Psilocin, Bufotenine and Serotonin: Historical and Biosynthetic Observations

W. SCOTT CHILTON;* JEREMY BIGWOOD** & ROBERT E. JENSEN*

The structural relationships between psilocin, its isomer bufotenine, and the neurotransmitter serotonin are well-known. The structural similarity is thought to be intimately involved in the action of psilocin as an hallucinogen when the brain serotonin is overwhelmed by a flood of psilocin, although this mechanism is not yet understood in detail on the molecular level. It is well to remember, however, that serotonin has important peripheral nervous system effects as well as its effects in the brain and was, in fact, first detected and isolated from the observation of its effect in constricting the blood vessels (an effect noted by Ludwig as early as 1868 and studied by Ersparmer from 1930 on).

When blood clots, a potent vasoconstrictor passes from the disintegrating platelets into the serum and helps to restrict bleeding from small vessels before they are closed by clots. Ersparmer named the elusive principle with these properties "enteramine" in 1930, but the credit for pursuing and isolating this factor as a crystalline chemical goes to Maurice Rapport, Arda Alden Green and Irvin Page at the Cleveland Clinic in 1948. Hence we know this factor by the name Rapport gave it, serotonin, revealing its provenance, blood serum, and its physiological function, maintenance of the tone of the blood vessel walls. On the basis of chemical characterization and elemental analysis, Rapport quickly proposed the correct structure for serotonin, at first a 5-hydroxyindole with a C_2H_8NO side chain, refined to $C_2H_6N + H_2O$, by recognition that serotonin crystallizes with a molecule of water, and by Rapport's *hunch* that the remaining C_2H_6N would be an ethylamine side chain (Rapport 1949), "by analogy to those compounds known to exert such powerful pharmacological effect," such as epinephrine (adrenaline) and mescaline. Rapport's hunch was proved by the unambiguous synthesis of serotonin by Speeter and coworkers at the Upjohn Pharmaceutical Co. in Kalamazoo, Michigan in 1951. Subsequent research at Upjohn led to one of the major routes for synthesis of tryptamines, including DMT: the Speeter and Anthony oxalyl chloride route in 1953.

In the early 1950s detection and wet chemical analytical techniques were developed for serotonin based both on its being an indole and on the presence of a phenolic group. Many studies appeared on species and organ distribution of serotonin, including the first report of its occurrence in mammalian brain in 1953. One of the first suggestions that serotonin might play a role in the brain was put forward in 1954 by Woolley and Shaw of the Rockefeller Institute. This tentative conclusion was based on a study of a variety of *anti*-serotonins (Woolley & Shaw 1954).

> Thus ergot alkaloids, harmala alkaloids and yohimbine function in smooth muscle as anti-metabolites of serotonin. These natural drugs are structurally related, each in a different way to serotonin. Among each of these classes of compounds are substances that

*Department of Chemistry, University of Washington, Seattle, Washington 98195.

**The Evergreen State College, Olympia, Washington 98505.

> cause mental aberrations . . . LSD, harmaline, yohimbine . . . are such representatives. The demonstrated ability of such agents to antagonize the function of serotonin in the smooth muscle, and the finding of serotonin in the brain suggest mental changes caused by the drugs are a result of a serotonin deficiency which they induce in the brain.

Bufotenine, the dimethyl derivative of the neurotransmitter serotonin, was isolated as a pure chemical by Handovsky 30 years before serotonin as one of the minor components of a toxic secretion of the toad (Handovsky 1920). The secretion is a complex mixture of substances, each with its own physiological effect, but its major lethal effects are ascribed to digitalis-like cardiotoxins. The toad's warty poison glands are found behind each ear. The cells of the glands develop to enormous size, their entire plasm becoming the secretion. When the poison is discharged, one of the surrounding undeveloped glands grows to replace the discharged gland. The secretion can be collected by squeezing the parotid gland with forceps, catching the secretion as it spurts out in a large bowl held inverted over the toad. It quickly dries in air to form hard, brittle yellow scales. Administration of highly diluted toad toxin by injection into animals causes slowing of the heart until it comes to a complete stop in the contraction phase. Many scientists noted in the 19th century the similarity in action of toad secretion and digitalis.

Figure 1. Chinese toad from Pen-ts'ao Kang-Mu

The discovery of the toxicity of toad secretion probably occurred in prehistoric times in the major continents where toads live. Juvenal (60-128 A.D.) described the use of toads by Roman poisoners. The Chinese pharmacopoeia *Pen-ts'ao kang-mu* describes a drugs, chan su (= Japanese senso), prepared from dried toad skins (Figure 1). Toad drugs are contained in the European pharmacopoeias, *Thesaurus Pharmakologicus* by Johannes Schröder (Leyden, 1672), *Pharmacologia* by Samuel Dale (London, 1692) and in *The London Dispensatory* by William Salmon (London, 1702). Preparations were recommended for dropsy, fever and incontinence of urine. Michael Etmüller, professor of medicine at Leipzig, recorded about 1670 what was certainly not a new observation: "living toads aroused to the point of fury are venomous, but found dead, they are entirely devoid of poison." He was undoubtedly referring to the presence or absence of the toxic surface secretion. This widespread knowledge in the Old World is probably the basis on which the *Talmud* differentiates the toad[1] from the frog and classes it with the animals whose touch contaminates — a belief that persists today in European cultures.

Lacerdo de Filho reported (Abel & Macht 1911-12) in 1878 that natives of the Amazon made an arrow poison from the giant toad *Bufo agua* "whose venom it would be worthwhile studying." Pagenstecher in 1906 cited use of a toad arrow poison by the Choco Indians of Colombia which was prepared by heating a toad in a bamboo tube over a fire (Abel & Macht 1911-12). "The toad soon becomes covered with a yellow juice which is collected in small pots in which it gradually acquires the consistency of curare." The toads are apparently not killed in the process since Pagenstecher states that a further supply of poison can be obtained from toads thus treated. "The poison is smeared onto the tips of arrows which are shot into game from blowing tubes . . . a jaguar is killed by a poisoned arrow in from 4 to 8 minutes."

European poisoners' recipes for extracting toxin

survive from the 16th century (Lewin 1920): "Place a toad in a sack with a little salt and shake well. Use the salt for giving to men." Such salt was recommended by Italian poisoners for slow, chronic poisonings. A modification of this procedure was used to put toad toxin on cannon shot and to toxify saltpeter used in making gunpowder. Such shot was used at the seige of Groningen in 1672 where it was, doubtless, completely ineffective.

The toad secretion is a complex mixture of neurotransmitters and cardiotoxins. The more dramatic lethal effects are certainly due to non-alkaloidal, digitalis-like, dienolide cardiotoxins, whose discovery and chemistry have been outlined by Deulofeu (1948). The presence of nitrogenous alkaloids related to mammalian hormones was suspected at the beginning of the 20th century. Vasoconstricting effects of diluted toad secretion placed in the eye were noted by Abel and Macht (1911-12) at Johns Hopkins. John Abel had been testing the toxicity of synthetic dyes with a number of experimental animals including the tropical American toad *Bufo agua*.

> While engaged in this study our interest was aroused by the milky secretion which exuded from its parotid glands when the animal is greatly irritated. Scraping off . . . the secretion with a knife, we were struck by the bluish-green discoloration which appeared on the blade. This led us to test the secretion with ferric chloride.

The color reaction with ferric chloride led Abel to suspect that "we were dealing with a substance which is identical with the suprarenal principle." Abel had earlier (1897) isolated the alkaloidal vasoconstricting principle of the suprarenal or adrenal gland of sheep, which he named epinephrine.[2]

The Austrian chemist Handovsky reexamined fresh toxin at the University of Prague during World War I. He isolated a further crystalline alkaloid from toad secretion to which he gave the name bufotenine, a name first suggested by the French scientists Phisalix and Bertrand in 1893. Handovsky found that he could produce an intense carmine red color on a pine splint by dipping the splint first into a solution of the new alkaloid and then into concentrated hydrochloric acid. This test is essentially the equivalent of the more frequently used Ehrlich test for indoles and pyrroles. Because of difficulties in obtaining accurate elemental analyses for bufotenine, Handovsky thought he had isolated a pyrrole rather than an indole. It was not until 1934 that Heinrich Wieland's lab in Munich showed that bufotenine is actually an indole and proposed the correct structure, which Toshio Hoshino confirmed two years later by synthesis in Tokyo.

Early pharmacological testing of bufotenine was limited by the small supply available either by isolation or synthesis, as well as by experimenters' preoccupation with its demonstrated effects in raising blood pressure. Thus experiments such as Handovsky's, carried out on decapitated cats, were specifically designed to *preclude* observation of any central nervous system effects.

The recognition, beginning about 1953, that the unmethylated analog of bufotenine, serotonin, is probably a natural central nervous system neurotransmitter involved in the mechanism of action of LSD and the isolation of bufotenine (along with DMT) in the same year from the hallucinogenic snuff cohoba, indicated the desirability of testing bufotenine for central nervous system effects in man. Several of these tests in man had been completed by the time Albert Hofmann disclosed that the potent hallucinogen psilocin is an isomer of bufotenine. Some of the early work, while reporting rather similar observations of the effect of bufotenine in humans, came to conflicting conclusions about the central nervous system effects of this indole. In 1955 bufotenine was administered by intravenous injection in increasing doses, up to 16 mg, to prisoners at Ohio State Penitentiary under the supervision of Fabing and Hawkins (1956). At the highest dose the subject's face turned a livid purple and he experienced a generalized tingling of the body. During the third minute he vomited. "At that time he saw red spots passing before his eyes and red-purple spots on the floor, and the floor seemed very close to his face. Within two minutes these visual phenomena were gone, but they were replaced by a yellow haze, as if he were looking through a yellow lens filter." The subject's face, which was described as having the unique purple hue of an eggplant, returned to its normal color at the end of an hour. Based on this very limited observation Fabing and Hawkins commented that bufotenine's effects are reminiscent of LSD and mescaline, and later referred to the hallucinogenic effects of bufotenine.

Dr. Harris S. Isbell at the Public Health Service Hospital in Lexington, Kentucky experimented with bufotenine as a snuff. He reported (Turner & Merlis 1959) in 1956, "no subjective or objective effects were observed after spraying with as much as 40 mg bufotenine." However subjects who received 10-12 mg injected intramuscularly reported "elements of visual hallucinations consisting of a play of colors, lights and patterns." Turner and Merlis (1959) experimented with intravenous injection of bufotenine into schizophrenics at a New York state hospital. They reported that when the subject received 10 mg during a 50-second interval,

"the peripheral nervous system effects were extreme: at 17 seconds, flushing of the face; at 22 seconds, maximal inhalation, followed by maximal hyperventilation for about two minutes, during which the patient was unresponsive to stimuli; her face was plum-colored." Finally Turner and Merlis report that:

> on one occasion, which essentially terminated our study, a patient who received 40 mg intramuscularly, suddenly developed an extremely rapid heart rate; no pulse could be obtained; no blood pressure measured. There seemed to have been an onset of auricular fibrillation . . . extreme cyanosis developed. Massage over the heart was vigorously executed and the pulse returned to normal. . . . Shortly thereafter the patient, still cyanotic, sat up . . . saying: "Take that away. I don't like them."

After pushing dosage levels to the morally admissible limit without observing hallucinations, Turner and Merlis conservatively conclude: "We must reject bufotenine . . . as capable of producing the acute phase of cohoba intoxication." Only animal studies on bufotenine have been reported since this work and no serious investigator has proposed that bufotenine alone is hallucinogenic. Nevertheless bufotenine has been referred to as an hallucinogen or psychotomimetic in a scattering of scientific papers from fields other than pharmacology, psychiatry or behavioral sciences, perpetuating the misappellation in the first report of human testing by Fabing and Hawkins.

In September, 1967 the *Federal Register* listed bufotenine, diethyltryptamine (DET) and ibogaine as depressant or stimulant drugs under the Food, Drug and Cosmetic Act because of their hallucinogenic effects. In January, 1968 the use of bufotenine and ibogaine for clinical testing in man or animals was prohibited because they "have a potential for abuse similar to diethyltryptamine." Perhaps the true proving ground for hallucinogens is the street market which appears to ignore bufotenine.

There is not only an obvious structural and implied functional relationship between serotonin, bufotenine and psilocin, but also the possibility of a close relationship in the way in which man, toad and toadstool make these compounds from the more common chemicals of life, in this case the amino acid tryptophan. The possibility that there might be a biosynthetic similarity is strengthened by the detection of these closely related compounds in a phylogenetically more homogeneous group than man, toad and toadstools. Psilocin, serotonin and bufotenine are all found in toadstools, and in some cases such as *Panaeolus retirugis*, psilocin and bufotenine occur together in the same mushroom.

Bufotenine is found in three *Amanita* species; two of these, *A. citrina* and *A. porphyria* also contain the lower methylated compounds serotonin and N-methylserotonin, and one, *A. citrina* contains dimethyltryptamine (DMT) at low level. Three quite different *Amanita* species contain 5-hydroxytryptophan; two of these species, *A. bisporigera* and *A. virosa* also contain the derivative 6-hydroxytryptophan bound in the deadly toxin amanitin. The distribution of 4-hydroxylated tryptamines and their phosphate esters psilocybin, baeocystin and norbaeocystin has been reviewed by Pollock (1976). They are found in a fair fraction of *Psilocybe, Panaeolus* and *Conocybe* species, and have been recently detected in two *Gymnopilus* species. Several *Panaeolus* species are interesting because they have been reported to contain both the 5-hydroxylated serotonin as well as the 4-hydroxylated psilocin derivatives in the same species. These include *Panaeolus cyanescens, P. retirugis* and *P. sphinctrinus*.

A possible biosynthetic relationship between these 4-hydroxylated and 5-hydroxylated tryptamines comes out of studies of enzymatic hydroxylations carried out at the National Institutes of Health in the 1960s under the direction of Jerina, Daly, Witkop and others (Daly, Jerina & Witkop 1972). The discovery of a new class of aromatic hydroxylations was made during the investigation of the hydroxylation of phenylalanine to give tyrosine. When a radioactive hydrogen (tritium) at C-4 of phenylalanine was replaced enzymatically by the hydroxyl group, the radioactivity was not lost from the product tyrosine. The radioactive hydrogen was shown to have shifted to the neighboring carbon atom. This shift, which was shown to occur frequently in enzymatic hydroxylation of aromatic compounds, was given the name "NIH shift" in honor of the Institute where it was discovered.

One of the first enzymatic hydroxylations for which the NIH shift was demonstrated was the hydroxylation of tryptophan to 5-hydroxytryptophan, the immediate precursor to serotonin in mammals. 5-Hydroxytryptophan was suspected as an intermediate in the mid-1950s. It was observed to accumulate in humans suffering from carcinoidosis, a cancer, producing cells stainable with silver nitrate (argentaffinoma). Udenfriend at NIH showed in the mid-1950s that radioactive 5-hydroxytryptophan is efficiently converted to serotonin in mammals. Further, Udenfriend showed that a liver extract which converts radioactive tryptophan to radioactive serotonin, produces no serotonin from

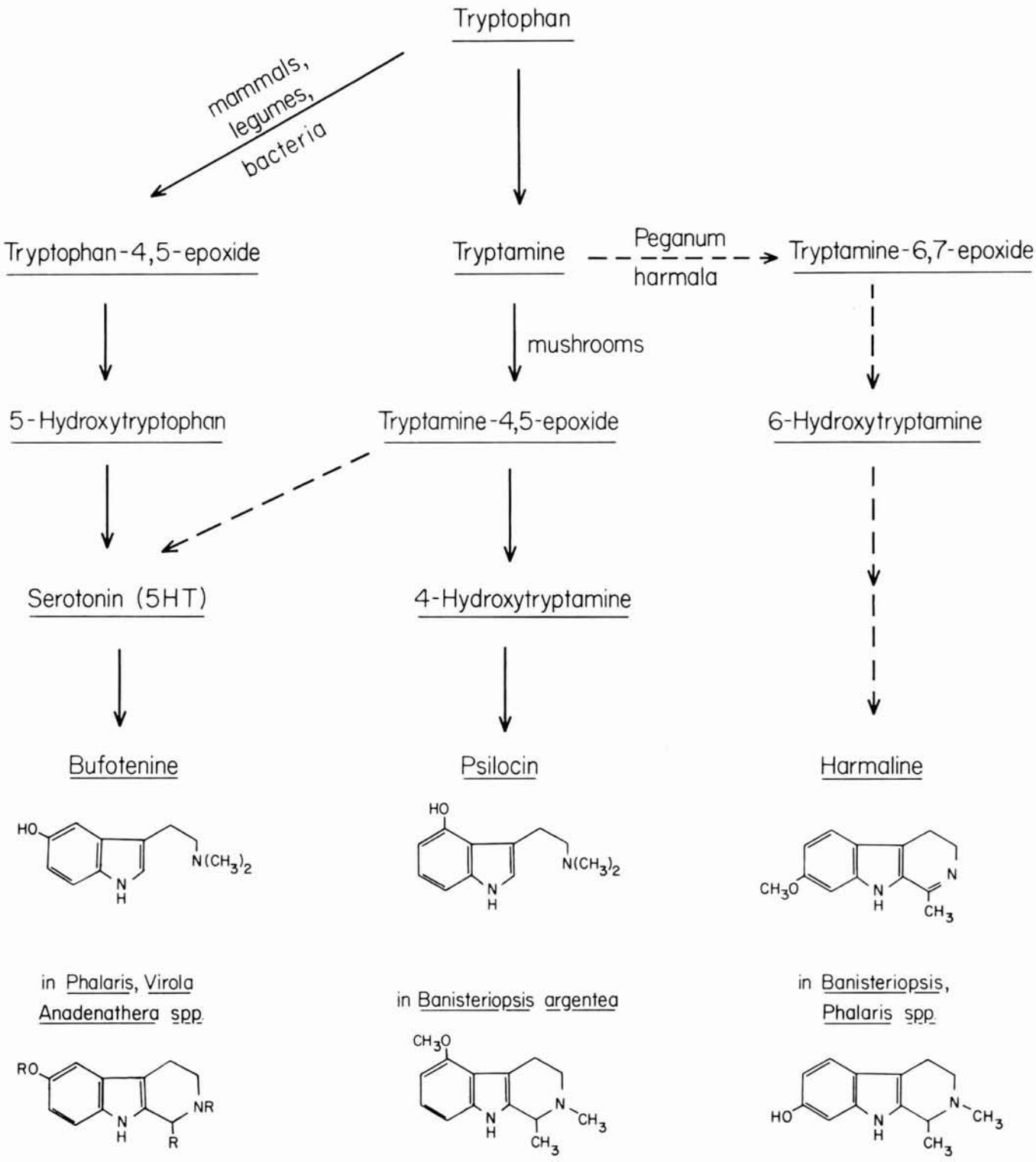

Figure 2. **Biogenetic relationships between psilocin, harmaline and serotonin.**

radioactive tryptamine, meaning that tryptamine is not on the biosynthetic pathway to serotonin (Figure 2) in the mammals studied.

The observation of the NIH shift in both tryptophan hydroxylation and phenylalanine hydroxylation led immediately to the plausible hypothesis that enzymatic oxidation by air oxygen produces first an epoxide, too unstable to isolate or observe directly. The idea was not entirely new: Boyland had proposed in 1950 that epoxides were involved in the first step of biological oxidation of polynuclear aromatic hydrocarbons. The NIH Shift – Epoxide Theory has been particularly fruitful since 1966 in understanding the mechanism of polynuclear aromatic hydrocarbon carcinogenicity on the molecular level. Tryptophan-4,5-epoxide, implicated in the oxidation of tryptophan to 5-hydroxytryptophan is not expected to be sufficiently stable for isolation, nor has any other indole-epoxide yet been synthesized or detected directly *in situ*. If such a tryptophan-epoxide could be prepared in the laboratory, it would be expected to have only a very short lifetime, opening spontaneously to either 4-hydroxytryptophan, a potential precursor[3] to the 4-hydroxytryptamine series (psilocin, psilocybin, baeocystin) or to the 5-hydroxy series, serotonin and bufotenine. Therefore the question logically arises: is a 4,5-epoxide a common intermediate leading to the 4-hydroxytryptamines and to the 5-hydroxytryptamines in any organism? The question is particularly pertinent for those species and genera which produce both 4-hydroxy- and 5-hydroxytryptamines together.

Brack and Hofmann showed in their original work on psilocin and psilocybin in 1958 that radioactive tryptophan is incorporated into these compounds by cultures of *Psilocybe semperviva* (Hofmann et al. 1959). In 1967 Leung and Paul at the University of Michigan showed that incompletely methylated psilocybins (baeocystin, norbaeocystin) are present in *Psilocybe baeocystis* mycelia (Leung & Paul 1968). This observation has since been extended to the actual mushrooms of several other species, including *P. cubensis* on which our work was carried out. Detection of incompletely methylated psilocybins suggests, but does not prove, that methylation might occur as the last step in biosynthesis of psilocybin.

The remaining work on psilocybin biosynthesis was reported in 1968 by Stig Agurell and J.L.G. Nilsson at the Royal Pharmaceutical Institute in Stockholm. They grew *Psilocybe cubensis* mycelia in water containing labeled tryptophan and tryptamine of known specific radioactivity. They isolated psilocybin from the mycelia and measured its specific radioactivity. From these measurements they were able to calculate how much the hypothetical precursor in the diet was diluted along the biosynthetic stream leading to psilocybin. The idea is the further "upstream" the hypothetical intermediate, the greater will be its dilution at the downstream, product end. By this criterion tryptamine (dilution 33:1) appears closer to psilocybin than does tryptophan (dilution 132:1). 4-Hydroxytryptophan (dilution more than 500:1) appears to be a particularly poor precursor. Since 4-hydroxytryptophan is not on the biosynthetic stream leading to psilocybin, there is a formal divergence from the mammalian biosynthetic route to serotonin (Figure 2) at an early stage, namely in the mushroom decarboxylation to tryptamine precedes hydroxylation; in the mammal hydroxylation precedes decarboxylation.

We have investigated the biosynthesis of psilocin in a strain of *Psilocybe cubensis* from the Amazon valley, employing the non-radioactive deuterium label. Experiments were carried out to find the smallest size culture which would reliably produce mushrooms in order to maintain a high concentration of deuterated compounds without having to use a large amount of labeled compounds. Although mushrooms were obtained on as little as 17 grains of rye, a more reliable fruiting mass was obtained on minicultures of 10 g rye grain in 15 g water. Two weeks after inoculation the minicultures (Figure 3) were cased with vermiculite, peat moss, sand and crushed oyster shell. Fruiting occurred five to six weeks after inoculation (Figure 4). The yield of mushrooms (Figure 5) appeared relatively unaffected by addition of up to 100 mg of tryptamine to 10 g of rye grain. Minicultures continued to produce mushrooms for up to 20 weeks, and average minicultures produced a total of 2.7 g dry weight of mushrooms. Minicultures actually produced a higher yield of mushrooms per g of rye grain than did larger scale cultures.

Using the miniculture technique we found that a wide range of tryptamines, including the unnatural substrates diethyltryptamine (DET) and alpha-methyltryptamine (AMT), were readily absorbed by the mycelia and translocated into developing mushrooms. We noted that deuterated tryptamine was incorporated more efficiently into psilocin and psilocybin than were monomethyltryptamine (MMT) or dimethyltryptamine (DMT). Both of the latter two were incorporated, however, without prior demethylation to tryptamine. This suggests that the hydroxylation enzyme operates normally on tryptamine, but may be sufficiently flexible to oxidize dimethyltryptamine or other unnatural substrates forced on it at high concentration. The hydroxylation of dimethyltryptamine in minicultures to give psilocin was observed to occur with NIH shift. Thus

Figure 3. Dosing miniculture with deuterium-labeled tryptamine solution.

Figure 4a. Fruiting miniculture.

Figure 4b. Fruiting miniculture with casing and container removed.

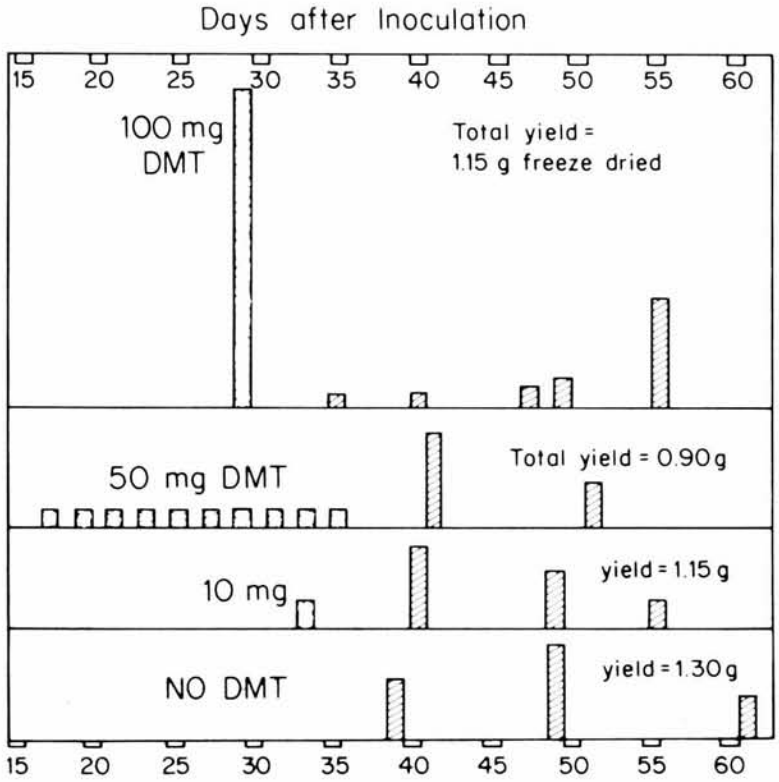

Figure 5. Effect of DMT on fruiting minicultures.
Open bars proportional to amount of DMT administered; cross-hatched bars proportional to yield of mushrooms.

a tryptamine-4,5-epoxide is the probable intermediate between tryptamine and psilocin (Figure 2).

It is still unknown whether the tryptamine-4,5-epoxide is also an intermediate to serotonin and bufotenine in mushrooms. The occasional detection of 5-hydroxytryptophan in mushrooms by chromatography suggests that bufotenine synthesis in mushrooms, while involving a 4,5-epoxide, may be formally separate from psilocin biosynthesis, following the mammalian route. Even if the major route to bufotenine in mushrooms turns out to proceed via the mammalian tryptophan-4,5-epoxide route, it is still possible that some bufotenine might arise by "leakage" in the selectivity of opening of tryptamine-4,5-epoxide to psilocin. The possibility would also exist of a single, non-specific oxidative enzyme which epoxidizes both tryptophan and tryptamine.

Plenty of precedent exists in plants for formation of the serotonin-bufotenine series of compounds via oxidation of tryptamine rather than tryptophan. Plants which have been shown to accomplish 5-hydroxylation by oxidation of tryptamine include tomato, barley, *Anadenathera peregrina* and *Peganum harmala*, the source of a series of hydroxylated carboline alkaloids (Figure 2) some of which are also found in plant sources of the hallucinogenic South American snuffs ayahuasca, caapi and cohoba. *Peganum harmala* is interesting because it produces not only a series of oxygenated alkaloids from tryptamine by a presumed 4,5-epoxide, but also a series of alkaloids which could be derived from a 6,7-epoxide (Figure 2). It is clear from the experiments of Nettleship and Slaytor (1974) that the 5-hydroxylated indole alkaloids of *Peganum harmala* are derived from oxidation of tryptamine or a tryptamine derivative, but it is not presently known whether the 6-hydroxylated indole alkaloids come from oxidation of a tryptamine or of a tryptophan.

Plants which hydroxylate via the 4,5-epoxide route all have the genetic potential for production of psilocin, or psilocin-related compounds. Such a psilocin-related alkaloid has already been found in *Banisteriopsis argentea* by Ghosal and Mazumder (1971). Phytochemists investigating the genera discussed above could encounter surprising new sources of psilocin. We feel that further chemotaxonomic survey of serotonin-bufotenine accumulating plant (and animal) genera is warranted and that further study of the biological hydroxylation of indoles should be encouraged.

NOTES

1. The Hebraic word *tsav* (Russian cognate *zhaba* = toad) is somewhat ambiguous, meaning either toad or lizard. It is translated in the King James version of *The Bible* as lizard. Leviticus 11:29.

2. Takamine isolated the same compound independently and called it adrenaline (ad renal = near the kidney) in 1901. Takamine claimed Abel's compound was not as pure or as active as his. In the ensuing controversy over priority of discovery of the first hormone, sides were quickly taken and the participants refused to agree on a single name. The two names epinephrine and adrenaline survive today.

3. In man 4-hydroxytryptophan is virtually without central nervous system effect, even at oral doses as high as one g! If even a few percent of that 4-hydroxytryptophan had been decarboxylated to 4-hydroxytryptamine in the human brain, a dramatic effect might have been expected.

REFERENCES

Abel, J.J. & Macht, D.I. 1911-12. Two crystalline pharmacological agents obtained from the tropical toad, *Bufo agua*. *Journal of Pharmacology and Experimental Therapeutics* Vol. 3: 319.

Agurell, S. & Nilsson, J.L.G. 1968. Biosynthesis of psilocybin. II. Incorporation of labelled tryptamine derivatives. *Acta Chemica Scandinavica* Vol. 22: 1210-1218.

Daly, J.W.; Jerina, D.M. & Witkop, B. 1972. Arene-oxides and the NIH shift: The metabolism, toxicity and carcinogenicity of aromatic compounds. *Experientia* Vol. 28: 1129-1149.

Deulofeu, V. 1948. The chemistry of the constituents of toad venoms. *Progress in the Chemistry of Organic Natural Products* Vol. 5: 241-266.

Fabing, H.D. & Hawkins, J.R. 1956. Intravenous bufotenine injection in the human being. *Science* Vol. 123: 886-887.

Ghosal, S. & Mazumder, U.K. 1971. Alkaloids of the leaves of *Banisteriopsis argentea*. *Phytochemistry* Vol. 10: 2840-2841.

Handovsky, H. 1920. Ein Alkaloid in Gifte von *Bufo vulgaris*. *Archives of Experimental Pathology and Pharmacology* Vol. 86: 138-158.

Hofmann, A.; Heim, R.; Brack, A.; Kobel, H.; Frey, A.; Ott, H.; Petrzilka, T. & Troxler, F. 1959. Psilocybin und Psilocin, zwei psychotrope Wirkstoffe aus mexikanischen Rauschpilzen. *Helvetica Chimica Acta* Vol. 42: 1557-1572.

Leung, A.Y. & Paul, A.G. 1968. Baeocystin and norbaeocystin: New analogs of psilocybin from *Psilocybe baeocystis*. *Journal of Pharmaceutical Science* Vol. 57: 1667-1671.

Lewin, L. 1920. *Die Gifte in der Weltgeschichte*. Berlin: J. Springer.

Nettleship, L. & Slaytor, M. 1974. Limitations of feeding experiments in studying alkaloid biosynthesis in *Peganum harmala* callus cultures. *Phytochemistry* Vol. 13: 735-742.

Pollock, S.H. 1976. Psilocybian mycetismus with special reference to Panaeolus. *Journal of Psychedelic Drugs* Vol. 8(1): 43-57.

Rapport, M.M. 1949. Serum vasoconstrictor (serotonin). V. Proposed structure of the vasoconstrictor principle. *Journal of Biological Chemistry* Vol. 180: 961-969.

Turner, W.J. & Merlis, S. 1959. Effect of some indolealkylamines on man. *Archives of Neurology and Psychiatry* Vol. 81: 121-129.

Woolley, D.W. & Shaw, E. 1954. A biochemical and pharmacological suggestion about certain mental disorders. *Science* Vol. 119: 587-588.