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TRYPTAMINE DERIVATIVES IN EPENÁ AN INTOXICATING SNUFF USED BY SOME SOUTH AMERICAN INDIAN TRIBES

BY

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Intoxicating snuffs used for ceremonial purposes and commonly called Paricà or Yopo have a wide-spread use in Northern South America. The botanical and ethnological aspects of this habit are well documented in a series of review articles (24, 37, 40, 21). Many of these powders are reported having as their main constituent the seeds of the Leguminous plant *Piptadenia peregrina*. A careful analysis of the alkaloid content of the plant as well as of certain specimens of snuff has revealed the existence of tryptamine derivatives of current pharmacological interest (30, 9, 8, 20, 18).

Judged by ethnological and botanical explorations in recent years it would seem, however, that *Piptadenia peregrina* is not the main constituent in all snuffs used by the South American Indians. Powders of other botanical origin have been collected by SCHULTES (27), who found them to be prepared from two species of *Myristicaceae* (*Virola calophylla* Warburg and *Virola calophylloidea* Markgraf). Intoxicating snuffs of possibly similar or identical composition have been described by ZERRIES (41, 42, 43, 44), BECHER (2) and SEITZ (28). By courtesy of Mr Georg J. Seitz a specimen of the powder Epená used for inhalation by the Waica tribe has been placed at the author's disposal, and it was judged interesting to compare this to the Paricà powder previously analyzed. Because of the interest attached to the central action of tryptamine derivatives in modern psychopharmacological research special attention was focussed on this group of compounds.

During the course of this investigation both bioassay and conventional

biochemical techniques were used. Eventually, it was found that gaschromatography provided the best means of identification of the components in the alcaloid fraction (14).

Materials and Methods

Epená snuff obtained from Mr Georg J. Seitz, Caixa postal 2605, Rio de Janeiro, and collected in 1961. It is a grey-brownish finely powdered material. Upon arrival the Epená snuff was freeze dried and kept in the cold until further used.

Chemicals used.

Unless otherwise stated amines are given as bases.

5-Hydroxydiethyltryptamine, 5-hydroxydiethyltryptamine oxalate, 5-hydroxy-ω-N-ethyltryptamine oxalate, 5-hydroxy-ω-N-methyltryptamine bioxalate, 5-hydroxygramine hydrochloride, psilocine, α-methylpsilocine, 6-hydroxydimethyltryptamine, 7-hydroxy-dimethyltryptamine.

The above chemicals were kindly placed at the author's disposal by Dr A. Hofmann, Sandoz A.G., Basle. Details about most of them will be found in Stoll *et al.* (29) and Troxler *et al.* (35).

5-Methoxy-N, N-dimethyltryptamine was kindly placed at disposal by Dr Merlin Bumpus, Cleveland Clinic, Cleveland 6, Ohio. Dimethyltryptamine hydrogenoxalate and diethyltryptamine (California Corporation for Biochemical Research, 3625 Medford Street, Los Angeles 63, Calif.). 5-Hydroxyindolacetic acid (Delta Chemical Works, Inc., 23 West 60th St., New York 23, N.Y.). DL-tryptophan (S.A.F. Hoffman-La Roche & Co. Ltd., Basle). Serotonin creatinsulphatemonohydrate (Fluka A.G., Buche S.G., Switzerland).

Bufotenine. Several kinds of bufotenine were used : A preparation of pure bufotenine base from *Piptadenia peregrina* (prepared by E. Horning, Baylor University College of Medicine, Texas Medical Center, Houston, Texas). Bufotenine bioxalate (California Corporation for Biochemical. Research, 3625 Medford Street, Los Angeles 63, Calif.). Bufotenine Bioxalate (Carl Roth Feinchemikalien, Karlsruhe).

In addition to the compounds mentioned above the N-oxides of dimethyltryptamine, 5-hydroxydimethyltryptamine and 5-hydroxydiethyltryptamine were prepared according to the method described by Fish *et al.* (9) and used for chromatography in the way described below.

Procedure.

Preparation of powder for preliminary testing with Ehrlich's reagent : 0.7 g of the powder was shaken in 10 ml of equal parts of ethanol chloroform and Ehrlich's reagent (2.5 g *p*-dimethyl aminobenzaldehyde mixed with 25 ml conc. HCl to which was added 100 ml acetone. The reagent was always freshly prepared). Positive reaction was always blue or reddish blue.

Isolation of organic bases.

Ten g of the powder was treated according to the procedure described by Fish *et al.* (9). The isolation procedure was followed in detail but the amounts of solvents were reduced with respect to the initial weight of the sample.

The steps of the isolation procedure were followed with tests using Ehrlich's reagent. After drying with magnesium sulphate the final product was obtained upon removal of the solvent. The total alkaloids obtained were then dissolved either in 2 ml 0.1 N HCl or in tetrahydrofurane.

The main constituents were further isolated by preparative paper-chromatography

in the following way. On a Whatman MM3 paper 0.05–0.1 ml of the alkaloid fraction was applied along the starting line of the chromatogram with a width of 20–25 mm. Three such spots were applied with a distance between them of 60–70 mm. The chromatogram was run descendingly in 20 % KCl. After drying the middle part of the chromatogram was cut out and the lateral parts developed with Ehrlich's reagent. The middle part was then restored in place and the positions of the spots calculated. The spots were then separated and extracted with 30 ml absolute alcohol. After evaporation to dryness the remaining substance was dissolved in 0.3 ml of equal parts of absolute alcohol and aqua dest. The latter solution was used for the final paper chromatograms and other identification tests.

Two spots giving positive reaction with Ehrlich's reagent were identified in the above way, one running slowly giving a dark blue colour and one running fast giving a red-blue colour. They will in the following be called fraction A and B, respectively.

Analytical paperchromatography.

Around 10 micrograms of test substances and corresponding amounts of the fractions calculated on basis of spectrophotofluorimetrical measurements were put on paper.

Descending paper chromatograms were run overnight in several solvent systems. After drying the chromatograms were developed with Ehrlich's reagent and the colour changes observed carefully and Rf-values calculated.

Thin layer chromatography.

Thin layer chromatography was run on silica gel in the cold room for 3½–4 hours. The solvent used was isopropanol/ammonia (10/1). 1 % solutions of the free bases in tetrahydrofuran (THF) were put on the plate in microliter quantities. The plates were dried and sprayed with Ehrlich's reagent.

Gaschromatography.

Relative retention times were obtained with a Barber-Colman Model 10 instrument and with an EIR Model AU-8 instrument. Both were equipped with argon ionization detection systems with radium foil sources. The columns were 6 ft × 4 mm glass U-tubes. The preparation of the column packings has been described by HORNING *et al.* (15). The support was Gas-Chrom P, 80 to 100 mesh, inactivated with dichlorodimethylsilane. Coating was carried out by filtration technique. The phases were (1) a mixture of 7 % of F-60 (a methyl *p*-chlorophenylsiloxane polymer; Dow Corning Corp.) and 1 % EGSS-Z (a copolymer from ethylene glycol, succinic acid and methyl phenyl siloxane monomers; Applied Sciences Laboratories, Inc.), and (2) 10 % NGS (neopentylglycol succinate). The "flash heater" was kept 30–40° above the column temperature, and the detection cell was held at 240°. Samples (μl volume) were injected in tetrahydrofuran or acetone solution. The Epená extract was used as such without previous group separation on thin layer. Trimethylsilyl (TMS*i*) ethers were prepared by reaction with hexamethyldisilazane in tetrahydrofuran or acetone solution (19). Other details about the technique will be found in HOLMSTEDT *et al.* (14).

Spectrophotofluorometry.

Activation and fluorescence spectra were run in an Aminco-Bowman spectrophotofluorometer and recorded on an X-Y-recorder (Houston Co.). The solutions used were in water, ethanol or various normalities of HCl.

Bioassay.

For the pharmacological analysis of serotonin-like activity a modification of the method of VANE (38) was used. Instead of the long stomach fundus strip a part of the fundus approximately 5 × 30 mm was mounted in a 5 ml bath, equipped with an automatic

timer for change of the bath fluid. The upper part of the strip was attached to a force displacement transducer FTO 3, the output of which was fed into a polygraph amplifier (Grass Instrument Co.) and the results recorded on an Easterline Angus ink recorder (Indianapolis). The substances to be tested were added in molar concentrations to the top of the test bath and the deviations of the recorder were plotted against the neg. log. molar concentration of the compounds tested.

Results

The author has had the opportunity of looking at a large number of South American drugs used for inhalation. Generally, they consist of black lumps that have to be powdered in a special mortar. By contrast, the Epená powder as kept in the container used by the Waica Indians (Fig. 1) is a fine brownish grey powder which may very well have been sifted. Primarily, and during all stages of the preparation, it gives a positive Ehrlich reaction.

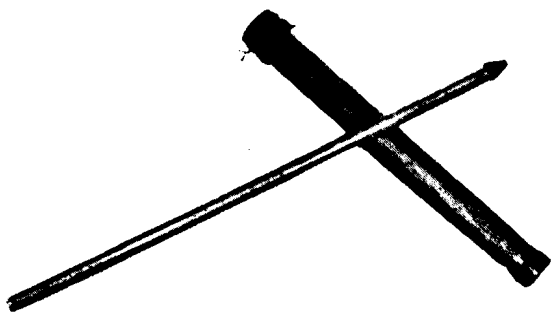

Fig. 1

Equipment used for administration by Waica indians. — *Left* tube for blowing. — *Right* container for Epená powder.

Paperchromatography.

The fractions A and B isolated from the Epená powder were compared to a large number of synthetic tryptamine derivatives in several solvent systems. Because of the occurrence of bufotenine in similar plant material attention was first focussed on this compound. The oxidation product of bufotenine as described by Fish *et al.* (9) was also put on paper. An experiment of this kind is shown in Fig. 2. It will be seen that neither bufotenine nor bufotenine-N-oxide are identical with the other compounds investigated.

When all the tryptamines available during this stage of investigation were compared to fractions A and B, two of them had Rf-values comparable to those of the fractions. They were respectively 5-hydroxy-

N.N-diethyl tryptamine (5-OH-DET) and N.N.-dimethyl tryptamine (DMT). The Rf-values in 3 solvent systems are presented in Table I. No other compounds available at the time showed any similarity with fraction A and B in this respect.

FIG. 2

Paperchromatogram. Solvent *n*-butanol-acetic acid-aqua (120 : 30 : 50). Time 16 hours.

	Rf-values :
Fraction A	0.72
5-OH-N,N-diethyl tryptamine (5-OH-DET)	0.72
Fraction B	0.78
N,N-dimethyl tryptamine (DMT)	0.78
Bufotenine (BUF)	0.60
Bufotenine oxide (BUF-O)	0.65

Thin layer chromatography.

The analytical thin layer chromatography disclosed one difference from the paperchromatography in that 5-OH-DET gave a yellow colour instead of a blue one. It was not possible to achieve anything but a group

TABLE I

Substance	Rf-value	Rf-value	Rf-value
	Solvent *n*-butanol, acetic acid glacial, water 120 : 30 : 50	Solvent *n*-propanol, ammonia 5 : 1	Solvent *t*.-butanol, water, formic acid 207 : 87 : 6
Fraction A	0.71	0.90	0.73
5-OH-N.N-diethyl tryptamine base	0.71	0.89	0.72
Fraction B	0.80	0.91	0.69
N.N-dimethyl tryptamine (hydrogen oxalate)	0.80	0.91	0.69

separation of the tryptamines in the Epená extract. The spot given by the extract had an Rf-value between those of DMT and 5-OH-DMT and a blue colour. No trace of the yellow tinge of (5-OH-DET) could be refound in the group separated extract. The analysis was therefore carried further by means of gaschromatography.

Gaschromatography.

Naturally occurring compounds related to tryptamine contain a variety of side chain structures. A differentiation of tertiary amine structures might be made either on the basis of direct gas liquid chromatography (GLC), or through the separation of derivatives. For phenolic amines the reaction leading to a trimethylsilyl (TMSi) ether may be carried out in solution. The formation of this type of derivatives is demonstrated in Fig. 3. N substitution usually leads to altered retention times when methyl or ethyl groups are introduced. Because of the data from the paperchromatography one could suspect the presence of ethyl groups. One chief consideration was therefore the effective separation of compounds with $-CH_2CH_2N(CH_3)_2$ and $-CH_2CH_2N(C_2H_5)_2$ side chains. Fig. 3 and 4 conclusively demonstrate the longer retention time of compounds with a $-CH_2-CH_2-N(C_2H_5)_2$ side chain.

However, when the Epená extract was analyzed by direct GLC separation the results were those in Fig. 5 and 6 upper parts and Table II. The minor components had retention times corresponding to N,N-dimethyltryptamine and to bufotenine, but the major alkaloid did not

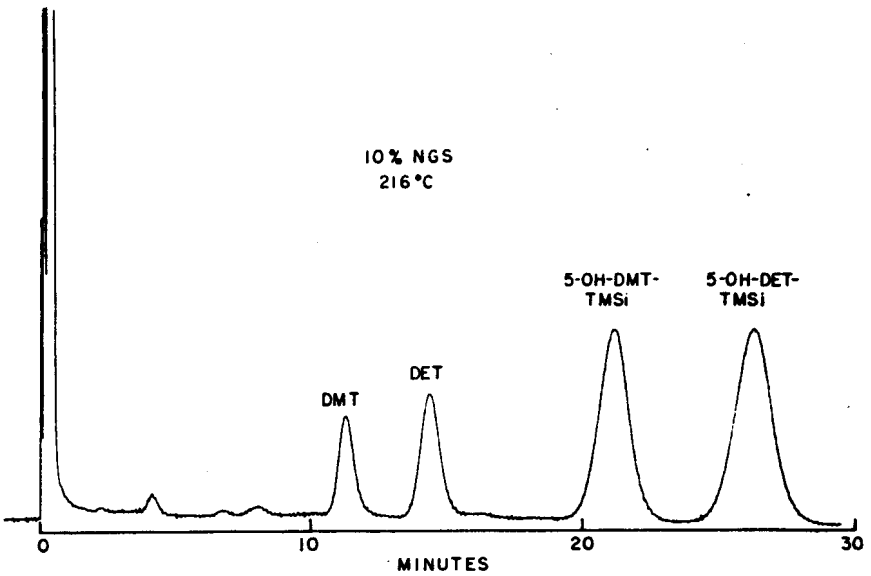

FIG. 3

Separation of N, N-dimethyltryptamine (DMT), N, N-diethyltryptamine (DET), 5-trimethylsilyloxy-N, N-dimethyltryptamine (5-OH-DMT-TMSi) and 5-trimethylsilyloxy-N, N-diethyltryptamine (5-OH-DET-TMSi). — *Conditions*: 10 % NGS on 100- to 120-mesh Gas Chrom P, 216° C., 19 p.s.i.; argon ionization detection system.

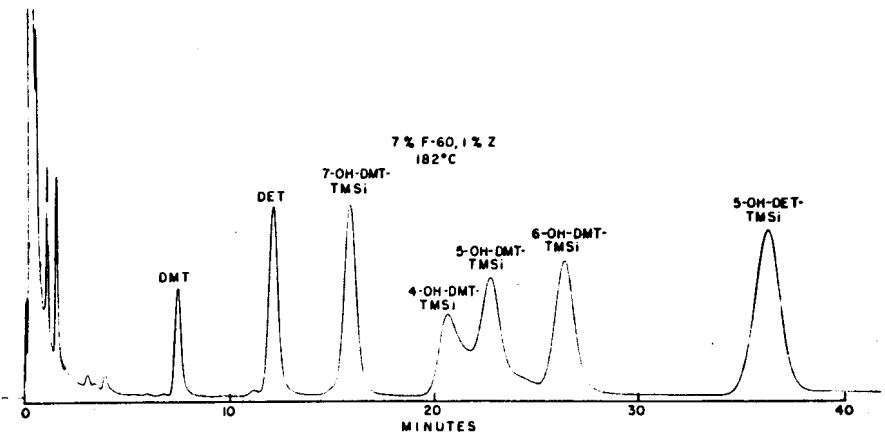

FIG. 4

Separation of tryptamine-related indole bases.

The compounds are N, N-dimethyltryptamine (DMT), N, N-diethyltryptamine(DET), 7-trimethylsilyloxy-N, N-dimethyltryptamine (7-OH-DMT-TMSi), 4-trimethylsilyloxy-N, N-dimethyltryptamine (4-OH-DMT-TMSi), 5-trimethylsilyloxy-N, N-dimethyltryptamine (5-OH-DMT-TMSi), 6-trimethylsilyloxy-N, N-dimethyltryptamine (6-OH-DMT-TMSi), and 5-trimethylsilyloxy-N, N-diethyltryptamine (5-OH-DET-TMSi). *Conditions*: 7 % F-60, 1 % EGSS-Z, on 100- to 120-mesh Gas Chrom P, 182° C, 18 p.s.i.; argon ionization detection system.

correspond to reference substances which were at hand. The absence of a reactive primary amino group was established by the failure to form an acetone condensation product. The absence of a phenolic group was indicated by a failure to form a TMSi ether. Inspection of the retention time data suggested that a methoxy-N,N-dimethyltryptamine structure was likely. Through the courtesy of Dr. Merlin

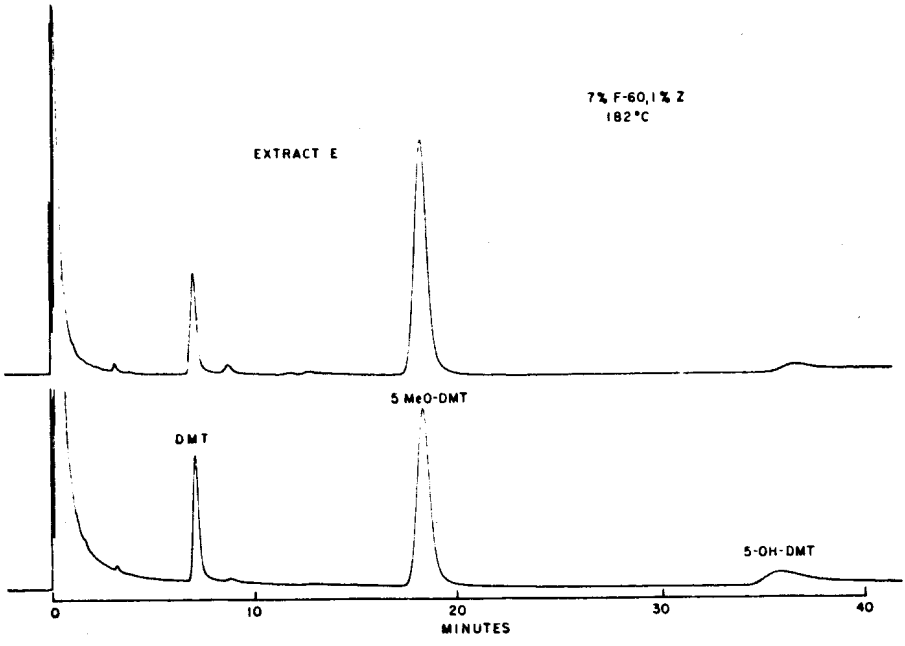

FIG. 5

Comparison of the gas chromatographic analysis of the indole base fraction of an extract of the South American snuff *epená* (EXTRACT E) with a gaschromatographic analysis of a synthetic mixture of N, N-dimethyltryptamine (DMT), 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT) and 5-hydroxy-N, N-dimethyltryptamine (5-OH-DMT). — *Column conditions*: 6 ft. × 4 mm glass column; 7 % F-60 and 1 % EGSS-Z on 80–100 mesh Gas Chrom P; 182° C; 18 p.s.i.

Bumpus an authentic sample of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) was used for comparison and identity was established by GLC techniques with the columns used for Table II. The compound was also prepared by methylation (diazomethane) of bufotenine. A mixture of bases was made to correspond approximately to the composition seen for the natural mixture of indole bases, and a comparison of the GLC records for the two mixtures is shown in Fig. 5 and 6.

Spectrophotofluorometry.

Activation and fluorescence spectra of fraction A as compared to

5-OH-DET and 5-MeO-DMT and of fraction B and DMT are presented in Fig. 7 and 8. These spectra were run in water with both fractions and test substances, and the magnification of the Aminco-Bowman instrument was adjusted to give approximately the same heights of the spectra. As seen from the curve the spectra are superimposable and for all practical reasons identical.

TABLE II

Relative retention times of Epená extract (Seitz) and synthetic compounds

Comp.	Phase	Temp.	PSi	RT	RRT
ExtrE	NGS 10 %	216°	19	DMT peak 5-MeO-DMT peak	1.68 (1) 5.13
DMT 5-MeO-DMT					1.68 5.10
ExtrE	7 % F 60 (2) 1 % Z	182°	18	DMT peak 5-MeO-DMT peak 5-OH-DMT peak	1.0 (3) 2.67 5.35
DMT 5-MeO-DMT 5-OH-DMT					1.04 2.68 5.25

(1) Anthracene time, 8.6 min.

(2) The column was in use for 2 months at the time of comparison of compounds described in this Table. The polarity of the column decreases slowly with continued use.

(3) Anthracene time, 8.7 min.

It is well known that fluorescence spectra of 5-substituted tryptamines when run in 3 N HCl show a shift of the peak to higher wave-lengths. This occurs also with fraction A as will be seen from Fig. 9, where (in acid solution) a peak is obtained in the region of 540 mμ. This fact gives additional proof for the substitution of fraction A in 5 position, since the shift described is not known to occur with tryptamine compounds, substituted in other positions.

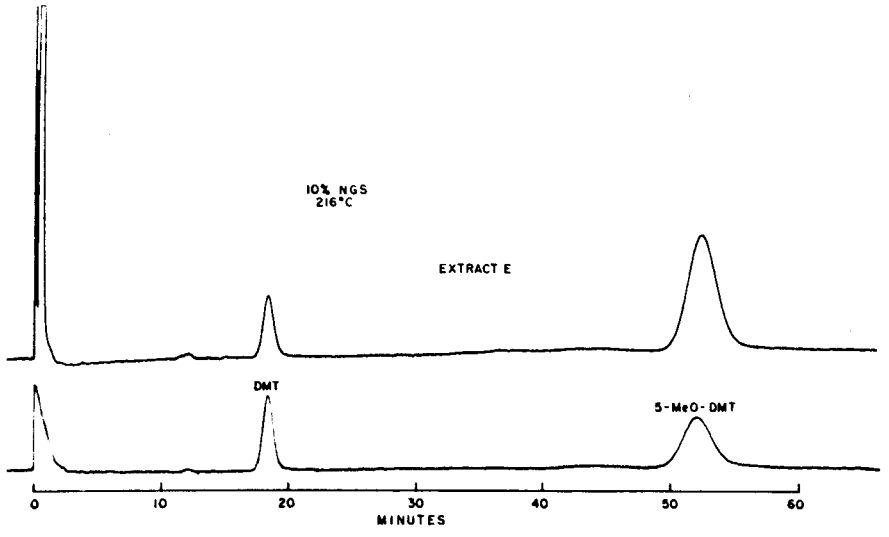

FIG. 6

Comparison of gaschromatographic separation of bases for : upper panel, extract (E) from epená, and, lower panel, mixture of reference samples of N, N-dimethyltryptamine (DMT) and 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT). — *Conditions* : same as for Fig. 3.

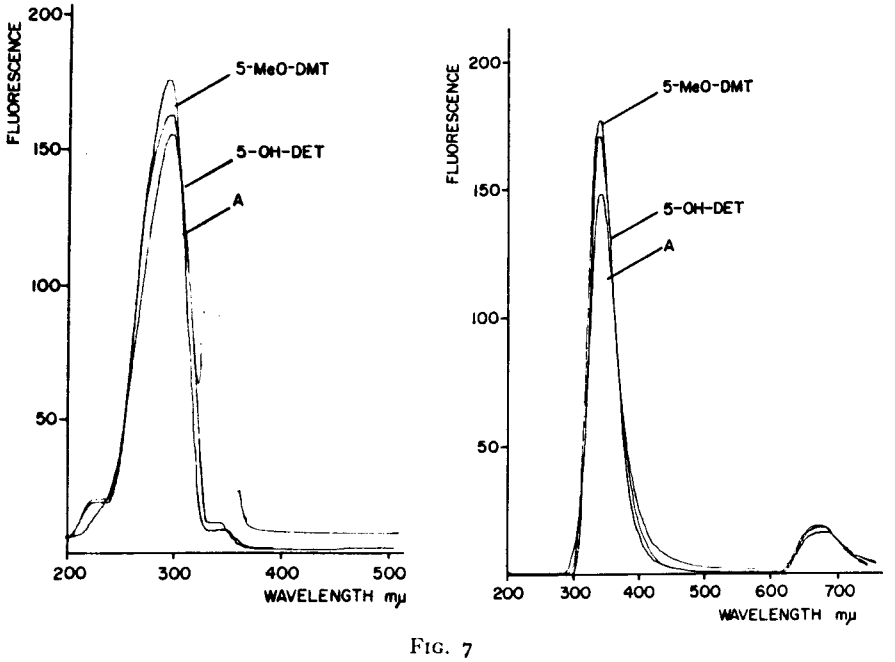

FIG. 7

Comparison of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT), 5-hydroxy-N, N-diethyl tryptamine (5-OH-DET) and fraction A (A). Medium aqua. Left activation spectrum. Right fluorescence spectrum at activation maximum of 295 mμ. Fluorescence peak at 340 mμ.

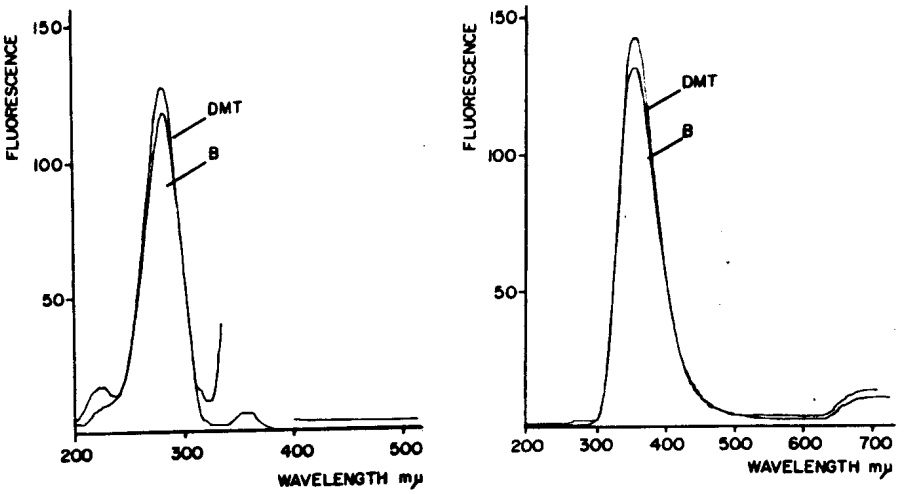

FIG. 8

Comparison of N, N-dimethyl tryptamine (DMT) and fraction B (B). Medium aqua. Left activation spectrum. Right fluorescence spectrum at activation maximum 278 mμ. Fluorescence peak at 350 mμ.

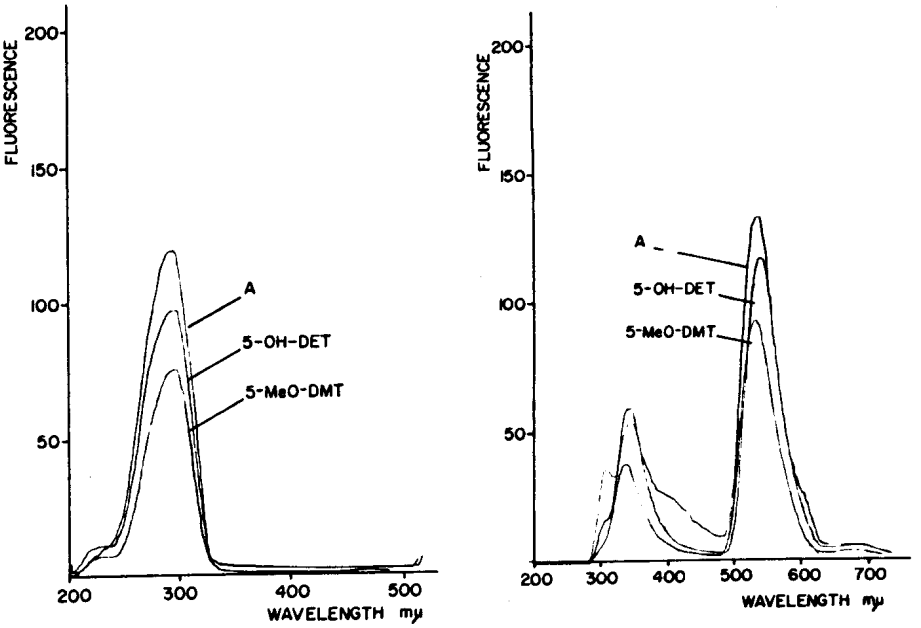

FIG. 9

Comparison of 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT), 5-hydroxy-N, N-diethyl-tryptamine (5-OH-DET) and fraction A (A). Medium 3 N HCl. Left activation spectrum. Right fluorescence spectrum at activation maximum 295 mμ. Fluorescence peaks at 340 and 540 mμ. Maximum at 540 mμ.

Bioassay.

In the VANE method for the bioassay of tryptamine derivatives serotonin (5-HT) was used as standard and bufotenine included in the experiments. When the curves for 5-OH-DET and 5-MeO-DMT were plotted they were found to coincide but showed separation from bufotenine. The bioassay may consequently serve to distinguish bufotenine from those two compounds but is of no use for the identification of fraction A (FIG. 10).

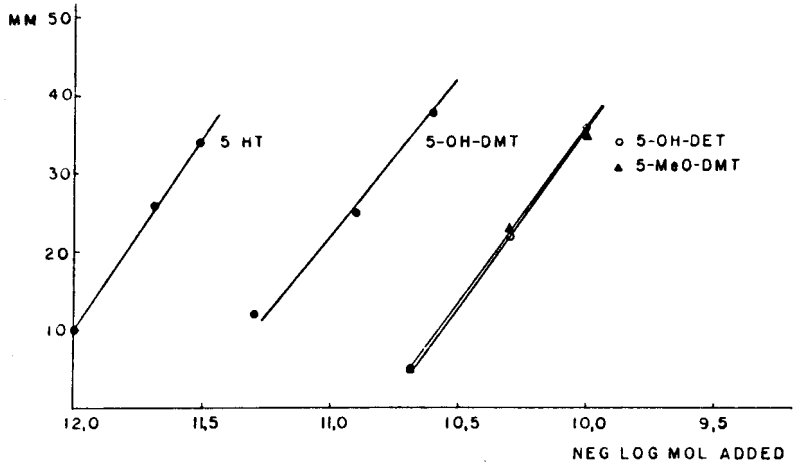

FIG. 10

Bioassay of tryptamine derivatives. *Abscissa* neg. log. mol. added. *Ordinate* contraction height in mm.

Modified rat fundus strip preparation according to Vane. 5 HT = 5-hydroxytryptamine. Explanation see text. Volume of test bath 5 ml. Volume of active substance added 0.25 ml.

DISCUSSION

Botanical considerations.

In spite of the careful investigations, mentioned in the introduction, the botanical origin of many of the snuffs used among South American Indians is still enigmatic. It emerges, however, more and more that several hitherto unknown constituents are included in these powders, contradicting the previous general belief that they were all made up with the seeds of *Piptadenia peregrina* as the active component. VON REIS (21) has carried out a careful study where the inhalation habits among West Indian and South American tribes have been related to the occurrence of the species *Piptadenia*. An important result of these

studies is the fact that in many places where the habit exists the species *Piptadenia* is not known to occur.

Many other reports indicate that several botanically different powders exist. SCHULTES (27) uncovered the use amongst certain Indians of Eastern Colombia and North Western Brasil of several species of the myristicaceous genus *Virola* in the preparation of an intoxicating snuff, employed by the medicine men in witchcraft divination and the diagnosis of illness. SCHULTES (27) verified *Virola calophylla* Warburg and *Virola calophylloidea* and possibly other species of *Virola*. The desired product is prepared by boiling the resin from the bark of the tree. An alkaline admixture of ashes of bark from a species of wild cacao tree (*Theobroma subincanum*) is added to the powder, and the resulting preparation is sifted to form the final snuff.

In his paper from 1954 SCHULTES (27) also describes other kinds of resinous snuffs, in all probability different from the one the making of which he himself witnessed and also tried personally. Further proofs for the different sources of powder to be inhaled are given by ZERRIES (41).

"The Tukuna and Uitoto, who can be considered to a certain extent as marginal, also use some kind of snuff". — "The Carenari, also a primitive Arawak tribe, snuff a certain green powder of a yet unknown kind".

Also in other anthropological literature we find evidence for the use of powders of many different origins (17, 25). KOCH-GRÜNBERG (17) describes the use of the bark of a tree for the preparation of the powder, whereas SALATHÉ (25) mentions a small plant as the origin. Everyone who has gone into the literature on this topic will agree with SCHULTES "that the identification of the botanical sources of South American narcotic snuffs in general and of these called Paricà in particular is in a state of extreme confusion".

Of particular interest to the present study are the botanical and ethnographical papers of SCHULTES (27), ZERRIES (42, 44), BECHER (2) and SEITZ (28). The plant material used for the isolation of tryptamine derivatives was obtained from SEITZ (28) who in his book and in a letter (1961) explicitly states the following (translation by the author):

"I have had occasion to see repeatedly the manufacture of the snuff. It contains the following ingredients: (1) The phloem of the bark of a tree (called Epená-Kesi). This phloem is dried, roasted and made into a powder. (2) The superficial parts of the bark of young trunks from an Acacia (called Ama-Asita). This is dried and burned to ashes (called Jupu-Uschi). (3) A herbaceous plant with a height of about 30 cm (called Maschi-Hiri) which is dried, powdered and mixed with the two other ingredients".

SEITZ obtained the powder and watched its preparation by the Waica Indians who inhabit the Orinoco head waters region and the adjacent

Brazilian area. Botanical material supplied by SEITZ has been mailed to Dr. Eberhard SCHMIDT (Abteilung Anatomie u. Pathologie des Holzes, Institut für Holzforschung und Holztechnik der Universität München), who states the following (26) (translation by the author):

"Messrs SEITZ and ZERRIES had only given small branches without leaves of the Brazilian 'Epená' to the institute in München-Nymphenburg, and one hoped that the wood anatomist would solve the question. In this case, I also came to the unequivocal conclusion that the specimen was *Virola*, fam. Myristicaceae. To my great content I afterwards found the following statement: *Engler-Prantl*, Die natürlichen Pflanzenfamilien, 2. Aufl., Band 17 a II, p. 193: The bark from *Virola calophylla* Warburg and the *V. calophylloides* Markgr. gives a narcotic snuff powder (Yá-ka, Yá-lo) used by various Indian tribes in the Amazon region and in Colombia".

It would thus seem as if at least one ingredient in the powder described by SCHULTES and SEITZ is the same and there is no reason whatsoever to believe that the seeds of *Piptadenia peregrina* are contained in the powder investigated by the present author. Also both BECHER (3) and ZERRIES (45) admit their ignorance of the exact plant origin of the powders they have described although they are aware of *Piptadenia* being used in similar material.

Equipment for inhalation.

The Waica Indians belong to a group of ethnologically related tribes called the Yanonámi who inhabit the region between the Rio Negro and Rio Branco in Northwest Brazil and who have been thoroughly investigated by ZERRIES (41, 42, 43, 44) and BECHER (2). In the Yanonámi tribes the equipment used for the administration of the powder consists of an oblong container for storage of the powder and a 60 cm long straight tube for blowing the powder into the nostrils. The latter is equipped at one end with a palm kernel through which a hole has been bored (FIG. 1). This end is fitted into the nostril of one person while another person blows the powder forcefully through the opposite end of the tube. It ought to be mentioned at this point that other equipments for the administration exist in other tribes. The usual apparatus used in connection with the snuffing of Paricà from *Piptadenia peregrina* is the frequently described bifurcated tube (24). This is used for self-administration by means of direct inhalation. A third variation is a V-shaped tube also used for self-administration where one end is put into the mouth and the other end into the nostril after which the snuff is blown into the nasal cavity. Finally, a fourth type of equipment should be mentioned, viz. straight tubes fitted together like an X and used by the Indians for simultaneous blowing of the powder into each other's

nostrils (6). It would seem difficult at the moment to associate any type of equipment with any specific type of snuff.

Customs. Effects of inhalation.

All available evidence points to the fact the use of the Epená powder at least originally had a strictly ceremonial purpose. It is used by chieftains and medicine-men in witchcraft divination and diagnosis and treatment of illness. Unfortunately, very few detailed accounts of the effects exist. ZERRIES (44) describes how in the Waica tribes individuals by repeated inhalation of the snuff become intoxicated and are then able to establish contact with the *Hekula*, the spirits of rocks and water-falls in order to induce them to bring mishap and sickness to the enemies of the village. The medicine-man becomes possessed by spirits, excited and sometimes looses consciousness. The best description of the use of Epená is the one given by BECHER (2) relating details about the religious use of the compound and how during the ritual the Indians become so obsessed with the spirits that they have to be exorcised during the ceremony. Under the influence of the drug the Indians identify themselves with the gigantic spirits of animals and plants Hekurá and also have the impression that they personify themselves the Hekurá (Surára tribe).

BECHER who became a member of the Surára tribe gives a rare description of his own experience when taking the snuff. His symptoms were the following (translation by the author):

"A few minutes (after taking the snuff) I felt a terrible headache and nausea just as the boy who comes in contact with the drug for the first time. Shortly afterwards I had a very strange experience. I felt myself to be a giant among giants. Everybody around me, people as well as dogs and parrots, seemed suddenly to have become giants".

In a letter BECHER (3) in answer to a specific question emphasizes that he felt himself to be a giant and that *all* people, animals and *objects, appeared magnified.*

SCHULTES (27) made a self-experiment in which he took about one third of a level teaspoonful of the drug into inhalations using the characteristic V-shaped birdbone apparatus by means of which the natives blow the powder into the nostrils. This represents about one quarter the dose, usually absorbed by the medicine men.

"The dose was snuffed at five o'clock one afternoon. Within 15 minutes a drawing sensation over the eyes was felt, followed very shortly by a strong tingling in the fingers and toes. The drawing sensation in the forehead rapidly gave way to a strong and constant headache. Within one half hour there was a numbness of the feet and hands and an almost complete disappearance of sensitivity of the finger-tips; walking was possible with difficulty, as in a case of beri-beri. Nausea was felt until about eight o'clock, accom-

panied by a general feeling of lassitude and uneasiness. Shortly after eight, I lay down in my hammock, overcome by a heavy drowsiness which, however, seemed to be accompanied by a muscular excitation except in the extremities of the hands and feet. At about nine-thirty, probably, I fell into a fitful sleep which continued with frequent awakenings until morning. The strong headache over the eyes lasted until noon. A profuse and uncomfortable sweating, especially of the armpits, and what might have been a slight fever lasted from about six o'clock all through the night. There was a strong dilatation of the pupils during the first few hours of the experiment. No food was taken and no tobacco was smoked from the time the experiment began until one o'clock in the afternoon — that is, for twenty hours during the course of the experiment".

Unfortunately, not many reliable accounts about the dose, latency to action and the duration of symptoms exist in the literature. Of particular interest is the latency to action. Some authors state that only few minutes occur between administration and the onset of symptoms (2, 27, 17, 25), whereas in other tribes a longer latency to action seems to exist. Concerning the dose SCHULTES states the following (27):

"The dose employed by the medicine-men is sufficient to put them into a deep but disturbed sleep during which delirious mumblings or sometimes shouts are emitted; visual hallucinations or dreams are reported to accompany the narcotic sleep very often. These are 'interpreted' by an assistant who awaits the prophetic or divinatory sounds. Some medicine-men, it is said, are affected more violently than others, and uncontrollable twitching of the fingers and facial muscles and a popping of the eyes are not infrequent symptoms. There is one report of the death, about twenty years ago, of a Puinave medicine-man on the Inirida River whilst he was under the influence of *yákeé*. Some *payes* (witch-doctors) are said to take *yákee* as frequently as 4 or 5 times a month; usually, so far as I have been able to ascertain, one doctor will not undergo the diagnosis-narcosis with *Virola* snuff more than once a month. All reports would seem to indicate that it is a dangerous narcotic".

Pharmacological considerations.

It is difficult from the scanty data in the ethnological literature to judge anything about the pharmacological action of the Epená snuff. The latency to action seems, however, to be short which may be explained by the means of administration (see below). The symptoms consist of an initial violent excitation and a subsequent sedation and sleep. This is no abnormal pattern for many centrally acting drugs. Of particular interest is the phenomenon of macropsia, i.e. the appearance of the surrounding as magnified. Macropsia is known to occur due to interference with accommodation and convergence caused for instance by local action of drugs in the eyes (7). A central action of the drug in question does, however, not seem to be excluded or possibly a combination of both.

Concerning the short latency reported by some authors and the unique means of administration, i.e. the forceful blowing of the powder into the nostrils, it ought to be pointed out that anatomical reasons have been

proposed for the direct action on the CNS of cetain drugs such as cocaine through the nasal mucosa. The following veins communicate directly with the cranial cavity : the concomitant veins of the *arteriae ethmoidales* and a vein which accompanies a ramification of the anterior ethmoidal artery. The last one is an important connection between the nose and the cranical cavity. This vein accompanies the artery through the ethmoidal plate and makes connection within the cranial cavity either with the network of veins of *Tractus* olfactorius or directly with a bigger vein in the orbital lobe.

All the vessels mentioned are accompanied by lymph vessels and it is conceivable that drugs can act directly on the brain without having to be transported through the general circulation. Experimental proofs for this are, however, lacking and it remains largely a conjecture.

The present work has dealt exclusively with the indole derivatives in Epená because of the wellknown action on the CNS of many of these compounds. Until a few years ago truly psychotomimetic indole derivatives were thought to be substituted only in the 4-position. LSD is the most wellknown of these substances, but there is by now also well documented evidence for the action of other compounds in this group such as psilocybin, (23, 13). With few exceptions no psychotomimetic action has been ascribed to the derivatives substituted in the 5-position. On the other hand, certain indoles without ring substitution have been shown to have the ability of inducing abnormal mental states, (4, 5, 36, 32). It now seems to be beyond discussion that indole derivatives without hydroxyl groups can cause psychotomimetic effects in man. This is valid for both dimethyltryptamine (DMT), diethyltryptamine (DET) and similar amines. According to SZARA (32) the central action of DMT and DET is closely related to the occurrence of *in vivo* hydroxylation in the 6-position, Ways of enzymic formation of psychotomimetic metabolites *in vivo* from normally occurring compounds have also been pointed out by AXELROD (1) and GOLDSTEIN *et al.* (11).

The mere fact that the Epená powder contains one wellknown psychotomimetic substance (DMT) is of considerable interest. The major component of the snuff, however, is 5-MeO-DMT which has been found earlier by classical isolation methods in the bark (sic!) of *Piptadenia peregrina Bent* (18) and in *Dictyloma incandescens* D. C. (20). The use of GLC methods provided the most important means of identifying this compound in the mixture.

Very few data concerning the pharmacology of 5-MeO-DMT are available in the literature. The animal experiments by GESSNER and PAGE (10) have, however, pointed to the strong action of this compound

on the central nervous system, and it is conceivable that it may play an important role in the elucidation of central nervous mechanisms.

The occurrence of 5-MeO-DMT in the ceremonial snuff of the Waica Indians calls for a thorough pharmacological study of its properties in animals and man, especially in comparison with its analogue bufotenine. Experiments concerning the central actions of the latter compound have so far yielded conflicting results (16, 36, 40).

The emergence from the great South American fountainhead of drugs of the Epená powder with its tryptamine constituents indicates that still many more pharmacologically important compounds may be found among primitive people. The inability to demonstrate under experimental conditions the central action of some similar snuffs (16, 36), should not prevent us from proceeding with experiments with the new drug.

It is difficult to correlate at the present stage chemical and pharmacological experiments to the effects experienced by Indians and explorers and this has induced some people to think that the psychical phenomena produced by these snuffs are entirely emotional. It is well known in connection with compounds like mescaline, LSD and psilocybin that the personality of the subject as well as circumstances during the administration influence the result. However, to attribute the widespread use of these snuffs only to emotional or external circumstances seems extremely unlikely. It is the firm belief of the writer that Epená is pharmacologically active even though its subtle pharmacodynamics still have to be elucidated.

Summary

A snuff commonly called Epená and used by some South American Indian tribes has been analyzed for its contents of tryptamine derivatives. The powder stems from the Waicas who inhabit the region between the Rio Negro and Rio Branco in North-west Brazil. The active components of the drug are derived from species of Myristicaceae (Virola calophylla *Warburg* and Virola calophylloidea *Markgraf*).

Epená is used by the natives in divination and diagnosis and treatment of illness. According to available descriptions it causes excitation followed by sedation and sometimes loss of consciousness. Changes in perception during the intoxication include among other things macropsia and possibly parestesia.

Because of the interest attached to the central action of tryptamine derivatives in modern psychopharmacological research special attention was focussed on this group of compounds. During the course of the

investigation both bioassay and conventional biochemical techniques were used. Eventually it was found, that gaschromatography provided the best means of identification of the components in the alkaloid fraction.

The main component of the Epená is 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). In addition, the drug contains small amounts of N,N-dimethyltryptamine (DMT) and 5-hydroxy-N,N-dimethyltryptamine (Bufotenine).

The botanical origin and ethnological use of Epená is discussed especially with regard to the pharmacology of the tryptamine derivatives contained in the powder.

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