Effect of Some Indolealkylamines on Man

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Throughout an arc described by the islands of the Caribbean, the shores of the Amazon, and as far as the western ridges of the Andes, in Colombia and Peru, there has been used since pre-Columbian times a snuff variously known as *cohoba, niopo, parica,* and *yopo,* among other designations.[1-11] With minor variations, this snuff is prepared from seeds of Piptadenia peregrina by grinding with calcined clam shells or wood ashes. It is inhaled or is forcibly blown into the nostrils of the person to be intoxicated by it. Descriptions of the action of the snuff vary somewhat, but the one we have previously reported,[12] given us by Dr. Jacques Fourcand, is typical. The inhalation of the snuff is quickly followed by rigidity and staring and, at times, a convulsion. This gives way to an excited state, which may last an hour more or less and in which there have been reported, among other phenomena, talking with and seeing God or distant persons. This is ostensibly a chief reason for the use of this snuff, since it lends itself to religious or witchcraft practices.

Other observers have described prolonged action of this snuff, with a violent activity lasting for hours. The dramatic effects have overshadowed the less spectacular response to *cohoba.* Safford [1] quoted explorers who saw it being taken by a medicine man, a chief, who, after sitting quietly for a long time, would tell of his visions and supernatural experiences. Other travelers commented on the fact that members of tribes of quiet and gentle culture would use the snuff in a pleasant social gathering, much, it would seem, as we use tobacco.

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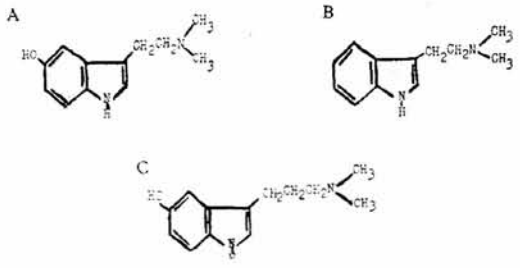
Ann Carl, B.S., and Lawrence Grolnick, B.S., participated in this study.

There has been the greatest difficulty in determining the amount of snuff absorbed. The descriptions we have been able to obtain of the tubes by which the snuff is taken indicate that they are leg bones of birds; the longest of these of which we have any report is about 7 in. and might contain 5 gm. of powder. Mr. Donald Overton, of the School of Tropical and Preventive Medicine, Loma Linda, Calif., wrote us that "they inhale approximately two level teaspoonfuls of powder, which produces a good 'drunk'." This amount would be equal to some 10 gm. and would contain about 100 mg. of total alkaloids. On the other hand, many reports state that only the least bit is taken, for it is quite powerful.

The alkaloidal constituents of Piptadenia seeds are 5-hydroxy-3-(2-dimethylaminoethyl)indole) (bufotenine), *N,N*-dimethyltryptamine (DMT), their respective nitrogen oxides, and a still unidentified indole [13,14] (Figure). This composition is of great interest, since bufotenine is the dimethyl derivative of 5-hydroxytryptamine, otherwise known as serotonin [15] or enteramine.[16] As is well known, serotonin is thought to be an ancient neurohumor.[17] Two theories of schizophrenigenesis have been proposed implicating disturbance of sero-



A, bufotenine; *B*, *N,N*-dimethyltryptamine; *C*, 3-(3-dimethylaminopropyl)indole (U-6056).
Bufotenine and dimethyltryptamine are both found in seeds of Piptadenia. U-6056 is not found in nature.

tonin metabolism,[18,19] both arising out of evidence that lysergic acid diethylamide (LSD-25) is a potent antagonist of serotonin action. Since LSD-25 produces hallucinations of sight, and, in some persons, more complex alteration of perception, thought to be similar to phenomena occurring in schizophrenias, the discovery of a plant capable of producing similar disturbances and containing, moreover, alkaloids which have been found to occur in animals, has provided a powerful support to the concept that a metabolic error of tryptophan metabolism is related to schizophrenia.

Fabing and Hawkins [20] reported that intravenous injection, over a three-minute period, of 8 to 16 mg. of bufotenine in human volunteers (convicts at a state prison) resulted in primary visual disturbances, alteration of time and space perception, and paresthesias. Except for the cyanotic flushing of the face, physiological effects were minimal, consisting of nystagmus, mydriasis, and slight and transient rise of blood pressure. This physiological action, we must note, is almost identical with that observed in hyperserotoninemia associated with carcinoid.[21,22]

Fabing [23] attributed the phenomenon of "going berserk" to intoxication from mushrooms, especially Amanita muscaria. It is relevant to note here that muscarine has long been considered the chief toxic constituent of A. muscaria,[24,25] that the intoxication produced by the plant lasts for many hours, and that the toxic principle is passed in the urine and may be reused. Fabing supposed this action to be due to bufotenine.

More recently, Hochstein and Paradies [26] have isolated about 3 gm. of *N,N*-dimethyltryptamine (DMT) from 2 liters of an aqueous extract of the leaves of Prestonia amazonica. This plant, denoted as Haemadictyon amazonicum by many writers, has been implicated as an intoxicant on a number of occasions. Lewin,[2] for example, thought that it was used to potentiate the hallucinogenic activity of Banisteria caapi in the drink called variously *caapi, yajé, ayahuasca,* etc., or that it was used alone in a decoction called *yagé.* The literature on this is too involved to go into at this time, but the demonstration of DMT in a plant reputed to have hallucinogenic or narcotic properties when taken by mouth would of itself require study of the psychic action of the compound.

At the present time two reports dealing with the action of DMT in man have appeared. Both of these concern the action of DMT injected intramuscularly into nonpsychotic volunteers. St. Szára [27] reported on 20 subjects who received 0.7 to 1.1 mg. per kilogram of body weight. Briefly, he "found it to have a psychotic effect similar to that caused by mescaline or LSD-25. The main symptoms are visual hallucinations and illusions, distortion of the spatial perception and body image, disturbances of thought and speech, and euphoria. . . . This model psychosis differs, however, from those hitherto known in some respects; the most striking difference is that the psychic symptoms appear in three to five minutes after the injection and pass away within one hour. This mode of action suggested the direct connection of the psychosis with the introduced DMT."

Arnold and Hofmann [28] administered the compound to psychologists, among whom one had had experience also with *N,N*-diethyltryptamine and with LSD-25. The observations of St. Szára were confirmed in detail, but the one observer considered that LSD-25 produced intenser and more frequent impressions of movement, with less marked color disturbance.

The work described above was carried out with nonpsychotic volunteers, with the thought that a "schizophrenia" might be induced. It has seemed to us necessary to test the action of these materials on persons already schizophrenic. It might be reasoned, for instance, that the nonschizophrenic has enzyme systems within the limbic lobe which are capable of rapid destruction of a tryptophan-containing polypeptide which is offered for fragmentation

at neuronal microsomes, and that this destruction goes on via serotonin in these persons, whereas in schizophrenia this does not occur, but, rather, a slower process over another pathway becomes the limiting "master reaction." Under these conditions it might not be possible to render a normal person the equivalent of a schizophrenic, even if the factor of acuteness of symptomatology were not relevant. On the other hand, the introduction to the already burdened schizophrenic of a substance which would specifically increase his metabolic load might aggravate or lead to recrudescence of a psychosis, whether or not acuteness of reaction were relevant.

Materials and Methods

Piptadenia seeds were procured in Puerto Rico in March, 1956, collection being made under the guidance of Mr. Harold J. Winters, of the Experimental Agricultural Station at Mayagüez. The trees, pods, and seeds conformed in all respects to the description of Safford.[3] Seeds from the same trees were used by the workers of the National Institutes of Health, at Bethesda.[24] Snuff was prepared from these seeds by drying and pulverizing, and the addition of a little lactose. Another sample of snuff was obtained, through the courtesy of Miss Siri von Reis, as *yopo*, originally being sold in Peru by a *curandero*. It was in the form of a dark-brown mass, from which the snuff was made by pulverizing and, on one occasion, by warming the powder in a watch glass in an oven at about 110 C. A third sample of snuff was obtained from Prof. Otto Zerries, of Frankfurt, brought back by him from an expedition into the headwaters of the Amazon, where he had witnessed and photographed the administration of this snuff.[10]

Bufotenine, *N,N*-dimethyltryptamine, and 3-(3-dimethylaminoprophyl)indole have been supplied as free base and, in sterile ampules, as the creatinine sulfates, through the courtesy of Dr. Merrill Speeter, of The Upjohn Company. Preliminary toxicology was carried out on these compounds both by The Upjohn Company and by ourselves, using fish, mice, rats, and dogs.

For studies of snuff, one of us first endeavored to produce an intoxication in himself. Thereafter, schizophrenic subjects were tested throughout. These subjects were in various clinical states. All had EEG and EKG recordings run concomitantly with and following the administration of the snuff and of the pure indolealkylamines. Measurements of physiological variables were made at intervals on most occasions. In a number of instances tape recordings were made of interviews, which could be compared with those made on other occasions, without medication or after injection of, e. g., amobarbital (Amytal) sodium or isopropylnorepinephrine. Most subjects were well known to the examiners and had been interviewed repeatedly in other connections.

Results

Snuff.—We have been unable to induce an intoxication by the use of snuff prepared from Piptadenia. The largest dose of this we have employed was 560 mg., containing approximately 6 mg. of bufotenine. This was blown forcibly into the nostrils, as is the custom among the Haitians and Peruvians. It could be retained only for three minutes before violent gagging, coughing, and sneezing led to the rejection of most of the mass. A communication from Dr. Harris Isbell, of the U. S. Public Health Service Hospital at Lexington, Ky., states:

"*Cohoba* snuff was taken intranasally. It was available as 'raw' material, roasted snuff, fermented snuff, limed snuff, fermented and roasted snuff, fermented and limed snuff, and as fermented, limed, and roasted snuff. These various types of snuff were prepared by the Chemical Section of the National Heart Institute. Neither subjective nor objective effects were observed after inhalation of as much as 1 gm. of the snuff repeated at intervals of 30 minutes. The dose, of course, was unknown, since patients sneezed, coughed, and, in general, discharged most of the snuff." *

Bufotenine.—When pure bufotenine base or bufotenine as creatinine sulfate was blown into the nares, symptoms first began at about 6 mg. Up to 10 mg. the only symptoms were a feeling of fear, associated with flushing of the face, lacrimation, tachycardia, and tachypnea. Dr. Isbell observed: "No subjective or objective effects were observed after spraying with as much as 40 mg. of bufotenine creatinine sulfate." *

Reactions have been observed following the intravenous administration of bufot-

* Dr. Isbell permitted us to quote from his letter of Oct. 4, 1956.

enine into 14 schizophrenics. At a rate of 5.3μg. per kilogram per minute, 20 mg. was injected into one subject during a 77-minute interval with no psychological changes, and with physiological changes limited to slight decrease of alpha voltage and the appearance of some 5- to 7-cycle activity in the EEG. However, when the same subject received 10 mg. (204μg. per kilogram) during a 50-second interval, the effects were extreme. At 17 seconds there was flushing of the face. At 22 seconds there was maximal inhalation, followed by maximal hyperventilation, as to both rate and volume. This persisted for about two minutes, during which time the patient was unresponsive to stimuli, her face was reddish blue ("plum-colored"), and she became slightly restless. At the onset of flushing the EEG had already begun to show 5- to 7-cycle waves. With the onset of hyperpnea the activity dropped to about 3-cycle waves and continued to drop until at three to five minutes it was a ½- to 1-cycle wave per second with amplitudes up to 150μv.-200μv. During the third minute there was a period of apnea. In several subjects who had more than 10 mg. of bufotenine injected quickly, there was intense salivation. The present subject could easily have drowned in her own saliva, and she had to be turned on her side. The pulse rate rose slightly during the period extending from the end of the injection until some 10 minutes later, but without much change in blood pressure. Responsiveness returned at about 23 minutes, at which time the patient was entirely lucid and, in response to a query related to a preinjection suggestion, spoke of a long-repressed memory from the age of three years, when she came into the bathroom and saw her mother dying of a uterine hemorrhage. This was told without affect and had no therapeutic consequence.

Because experiments with dogs had suggested that fear associated with the injection could be avoided by this means and that there might be a later relief from anxiety, five patients had injections as they were coming out of insulin coma or following EST. In further investigation along this same line, patients had injections following reserpine (one subject) and following chlorpromazine (two subjects): Each of these injections almost proved fatal in small amounts (between 2.5 and 5.0 mg.). The patient who had had reserpine ceased to breathe after but one deep inhalation and resumed breathing only after a minute or so of artificial respiration. Injection in the chlorpromazine instances resulted in sharp drop of blood pressure and gallop rhythm of the heart.†

When the rate of injection was in the range of 100μg. per minute, the blood pressure usually showed a moderate rise and the pulse rate increased somewhat, but there were no EKG changes. Pupils usually dilated moderately for a short while. There was the marked flush which was noted by Fabing and Hawkins [20] and described above. This extended over the face, neck, and upper chest and involved the hands and feet more or less. Never have we obtained evidence of disturbance of sensation of any modality, particularly no visual or auditory disturbance aside from that associated with loss of consciousness. Abdominal distress and feeling of the need to defecate or to urinate were observed at times.

Psychologically, we have not noted any evidence that the patient's psychosis was aggravated, or relieved, either immediately following injection or later. It is true that at higher doses patients became frightened to an extreme degree, and one might expect thereafter accentuation of their defenses: but this did not occur.

Dr. Isbell's subjects reported elementary visual hallucinations after intramuscular doses of 10 to 12.5 mg. "These consisted of a play of colors, lights, and patterns." None of our subjects reported any such phenomena. It must be added, however,

† Dr. Isbell requests that we note from his experiences with intramuscular bufotenine that "in the EKG marked accentuation of sinus arrhythmia with fluctuating P-R interval was observed. In about half the cases, ventricular escape occurred with low nodal beats appearing."

that most chronic schizophrenic subjects do not report visual hallucinations after intravenous administration of mescaline.[29]

N,N-Dimethyltryptamine (DMT).—Intranasally, DMT powder has been administered to one of us and to four subjects, in amounts of 5 to 20 mg., with no effect other than a burning sensation in the back of the nose and throat. Once, with 10 mg., a patient reported a feeling of being "hit on the head"; this sensation was concomitant with unilateral flushing of the face and mydriasis.

Oral administration of DMT in single doses up to 350 mg. was completely without effect, physiological or psychological, in more than 10 trials.

Intravenous administration of 5-25 mg. within a three-minute period had no effect on the EKG or the EEG in five subjects, except that anxiety, which was evident clinically, was associated with low-voltage fast EEG activity in a subject who received 15 mg. Psychologically, the injections above 10 mg. seemed to be associated only with anxiety and some restlessness, but there was no evidence of disorientation. Visual disturbances were not in evidence; patients could read and recognize objects, hear, and respond appropriately to requests, such as, for instance, the request to close their eyes for the EEG.

It was only a week or so after the injections that we learned that psychological changes had indeed occurred, particularly with C., who complained to her sister that the injections (she had three: 5, 10, and 15 mg.) made her feel like an animal; she saw the nurses as rubber dolls and the walls as crumbling paper. This was like she had felt six years before, when she had come in the hospital; lately she had been better and did not like to have these things happen again. Control injections with saline did not produce such effects. Other patients who had the larger doses of DMT did not make any such complaints, but we cannot be sure they did not have similar experiences.

Intramuscular injections varied from single daily injections of 5 mg. for a week, up to 40 and 50 mg. in a single dose, in 10 subjects. The smaller doses were completely without effect. Nine subjects received intramuscular injections of 25 mg. or more. Each of these exhibited responses objectively; two were able to give a verbal report at the time, and one has been able to amplify this so fully that her response warrants special attention.

A., a woman, born in 1923 in New York, of Italian descent, was 57 in. tall and weighed 88 lb. She had always been dependent, was the baby of the family, and was told what to do and when to do it by anyone who felt moved by her helplessness. Following the onset of her psychosis, in 1947, she had several short periods of hospitalization, but most of the ensuing nine years was spent at home. For nearly a year following readmission in 1956 this patient was so withdrawn that practically no communication could be established. She was able to reply briefly to leading questions, but never offered spontaneous speech. Indeed, when she spoke, it was through lips that scarcely opened. On June 21, 1957, she received 50 mg. of DMT intramuscularly. The protocol of this injection follows.

10:40 a. m.: B. P. 90/70.
50 mg. DMT given intramuscularly.

10:45 a. m.: Patient feels strange, "can't stand it," needed to be taken to bed because she felt weak and fainting. She also complained of blurred vision.

10:50 a. m.: B. P. 50/90.
Patient showed tremendous anxiety, saying: "I want my mother; I am afraid of fainting; I can't breathe." Suddenly she would become angry and say: "I hate you. What have you done to me?" [to the interviewer] and began crying and screaming.

11:00 a. m.: Patient continues confused and anxious. "What do you want from me? Everything is blacking out. I love my mother so much." Asked why, she became very angry and said: "Because she is my mother. What else?" She complained that she could not breathe and called on the doctor for help.

11:05 a. m.: B. P. 150/90.
Patient feels cold and begins to tremble. She is very worried and asks: "Did I faint or something?" She asks for water.

11:10 a. m.: Patient seems in a dream-like state, continuously rambling in her conversation.

11:15 a. m.: Patient stopped trembling and had the appearance of waking from a dream. "I am here in Islip now. It is as if I were away from here for such a long time." "Where were you all this time?" "In a big place, and they were hurting me. They were not human. They were horrible (crying). I was alone. My mother left me. I don't want to die (with an expression of agony on her face); I was living in a world of orange people."

11:20 a. m.: Patient continues to show tremendous anxiety and remains in a dream-like state. "My mother hates me. All my family hate me. She gave me a party when I was 5. We suffered so much in the depression. She hates me because I look like my father. I wish I was like my mother." At times she would repeat: "I love my mother; she loves me," as if she were reciting a lesson. Suddenly she began crying again and screaming: "I love ————. My mother didn't let me marry him."

11:40 a. m.: B. P. 90/70.
Patient is still fearful, rambling and confused. She suddenly stopped rambling and asked the interviewer: "You are Dr. E. Did I faint?" She seemed to be very concerned about this.

12:00 m. to 1:30 p. m.: Patient continues confused and is talking continuously.

1:30 p. m.: Patient suddenly sat up in bed and said: "I am awake now." She was in good contact, relevant and smiling. However, she did not remember "after the injection." She remained in good contact for the rest of the day.

June 22, 1957

8:00 a. m.: Patient was confused and suddenly embraced a male attendant, calling him by her brother's name.

9:00 a. m.: Still confused, rambling, anxious and trembling. Reserpine, 2.5 mg., was given intramuscularly.

9:30 a. m.: Patient sleeping quietly; no trembling evident.

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In group psychotherapy today the patient said that she is still "going into the past" from time to time. She said that since yesterday she has felt more herself than ever in her life. "My hair seems to fall into place now. . . . It used to be when I combed it it wasn't my own and it would just fall flat." Again she said: "Even my thoughts and my face seem to be more real. My face used to seem to me like I had sunken spots at my eyes. Now I have eyes and cheeks."

This patient continued to work with one of us intermittently through the rest of the year. From time to time she would communicate; e. g., she would say that when she first became psychotic, she noticed that every time she walked around the corner, so that she was out of sight of her family, she would hear voices enticing her into bars, telling her that there were whores in the back and they would like her to join them. As soon as she returned around the corner toward her home, the voices would stop. She believed she could be seen by people on TV, who could read her thoughts.

On Jan. 14, 1958, this patient had 75μg. of LSD-25 by mouth. She became terrified; she clung to the attendants and to the doctor and claimed that her life was being reenacted before her, that she could no longer hold back all the thoughts that came; she felt that she was going into a bottomless pit, and there was no hope. She had a long interview,[30] followed by pentobarbital (Nembutal). In the days following she had intensive psychotherapeutic contacts with several interested associates. Later, in a meeting with her mother and brother, she revealed that her mention of the "orange people" at the time of her DMT injection was a reference to her sister, who had once told her that her bleached hair looked orange, like that of a local prostitute. This patient had been hallucinating for years, and all that she experienced under DMT was nothing new, only the eruption into speech of that of which she was conscious and which had been held back between her closed lips. This happened again with LSD, but the action of the latter drug was more prolonged and more terrifying. The whole experience had a salutary effect upon the patient. At the time of writing there is a virtual cessation of translation of her thoughts into physical sensations and perceptions.

Each of the nine subjects who received 25 mg. or more of DMT became restless, actively withdrawing from contact, with one or more evidences of fear ("You frighten me." "What have you done to me?"), and with occasional utterances or movements indicating that they were seeing things or expected to see something. There were complaints of dizziness and of expecting to faint. Three said that they were unable to keep their thoughts under control. "I think, doctor, that I am acting irrationally." With

this there were periods of perplexity and of irrelevant or incoherent speech, while the subject stayed in contact sufficiently to complete drawings for psychological tests.

On one occasion, which essentially terminated our study of this compound, a patient who received 40 mg. intramuscularly, and who had been extremely tense and apprehensive, suddenly developed an extremely rapid heart rate 12 minutes after the injection; no pulse could be obtained; no blood pressure could be measured. There seemed to have been an onset of auricular fibrillation. The patient moved at this time and tore off the EKG leads. Extreme cyanosis quickly developed. Massage over the heart was vigorously executed, and the pulse returned after a lapse of some 30 seconds. Shortly thereafter the patient, still cyanotic, sat up. Color returned quickly. At 15 minutes after the injection she was able to see well, and to respond to a microphone by saying: "Take that away. I don't like them." Eighteen minutes after the injection she stood up and demanded to return to the ward. It was quite evident that this patient had no delirium. The electroencephalogram showed no change which would lead us to think that there was action on the central nervous system. The patient's defensive solution had been to retreat, to become quieter, more passive and acquiescent. In the period immediately following the injection, after she returned to her bed, and in the days following, she remained very acquiescent and passive.

3-(3-Dimethylaminopropyl)indole (U-6056).—U-6056 has been injected into 10 subjects, the first 2 having received 5, and then 10 mg., intravenously, and the remaining 8 subjects having received from 20 to 70 mg. intramuscularly. In the maximum doses the only consequences were a slight rise in blood pressure toward the normal from a preexisting hypotension, and a rise in pulse frequency. Mild agitations reflecting anxiety were felt about 20 minutes after the injection. A subject who received 60 mg. intramuscularly had involuntary coughing 20-25 minutes after the injection, but with 70 mg. another subject showed no effect. There was no disturbance of vision with eyes open or closed, no disturbance of auditory or tactile sensations. The patient who received 70 mg. was an almost mute woman who half-smilingly mumbled, almost incomprehensibly, in reply to all efforts at communication. The doctor who knew this patient best, and who gave her the injection, observed her for two hours thereafter and reported that there was neither physiological nor psychological change in this subject.

Comment

Our work was started with the hope that investigation of the action of *cohoba* would throw some light on the neuropharmacology and neurophysiology of the central nervous system, which, in turn, might clarify some theories of schizophrenigenesis. Inability to produce intoxication in normals or in schizophrenics by maximally tolerated amounts of snuff, prepared in a variety of ways according to Indian methods, brought us to a dead end in this immediate regard. We were convinced that the South American Indians who take *niopo* and *yopo* snuff were able to tolerate 10 gm. of snuff. This contains some 50 mg. of bufotenine and 10 mg. or less of DMT. The production of intoxication would require that at least 50% of the former and all of the latter be taken into the blood stream within a three- to five-minute period. When it is considered that amines are inhaled with a large amount of "inert" carrier, and that even the pure compound administered intranasally is ineffective, the difficulties become so great that we must reject bufotenine and DMT as capable of producing the acute phase of *cohoba* intoxication. As to the longer-lasting effects of snuff, the properties of neither amine are such as to suggest their participation. It may be added that these properties likewise do not conform to the intoxication of A. muscaria, or to that of Prestonia amazonica. Further, among some tribes the Piptadenia

is taken as an enema, with intoxication lasting for hours.[4]

As to what other constituents produce the intoxication, we must be cautious. For instance, Gumilla, in 1741, wrote[3]:

> That which they add to it [the snuff], through the ingenuity of the devil, is what causes the intoxication and the fury. After eating certain very large snails which they find in the inundated areas along the river, they put their shells into the fire and burn them to quicklime, whiter than snow itself. This lime they mix with the *yupa* in equal quantities, and, after the whole is reduced to the finest powder, there results a mixture of diabolical strength; so great that in touching this powder with the tip of the finger, the most confirmed devotee of snuff cannot accustom himself to it, for in simply putting his finger which touched the *yupa* near to his nose he bursts forth into a whirlwind of sneezes.

The active agents in the hallucinogenic mushrooms[31] of Mexico will withstand only a few months of drying out.[32] The red oil of hashish rapidly changes its activity when it is exposed to oxidation.[33] On the other hand, it is not impossible that under the conditions of preparation of active snuff, i. e., heating it in the presence of excess calcium oxide, an oxidative transformation of the amine occurs. Suggestions along these lines, such as, for instance, those of Sherwood,[34] are readily constructed but are difficult to test. Bufotenidine, for instance, does not exert a prolonged action on mice, according to Ueda.[35]

As far as our data go, there is nothing to suggest that bufotenine plays any part in the secondary manifestations of schizophrenia. This cannot be said for DMT, which is indeed hallucinogenic to normal persons. In the two schizophrenic subjects who reported their experiences, especially A., we were able to learn that DMT intensified an already existing "primary process," i. e., the transformation of a concept into a percept. This action was not due to fear alone, as other medications had not had the same effect, although they alarmed the subject, and certainly the terrifying experience of bufotenine injection had no such consequence.

We are not thereby led to conclude that an indolealkylamine, such as DMT, is a "cause" of schizophrenia. In a field where experience may be so fallacious and judgment so difficult, we do not feel justified in making further statements.

As to U-6056, the thought had been that its side-chain might render it less susceptible to oxidative attack than DMT, and its action might be more intense and prolonged. Its failure in this regard will be of interest to biochemists concerned with the relationship between chemical constitution and biological action.

Summary

Snuff prepared from seeds of Piptadenia peregrina, of Puerto Rico, has not been found capable of producing the intoxication attributed to it by natives or by explorers, who have described the use of these seeds under the names *cohoba, parica, yopo,* and *niopo.* Two major constituents, bufotenine and dimethyltryptamine, did not appear capable of inducing the reputed action of the snuff, or that of Amanita muscaria. Bufotenine, up to 20 mg. intravenously, did not produce hallucinations in schizophrenic subjects, despite profound EEG changes, loss of consciousness, and intense peripheral action of serotonin character. Dimethyltryptamine had less intense physiological action but, above 20 mg. given intravenously or intramuscularly, eruption of preconscious ideations occurred. The action of both compounds was very rapid in onset and of brief duration. The compound 3-(3-dimethylaminopropyl)indole had no physical or psychological effect when given up to 70 mg. intramuscularly.

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The literature on Piptadenia and its use is very extensive, but generally either confused or repetitious. We have searched this rather thoroughly, aided in part by Miss Siri von Reis, Department of Ethnobotany, Ames Herbarium, Harvard University, who permitted us to read the manuscript she is preparing for her Ph.D. thesis. This is the

most complete and authoritative work on the subject we have seen. The references below are selected for their general availability or their special interest.

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