snufflers who had used commercial snuff for at least twenty years turned out to have a generalized atrophy of the nasal mucosa. Biopsy in four snufflers confirmed metaplasia of the ciliated columnar epithelium to squamous epithelium over the middle turbinal and adjoining nasal septum (Harrison 1964). Similarly, chronic abuse of cocaine via the nose may lead to inflammatory changes and perforation of the nasal septum (Sawicka and Trosser 1983). Natanson (1975) feels that the nasal perforation seen in immoderate cocaine sniffers should be attributed to the intense vasoconstrictor effect of cocaine.

In view of such data, it may well be that the regular use of snuff by South American Indians results in degeneration of their nasal mucosa. This factor should be taken into account, since nasal drug absorption may be decreased (Ritschel 1973) or increased (Parr 1983) by local inflammation. In recent rat experiments, the nasal absorption of the quaternary ammonium compound clofilium was substantially better when the administered concentration became so high that it damaged the nasal mucosa (Su et al. 1984).

- method of administration

Among some tribes, one Indian blows the snuffing powder forcefully through a tube into the nostril of another Indian, whereas other tribes know self-administration, either by direct inhalation through a bifurcated or straight tube, or by placing one end of a V-shaped tube into the mouth and the other end into the nostril (Cooper 1949; Wassén 1965; Schultes 1967b; Seitz 1967; Coppens and Cato-David 1971; Prance 1972; Reichel-Dolmatoff 1975). The forceful blowing through a V-shaped or straight tube is likely to give a more widespread deposition than direct inhalation (Holmstedt and Lindgren 1967). When tobacco snuff is inhaled cautiously, the snuff will probably reach no further than the anterior part of the nasal tract, whereby a small quantity will go down into the pharynx (Fraser Roberts 1962). In a study with chronic tobacco snufflers, inhaled pinches of barium sulphate

powder with an average size of 20  $\mu\text{m}$  could be primarily collected in the middle meatus of every snuffer (Harrison 1964). The forceful blowing in Indian practices will project the snuff against the well perfused semicavernous tissue of the nasal conchae (Holmstedt, pers. commun. 1983), and small particles may even reach the lungs (Chinachoti and Tangchai 1957; Fraser Roberts 1962; Huggins et al. 1962). According to text books, the particle size of a nasal powder should not be below 10–20 micrometer to prevent passage into the tracheal and pulmonary area (Gorman and Hall 1973; Dolder 1978). Holmstedt and Lindgren (1967) assume that, even in the case of forceful blowing, the main part of the administered material will affect the brain from the nose. There does not appear to be solid evidence that snuff constituents may pass directly into the brain without being transported through the general circulation. Consequently it should be accepted that snuff constituents are absorbed through the richly vascularized nasal mucosa, and reach the brain via the general blood-stream (Holmstedt and Lindgren 1967).

## 2.2.2. Specific constituents

### 2.2.2.1. Atropine

Vide section 2.2.2.8.

### 2.2.2.2. Bufotenin

Vide section 2.2.2.5.

### 2.2.2.3. Caffeine

Recent studies have demonstrated that an oral dose of 5 mg/kg of caffeine results in maximal plasma levels of 9–10  $\mu\text{g/ml}$  after half an hour, and in complete bioavailability (Blanchard and Sawers 1982, 1983). These good oral absorption characteristics and the physicochemical properties of caffeine (Windholz 1983) suggest that this alkaloid may be rapidly absorbed from nasal dosage forms.

To obtain anecdotal experimental evidence for this supposition, I have taken pure anhydrous caffeine (OPG, Utrecht) as a nasal powder. The powder had a particle size of 10–30  $\mu\text{m}$ , but many agglomerates of 100–300  $\mu\text{m}$  were present. At the time of the experiment, I was a non-inhaling tobacco smoker and a regular user of coffee and beer. After abstention from xanthine-

containing products for two days and after an overnight fast, a total dose of 6.4 mg/kg was self-administered into both nostrils with a glass tube. A small fraction of the dose was lost because of some nasal mucous discharge. Venous blood samples were drawn at 0, 10, 20, 35, 50, 100, 120, 240, and 360 min after administration. Each sample was centrifuged and the resulting plasma was kept frozen until submission to analysis.

Plasma levels were assayed by Jan H.G. Jonkman and Wim J.V. van der Boon (Pharma Bio-Research International, Assen). They used a sensitive high pressure liquid chromatographical method comparable to that developed by Jonkman et al. (1980) for theophylline. Details are provided in Appendix D.

After administration, some mild transient stimulation was felt, not unlike the effect of a first tobacco cigarette in the morning. The plasma level was already 7.9 µg/ml at 10 min and 10.9 µg/ml at 20 min. The level was still 9.8 µg/ml at 120 min, whereafter it declined in a semilogarithmic way to 6.3 µg/ml at 360 min. Some unabsorbed caffeine powder could be recovered from the nasal cavity one hour after the end of the experiment.

All in all, the nasal absorption of pure caffeine powder was rapid in onset, but still incomplete after seven hours.

#### 2.2.2.4. Cocaine

In official western medicine, cocaine is no longer used systemically, but because of its good local anaesthetic effects and potent vasoconstrictive properties, cocaine is still applied as a surface anaesthetic, especially in nasal surgery (Johns et al. 1977; Ritchie and Greene 1980). Cocaine is also a major drug of abuse, and a common method of recreational administration is snorting into the nostrils (Jaffe 1980). Consequently the medical profession needs clinical data on the kinetic behaviour and systemic toxicity of this alkaloid after nasal administration. Such data were not available some years ago, but this picture has been changed completely by the recent development of specific and sensitive methods for the determination of cocaine in biological fluids (Lindgren 1981; Barnett et al. 1981). Since 1976, there has been a continuous flow of publications on the plasma levels and/or systemic effects of nasal cocaine in an experimental setting (Van Dyke et al. 1976, 1978, 1982; Byck et al. 1977; Resnick et al. 1977a,b; Javaid et al. 1978, 1983; Wilkinson et al. 1980). It should be emphasized that most of the crucial results have been obtained in small series of three or four subjects. This is not surprising, as cocaine has a notorious reputation as a dangerous drug, and it is classified under

narcotic laws, so that legal problems are involved with its experimental use. Investigators in the United States spent approximately one year clearing the permissions and various consent forms through the requisite committees (Byck et al. 1977). From the methodological view, a small number of subjects is unfortunate, since the kinetic studies on nasal cocaine show large interindividual differences (Wilkinson et al. 1980; Javaid et al. 1983).

Van Dyke and associates have reported extensively on nasal cocaine kinetics (Van Dyke et al. 1976, 1978, 1982; Byck et al. 1977; Wilkinson et al. 1980). Their first study was carried out before they had solved the problem of the *in vitro* hydrolysis of cocaine (Barnett et al. 1981), and the subjects were surgical patients, who received other drugs concomitantly. However, the study shows some interesting results. Cocaine plasma levels could already be detected within 3 min after giving a nasal solution with 1.5 mg/kg of cocaine HCl, so the onset of nasal cocaine absorption was extremely rapid. The presence of unabsorbed cocaine on the nasal mucosa could be demonstrated for as long as 3 hours after administration, so the absorption was also prolonged. The latter phenomenon was attributed to the potent vasoconstrictive effects of the alkaloid (Van Dyke et al. 1976).

Van Dyke and associates have subsequently used healthy volunteers with a previous history of recreational cocaine use (Byck et al. 1977; Van Dyke et al. 1978, 1982; Wilkinson et al. 1980). In 1980, they reported on the influence of dose and dosage form on nasal cocaine kinetics. An increase in dose resulted in a higher peak plasma level of cocaine: nasal solutions with 0.19 mg/kg to 2.0 mg/kg of cocaine HCl produced mean peak concentrations of 13 ng/ml (after 41 min) to 170 ng/ml (after 91 min). The relative bioavailability was found to be independent of the dose. Unfortunately, these results were obtained in only a partially cross-over fashion. A cross-over comparison was made between the levels from a nasal solution and levels after snorting the same dose of crystalline cocaine HCl. The crystals tended to produce an earlier and higher peak as well as a larger area under the plasma concentration/time curve, but major differences in kinetics were not observed (Wilkinson et al. 1980).

Javaid et al. (1978, 1983) have tested nasal powders of 100 mg (consisting of 16, 64 or 96 mg of cocaine HCl mixed with lactose) in healthy volunteers with a history of cocaine use. In their first study, plasma levels were analyzed without the use of an internal standard, and Barnett et al. (1981) estimate the lower limit of reliability of their analytical assay to be in the range

of 50-100 ng/ml. The highest dose in the study (96 mg) produced a mean peak level of 206 ng/ml after 30 min (Javaid et al. 1978). An internal standard was included in the analytical procedure of the second study, which lowered the limit of sensitivity to 5 ng/ml. In contrast with the findings of Wilkinson et al. (1980), not only the mean peak concentration was found to be dose-dependent, but also the relative bioavailability. A nasal powder with 64 mg of cocaine HCl gave an average peak level of 67 ng/ml after 37 min, whereas a mean peak of 133 ng/ml was observed 41 min after the administration of 96 mg. The mean bioavailability (relative to an intravenous dose of 32 mg of cocaine HCl in the same subjects) was 28% for the dose of 64 mg, and 57% for the dose of 96 mg (Javaid et al. 1983).

From the preceding data, it can be concluded that cocaine absorption from nasal dosage forms is rapid in onset, but that unabsorbed cocaine remains present in the nose for a considerable time. This may explain, at least partly, why the bioavailability of nasal cocaine powders was found to be incomplete.

Several studies have compared the plasma levels and subjective effects of nasal cocaine in volunteers who had previously used cocaine recreationally. In general, maximal central effects tend to occur before the plasma level has reached a peak value (Van Dyke et al. 1978, 1982; Javaid et al. 1978). Van Dyke et al. (1982) found that 0.75 mg/kg and 1.5 mg/kg of cocaine HCl as a nasal solution produced maximal 'highs' within 30 min, whereas mean peak plasma levels of 43 ng/ml and 108 ng/ml, respectively, did not occur before 60 min. They also demonstrated that central stimulation is more intense during the rising phase of the plasma concentration/time curve than during the falling phase. The same phenomenon has been observed in coca chewers (Holmstedt et al. 1979).

The subjective effects of nasal cocaine are, not unexpectedly, dependent on dose, personality and setting. In the cross-over study by Van Dyke et al. (1982), 1.5 mg/kg of cocaine HCl produced a greater subjective response than 0.75 mg/kg. Their report shows, however, that the 'highs' produced by 0.75 mg/kg were less intense than those observed after an initial familiarization dose of 0.4 mg/kg. Apparently, the subjects responded differently during the first experiment than during the actual study. A dose of 0.2 mg/kg was also tested, but this dose did not elicit a greater response than 0.2 mg/kg of lidocaine HCl, a local anaesthetic without euphorizing properties. It would therefore appear that 0.2 mg/kg (14 mg/70 kg) is below the minimum threshold dose of cocaine HCl needed for central activity by the nasal route, whereas 0.4 mg/kg (28 mg/70 kg) is probably

above this threshold level. Similar data have been obtained by Resnick et al. (1977a,b), who compared subjective and somatic effects of nasal cocaine with those of lidocaine and tetracaine without analyzing cocaine plasma levels. Subjective effects after placebo and after 10 mg of cocaine (as a solution) were the same, whereas 25 mg of cocaine produced some significant subjective changes. More experienced cocaine users rated subjective effects lower than others who showed an equally large somatic response.

#### 2.2.2.5. Dimethyltryptamine and related compounds

There is substantial evidence to suggest that the active tryptamines in Anadenanthera and Virola species undergo extensive first-pass elimination by intestinal and hepatic enzymes (vide 1.1.2.2). Since the nasal route certainly can provide the advantage of bypassing such presystemic inactivation, this may explain why both genera are most often taken nasally in South America. So far as I know, conclusive clinical support for this assumption has not been published. Human studies on the nasal application of tryptamine alkaloids were conducted in the fifties, but they failed to demonstrate hallucinogen-like activity via the nasal route. This is probably due, at least in the case of DMT, to the testing of low and therefore subactive doses.

Turner and Merlis (1959) have assessed the effects of nasal DMT in one healthy volunteer and four schizophrenic individuals. DMT powder in quantities of 5 to 20 mg merely caused a burning sensation in the back of the nose and throat. On one occasion, 10 mg elicited a feeling of being 'hit on the head' in a patient, and this sensation was concomitant with unilateral flushing of the face and mydriasis. Since DMT is well lipid soluble at pH 7.4 (Glennon et al. 1979), poor nasal absorption is not the most likely explanation for the observed lack of psychoactive symptoms. A more obvious reason is inadequate dosing, as the tested nasal amounts were below the threshold dose of 30 mg, needed to elicit subjective perception changes in man by intramuscular injection (Szára 1957).

Turner and Merlis (1959) have also given bufotenin nasally to schizophrenic subjects, and just as in their nasal experiments with DMT, the tested dose range was low. When bufotenin (as pure base or as creatinine sulphate) was blown into the nares, quantities of up to 10 mg merely produced a feeling of fear, associated with flushing of the face, lacrimation, tachycardia, and tachypnea.

The inhalation of bufotenin by humans has also been studied by Isbell. In a letter to Turner and Merlis (1959), Isbell 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 1 part bufotenin base and 1.8 parts creatinine sulphate (Fabing and Hawkins 1956), so 40 mg provides 14.3 mg of bufotenin 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 manner of inhalation (nasal or tracheal), the test subjects (psychotic patients or not), and the studied doses (100 mg by inhalation or not). Fortunately, Isbell (pers. commun. 1984) has recently informed me that bufotenin was inhaled nasally, and that the subjects were physically healthy male volunteers, aged between 25 and 50, who were imprisoned for narcotic law violations. His communication leaves open, however, whether as much as 100 mg of bufotenin was inactive by oral ingestion only, or also by inhalation.

The subjects of Isbell experienced visual disturbances from 10-15 mg of intramuscular bufotenin (Isbell, quoted by Turner and Merlis 1959, and by Wassén and Holmstedt 1963), and other investigators have reported visual disturbances from 4-16 mg of intravenous bufotenin (Fabing and Hawkins 1956; Bonhour et al. 1967). This would seem to suggest that bufotenin may induce perception changes more readily by injection than by nasal application, which would be consistent with the chemical finding that bufotenin is poorly lipid soluble at pH 7.4 (Glennon et al. 1979) and might thus 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 in the rat (Hirai et al. 1981; Su et al. 1984; Fisher et al. 1985).

#### 2.2.2.6. Harmine

Experimental information on the nasal efficacy of harmine appears to be lacking. The physicochemical properties of this alkaloid (Hultin 1965) should permit a good diffusion through the nasal membrane. Harmine may possibly undergo substantial first-pass metabolism after oral ingestion, so that the nasal route might be superior to the oral one (vide 1.1.3.2).

To test this hypothesis, I have taken the same dose of 0.5 mg/kg of harmine base (Fluka, Buchs) nasally and orally on two different occasions. The dose was derived from a report by Slotkin et al. (1970) that 0.5 mg/kg of harmine HCl intravenously

results in substantial plasma levels and in transient somatic effects, but not in distinct central stimulation. At the time of the experiment, I was a non-inhaling tobacco smoker and a regular user of coffee and beer. First, harmine was self-administered into one nostril with a plastic tube as a pure nasal powder, consisting of needles with a length of 10–40  $\mu\text{m}$ . Five days later, harmine was ingested as an oral drink, prepared by dissolving the pure base in 100 ml of tap water, to which some citric acid (Merck, Darmstadt) was added. On both occasions, the harmine was taken after an overnight fast, and venous blood samples were drawn at 0, 15, 30, 60, 120 and 240 min after administration (in the case of the oral drink also at 90 min). Each sample was centrifuged and the resulting plasma was kept frozen until submission to analysis.

Plasma levels were assayed by Laurent Rivier (Institute of Legal Medicine, Lausanne) and Pierre Baumann (Psychiatric University Clinic, Lausanne). They used a gas chromatographical/mass spectrometric (GC-MS) method comparable to that described by Baumann et al. (1984) for harman and norharman. The assay is sensitive down to 2 ng/ml. Details are provided in Appendix E.

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 et al. (1970) reported levels in the range of 300–400 ng/ml at 10–60 min and 80 ng/ml at 240 min after a similar dose intravenously, the last result is unexpected, especially in the case of the nasal powder. Without additional experiments, it is difficult to ascertain, why there is such a large discrepancy between the nasal and intravenous data. The good nasal absorption of caffeine in another self-experiment (vide 2.2.2.3) would seem to argue against faulty absorption as the major cause. A more plausible explanation might perhaps be that the GC-MS method used in the nasal experiment is more reliable than the fluorometric assay used in the intravenous study.

#### 2.2.2.7. Nicotine

In the last few years, smokeless tobacco products have received increasing attention as potentially less harmful alternatives to cigarettes, since they provide nicotine to the craving user without introducing tar and carbon monoxide into the lungs and without contaminating the atmosphere for non-users (Rasche González 1980; Russell et al. 1980). This possibility has prompted studies on the pharmacokinetics of tobacco administration via the buccal route (Gritz et al. 1981), and via

the nasal route (Russell et al. 1980, 1981).

In the seventies, pharmacokinetic evidence that nicotine is absorbed from nasal tobacco snuffs was provided by Temple (1976) who demonstrated nicotine and its major metabolites in the urine of tobacco snuffers.

Russell et al. (1980, 1981) subsequently reported experimental data on the plasma concentrations of nicotine in tobacco snuffers, as measured by gas chromatography. Their first publication describes extremely rapid absorption in an experienced user of tobacco snuff: a single pinch of snuff raised his nicotine plasma level in 5 min from a baseline level of about 20 ng/ml (due to previous snuffing) to more than 40 ng/ml (Russell et al. 1980). The second report confirms this preliminary result, but substantial absorption could only be demonstrated in experienced users. In twelve occasional snuffers, the average increase in nicotine plasma concentration, measured within 8-17 min after a single pinch of snuff, was only 2 ng/ml. Four volunteers who had never used snuff before, did not show any increase at all. This lack of nicotine absorption in the novices may have been related to their initiation with small doses of a very mild snuff. In contrast, a single pinch of snuff raised the mean plasma level of nicotine in seven daily snuffers from 21.9 ng/ml to 34.5 ng/ml after 7.5-11 min. This mean value almost matched the average peak level of 36.7 ng/ml found in a large group of heavy cigarette smokers. As with cigarette smoking, the interindividual differences in nicotine plasma concentrations were large, and the observed increases varied considerably from 2.6 to 34.8 ng/ml. This divergence is probably partly due to the fact that the strength of the snuff, the size of the pinch, and the exact way of snuffing were uncontrolled variables (Russell et al. 1981).

Nicotine is said to undergo substantial first-pass elimination after oral ingestion (vide 1.1.9.2), and snuffing may provide the advantage of avoiding such an effect (vide 2.2.1). However, the principal Indian manner of tobacco use is not oral ingestion but smoking (vide 2.1.11.1). The latter method is rather complex, as it may lead to a bypass of the liver on the one hand and to partial pyrolytic conversion of nicotine (Larson 1960) on the other. Russell et al. (1983) have compared nicotine plasma levels produced by a nasal viscose solution containing 2 mg of pure nicotine with the levels from a commercial cigarette expected to deliver the same dose of nicotine. Both preparations already produced peak plasma levels at 7.5 min, and these levels averaged about 14 ng/ml and 26 ng/ml for the nasal solution and the cigarette respectively. The area under the plasma concentration/

time curve found after nasal administration amounted to 75 % of that produced by smoking. This result cannot be viewed without caution, however, since only three subjects were studied.

More recently, Russell and co-workers have studied the kinetics of repeated nasal doses of pure nicotine in viscose solution. The initial doses of 2 mg produced increases of 0.9–25.7 ng/ml after 7.5 min, and resulted in noticeable light-headedness in four of the five subjects (West et al. 1984).

#### 2.2.2.8. Scopolamine and related compounds

In the fifties, Tonndorf and co-workers conducted various experiments on the nasal administration of scopolamine and atropine in healthy human subjects. Comparisons were made with other routes of administration. The influence of certain parameters on the nasal absorption of these tropane alkaloids was also studied (Tonndorf et al. 1953; Hyde et al. 1953). Data were not obtained in a proper cross-over fashion, but in most experiments at least ten subjects were used for each different treatment. Gas chromatographical/mass spectrometric methods (Bayne et al. 1975) or radioimmunoassays (Wurzburger et al. 1977) with sufficient sensitivity to measure the very low therapeutic plasma concentrations of tropane alkaloids were not yet available. Instead, the research group assessed the anti-sialogogic activity during the first two hours after administration as an indication for the rapidity and degree of drug absorption. This test period of two hours is rather short, especially for the oral experiments, since the anti-sialogogic activity of oral scopolamine and atropine reaches a peak value after 1–2 hours (Mirakhur 1978). In other words, the results say more about the onset and degree of activity than about the duration of effects.

Scopolamine was studied because of its protective action against motion sickness. If its nasal absorption would be rapid, nasal dosing might be a practical way of self-administration with an obvious advantage over oral dosing in already nauseated patients. To test this premise, subjects received 0.65 mg as a subcutaneous injection, as an oral capsule or an oral liquid, and as nose drops. In all cases, the salivary flow dropped below control values. The decline was most marked and rapid after subcutaneous administration. The effect of nasal instillation occupied an intermediate position, and oral ingestion produced the slowest and least marked decrease. Testing of other doses revealed that nasal quantities of 0.1–0.4 mg gave a perceptible drop in salivary production, whereas an oral quantity of 0.35 mg

was without effect. An apparent superiority of the nasal route over the oral one was also found when a dose of 1.0 mg was given via both routes (Tonndorf et al. 1953).

There is substantial evidence to suggest that scopolamine undergoes extensive first-pass metabolism after oral administration (vide 1.1.4.2), so the observed superiority of nasal dosing may well be due to a bypass of presystemic elimination.

The efficacy of nasal atropine was tested, because this tropane alkaloid is an antidote against organic phosphoryl compounds. A comparison was made between 1.0 mg as subcutaneous injection, 1.5 mg as a nasal spray with detergent and as nose drops, and 1.6 mg in the form of sublingual tablets. The preparations did not yield the same response at each measure point, but there were no major differences which persisted throughout the test period. It is rather difficult to draw firm conclusions from these results, since nasal instillation of different doses did not clearly show that 1.5 mg was more effective than 1.0 mg or less effective than 2.0 mg (Hyde et al. 1953).

A comparison between nasal application and oral ingestion was not included in the studies. It may well be that oral atropine undergoes first-pass elimination (vide 1.1.4.2), so an advantageous bypass via the nasal route may be suggested not only for scopolamine, but also for atropine. In a recent cross-over study on the peripheral activity of these alkaloids, the ratio of equivalent intramuscular to oral doses appeared to be about 1 : 5-6 for scopolamine and 1 : 2 for atropine (Mirakhur 1978). Consequently scopolamine may profit more markedly than atropine, if nasal administration indeed provides the advantage of avoiding first-pass metabolism of tropane alkaloids.

As to the systemic toxicity of nasal atropine, it is noteworthy that instillation of 2.0 mg produced mild symptoms in some cases. One subject, who accidentally received more than 3.0 mg as a nasal spray with detergent, suffered from a moderately severe reaction, consisting of mydriasis, mild nausea, dizziness, and disorientation (Hyde et al. 1953).

### 2.2.3. Conclusion

The literature yields convincing clinical evidence that atropine, cocaine, nicotine and scopolamine are effective following nasal application, but experimental confirmation of the efficacy of nasal tryptamine alkaloids is still awaited. This seems to be due, at least in the case of DMT, to the testing of

low and therefore inadequate doses.

In self-experiments, caffeine produced substantial plasma levels via the nasal route, but harmine, when 40 mg was taken as a nasal powder, did not produce measurable plasma levels. Without additional experiments, it is difficult to give a definite explanation for this negative result.

## CHAPTER TWO PART THREE

### THE CHEMISTRY OF YOPO SNUFFS OF THE VENEZUELAN PIAROA INDIANS

#### 2.3.1. Introduction

The Piaroa Indians are a tropical forest people of the Salivan family. They are settled along tributaries of the Orinoco in the Guiana Highlands of the Federal Territory of Amazonas, Venezuela (Wilbert 1958; Kaplan 1975). Several sources indicate that the men of this tribe use an intoxicating snuff called yopo, niopo or niopa (Wavrin 1948; Gheerbrant 1952; Wilbert 1958; Wurdack 1958; Kaplan 1975). Gheerbrant (1952) states 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 (1958), 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 men snuffing use Y-shaped tubes of bird bone. Wurdack (1958) reports that the Piaroa are avid yopo snuffers, 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) has identified a yopo specimen, the seeds of which were said to be the source of an intoxicating Piaroa snuff, as Anadenanthera peregrina (formerly known as Piptadenia peregrina). The seeds of this species contain the indole alkaloids N,N-dimethyltryptamine (=DMT), bufotenin (=5-OH-DMT), and 5-methoxy-N,N-dimethyltryptamine (=5-MeO-DMT) (Schultes et al. 1977).

Although the Piaroa appear to be familiar with tobacco (Chaffanjon 1889; Gheerbrant 1952; Wurdack 1958; Kaplan 1975), the consulted literature has not yielded evidence that they ever use 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 that the Ventuari Piaroa also employ the vegetative parts of an unidentified bush for preparing a snuff (Wurdack 1958). 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 beta-carboline harmine is not an Anadenanthera constituent, but a major Banisteriopsis alkaloid. Unfortunately the snuff was collected without botanical voucher specimens, so it remains unknown, whether the harmine originated from Banisteriopsis or from some other vegetal ingredient. The most comprehensive review on the use of Banisteriopsis by South American natives does not include the Piaroa as a tribe familiar with Banisteriopsis drinks (Friedberg 1965).

Since harmine only rarely occurs in South American Indian snuffs (Bernauer 1964; Holmstedt and Lindgren 1967), the opportunity to study two different yopo samples of the Piaroa Indians was welcomed.

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

Sample B was collected by a German named Baumgartner, probably during the fifties or sixties. 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 of objects from Venezuelan Indians, including various snuff-taking paraphernalia. Among these items is a Piaroa snuff, which is still in its original 'kherime' container (museum number 74.76.594).

Sample A consisted of dry snuff lumps, while sample B was a dry granular powder.

### 2.3.2. Analytical methods

In cooperation with Laurent Rivier (Institute of Legal Medicine, Lausanne), both samples were submitted to gas chromatographical/ mass spectrometric procedures comparable to those described by Schultes et al. (1977). Details are reported in Appendix A.

To determine the presence of alkaline substances, 20 mg of ground snuff material was dissolved in 2 ml of freshly distilled water by ultrasounds for 5 min. The pH was determined by a combined electrode (Radiometer PHM 83 Autocal pH meter, Copenhagen).

### 2.3.3. Results and discussion

Sample A turned out to contain 10 mg/g of 5-OH-DMT, whereas sample B yielded a trace of 5-OH-DMT (<1 mg/g), as identified by retention time on capillary column and mass spectrum. 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, since the Piaroa Indians are reported as using 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 two snuff samples, viz. solid lumps (sample A) versus granular powder (sample B).

Sample B also contained a trace of a second substance with the same retention time on capillary column and mass spectrum as those 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. 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 an vegetal source yielding harmine. This conclusion indicates that the tracing of Indian drug materials in European museums and private collections for chemical analysis may lead to interesting results.

