

STUDIES ON HALLUCINOGENIC SNUFFS

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HISTORICAL BACKGROUND

An interesting custom observed by the discoverers of the New World was the practice by the natives of inhaling a peculiar type of snuff. Ramon Pane, who accompanied Columbus on his second voyage in 1496, wrote of this custom, saying: "This powder they draw up through the nose, and it intoxicates them to such an extent that when they are under its influence they know not what they do" (7). In Hispaniola, where this custom was first observed, the snuff and the ceremony of taking the snuff were called *cohoba*. When under the influence of the snuff, the necromancers, or priests, were supposed to be able to communicate with unseen powers and make prophecies. Medicine men were better able to perform their diagnoses and treatments if they had first taken *cohoba* (8).

It was later found by other explorers and historians that the practice was widespread through northern South America. The German naturalist, Alexander von Humboldt, observed it among the Otomac Indians on the Orinoco River in Venezuela. He described the preparation of the snuff and the method used for inhalation (5). This description closely parallels those made by Richard Spruce, a botanist, and others. In general, seeds of a particular tree were ground, with or without admixture of lime. Some observers say that this mixture was allowed to ferment. A paste was made which was allowed to harden in front of a fire. From this were obtained small, hard cakes which were stored in containers made from snail shells. Before use, the cakes were ground with a type of mortar and pestle. A bifurcated tube (fig. 1), made from the bones of a bird, was employed for the actual inhalation. This custom still is followed in various parts of the Antilles and in South America, particularly in the region of the Amazon and its affluents. The snuff is known by several names, depending on the area where it is used: *cohoba*, *huillca*, *yopo*, *paricá*, etc. The effects of the snuff have been variously described as intoxicating, narcotic, or intoxicating followed by a long

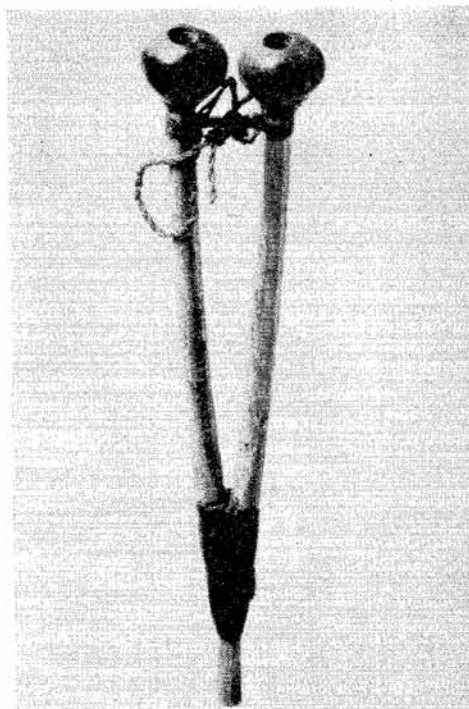


FIG. 1. Tube used by Indians of Colombia, South America, for inhaling snuff. Smithsonian Institution Cat. No. 325,331.

soothing action. The words, "debauchery" and "temporary madness", have also been employed in describing the effects.

It was not until 1916 that a botanist, W. E. Safford, produced evidence that the various snuffs had a common plant source, the seeds of species of *Piptadenia* (8). This tree is found in the areas where the use of the snuff has been reported.

The Laboratory of Chemistry of Natural Products of the National Heart Institute is currently making a study of these seeds and of snuff samples and has found additional evidence which supports Safford's proposal.

PHYSIOLOGICALLY ACTIVE COMPONENTS

Examination of seeds of *Piptadenia peregrina* (fig. 2) obtained from Puerto Rico showed that the principal alkaloid present was bu-

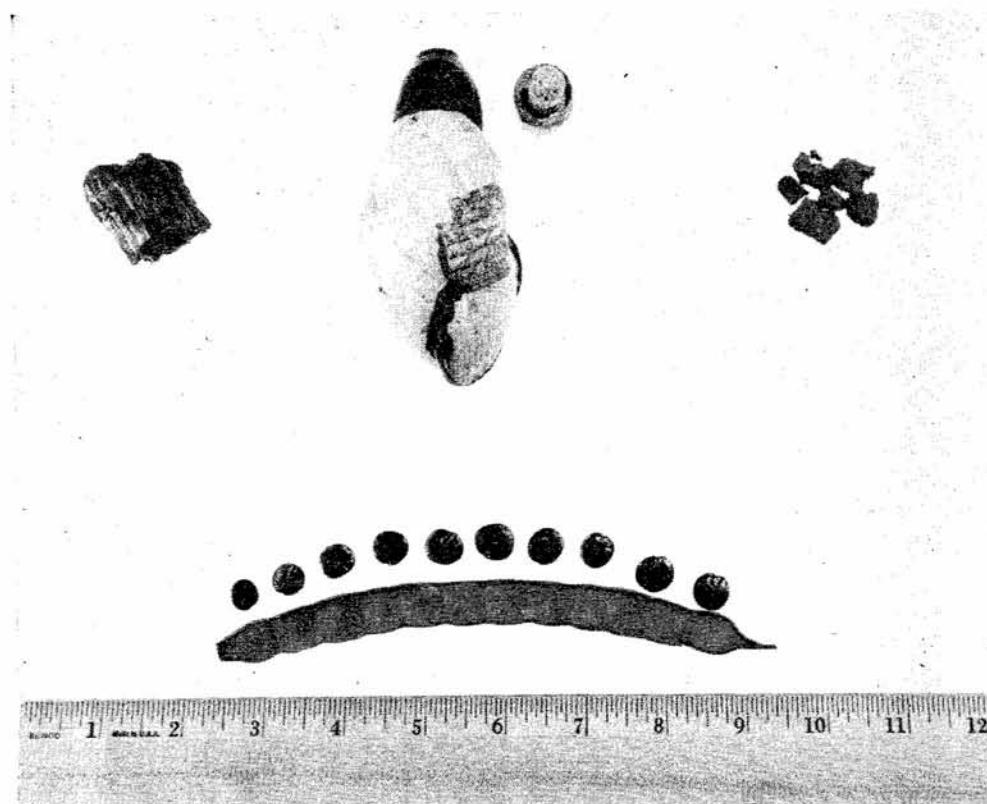


FIG. 2. Top (left to right): *Piptadenia* snuff from Llanos area of Colombia, South America; snail shell employed by Indians for carrying snuff. Collected in 1882 from Mauhes Tribe, Rio Negro, for Brazilian National Exposition; *Piptadenia* snuff collected from Piaroa Indian. Territorio Federal Amazonas, Venezuela. Bottom: *Piptadenia peregrina* seeds and pod, Puerto Rico.

fotenine, an indole compound closely related to serotonin (10). Bufotenine had never before been isolated from a plant source although it has been found in the skin glands of toads and in certain mushrooms. Later on, two samples of snuff (fig. 2), one from Venezuela and one from Colombia, were studied chemically; and, again, bufotenine was found to be present in large quantities. Since the seeds of *Piptadenia* sp. are the only presently known seed source of bufotenine, strong support for the claims of Safford was thus established. Paper chromatographic comparisons of extracts of the snuffs and seeds provided the analytical evidence (fig. 3).

Further chemical study of various seed extracts resulted in the isolation of additional organic bases closely related to bufotenine. One such source, *Piptadenia macrocarpa*, contained five related indole compounds: bufotenine, N,N-dimethyltryptamine, bufotenine oxide,

N,N-dimethyltryptamine oxide, and a substance of unknown structure (fig. 3) (2). Structural comparisons (figs. 4 and 5) of these materials with serotonin, the powerful vasoconstrictor which has received much attention recently, and with tryptophan from which all are undoubtedly derived, bring up interesting pharmacological questions: What physiological action, if any, do these compounds have? How do the slight variations in structure affect activity? Work done at the National Heart Institute and elsewhere (6, 9) has indicated that bufotenine, N,N-dimethyltryptamine and serotonin all have grossly similar effects on the cardiovascular system of the dog and cat. No obvious central nervous system effects were observed in these animals at a low dose level. The oxides were much less active than the bases. In the studies of Dr. Edward Evarts of the National Institute of Mental Health (1), it was found that the effects of bufotenine in

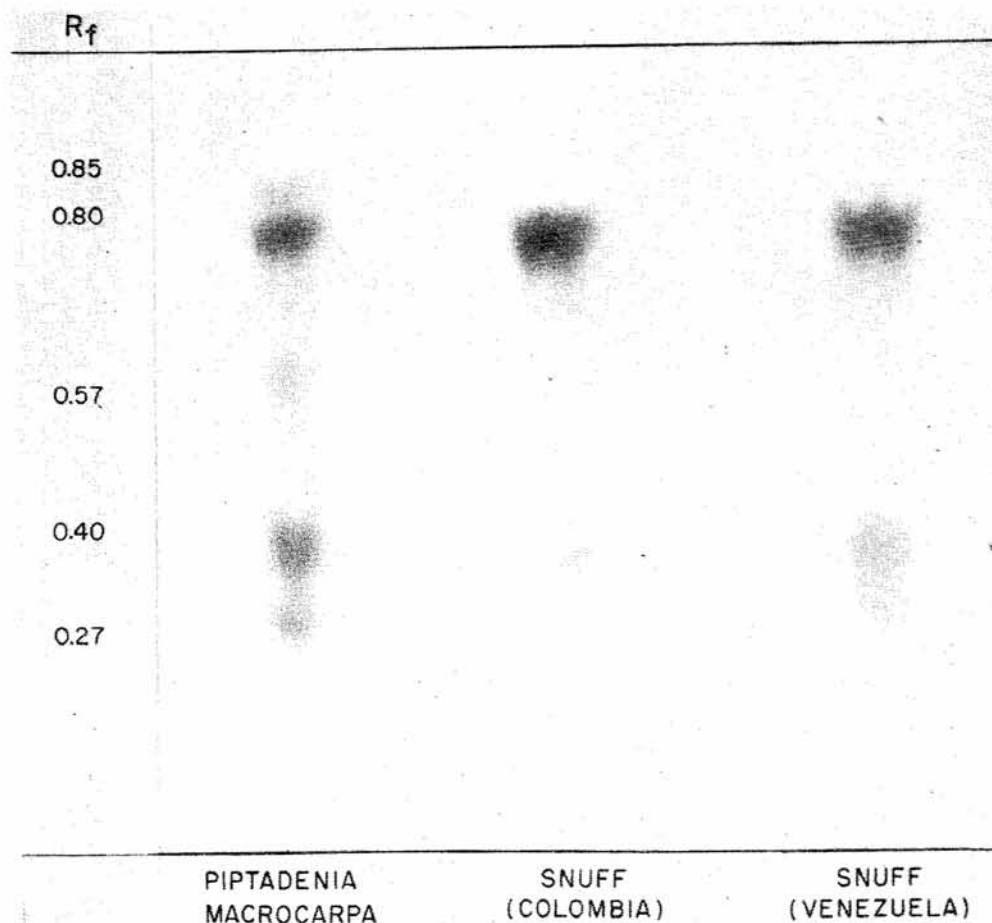


FIG. 3. Paper chromatogram sprayed with Ehrlich's reagent showing indole constituents of (left to right): *Piptadenia macrocarpa* extract; extract of Colombian snuff sample; extract of Venezuelan snuff sample. The intense spots with an R_f of 0.80 are bufotenine.

the monkey were very similar to those of LSD, and that bufotenine and *N,N*-dimethyltryptamine exhibited similar actions on the synaptic junction of the optic nerve of the cat at approximately equivalent dose levels.

It should be pointed out that pharmacological examination of other fractions of seed extracts has not, as yet, afforded any evidence that physiologically active agents other than the five indole compounds are present. This possibility must not be excluded, however, when one considers the frequent observations pertaining to species differences with respect to physiological activity, along with the fact that animals are not ideal subjects for the study of drug-produced psychoses. For example, in man, LSD is active at a dose level

of 0.0003 mg./kg. In the monkey, doses of 1 mg./kg. of LSD and 3 mg./kg. of bufotenine are employed for producing profound behavioral disturbances (1). This difference is 10,000-fold.

CHEMICAL, ENZYMATIC AND METABOLIC STUDIES

A great deal of work on the chemistry of these compounds has been in progress (3). It will be sufficient here to state only that some of these chemical studies were directed toward proof of structure of the indole components of the seeds and that others were directed, as closely as possible, to the duplication of enzymatic conditions. It was found in enzymatic work that some of the products obtained

were identical to those previously isolated from chemical reactions. For example, the soluble and microsomal fraction of mouse liver homogenate converts *N,N*-dimethyltryptamine to its oxide (4). When the oxide is incubated with whole homogenate, some of it is reduced back to the parent amine. These same reactions were also carried out under mild chemical conditions. The mitochondrial fraction of mouse liver homogenate converts *N,N*-dimethyltryptamine to 3-indoleacetic acid. This is not an unexpected result when one considers the metabolism of bufotenine in man. When Dr. H. D. Fabing administered bufotenine (the 5-hydroxy analog of *N,N*-dimethyltryptamine) to convicts at the Ohio State Penitentiary, urine samples were collected and examined. It

was found that a small fraction of the bufotenine was excreted unchanged, but the major portion was converted to and excreted as 5-hydroxy-3-indoleacetic acid (fig. 6). Since, as stated above, oxides of tertiary amines are formed by mammalian enzymes, the next step was to learn if these oxides would undergo an enzymatic reaction. Results with the oxides of bufotenine and *N,N*-dimethyltryptamine have, so far, been negative, but it was found that the oxide of *N,N*-dimethyltryptophan, an amino acid oxide which was prepared synthetically, did undergo this type of reaction. One of the *N*-methyl groups was eliminated from the molecule. Another unidentified product was formed. In the latter case, carbon dioxide was lost from the molecule.

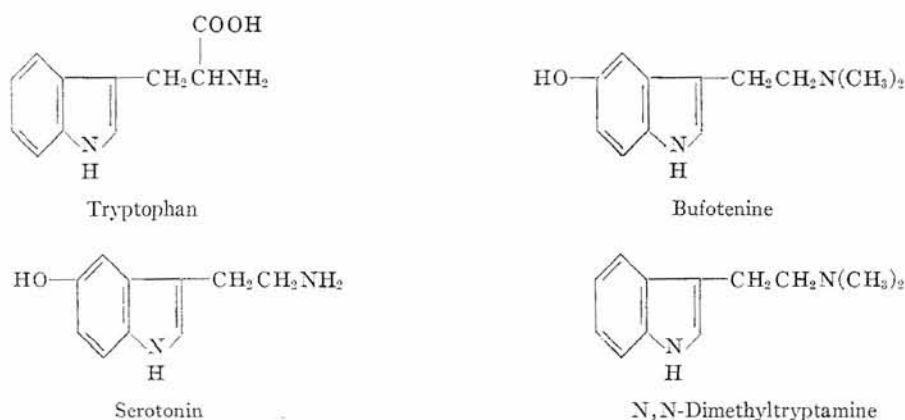


FIG. 4. Structural relationships of various naturally-occurring indoles

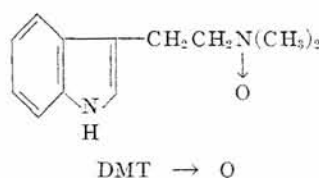


FIG. 5. *N,N*-Dimethyltryptamine oxide

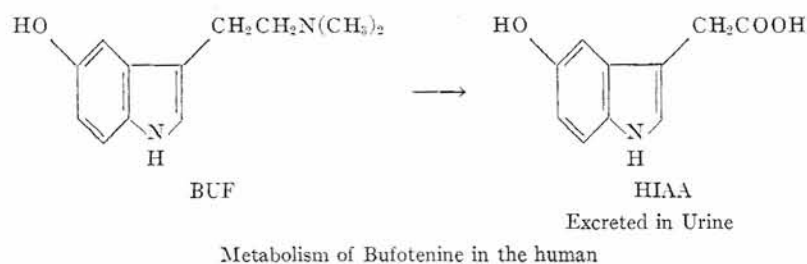


FIG. 6. Conversion of bufotenine to 5-hydroxy-3-indoleacetic acid in man

The results of these enzymatic experiments have led to the conclusion that a new sequence of tryptophan metabolism should be proposed for plants and possibly for mammalian organisms. The next step will be to learn if any of these compounds plays a vital role in normal or, perhaps, abnormal physiological processes.

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