R.H.F. Manske
The Alkaloids, Volume VIII
The Indole Alkaloids

——CHAPTER 1——

THE SIMPLE BASES

J. E. SAXTON

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I. Introduction

In view of the vital importance of indole-3-acetic acid as a plant growth hormone, and the central position occupied by tryptophan both as a constituent of plant proteins and as the common biogenetic precursor of the complex indole alkaloids, it is not surprising to find that several simple derivatives of indole, which are presumably closely related to the routes of biosynthesis and metabolism of indoleacetic acid or tryptophan, occur widely in the vegetable kingdom. Indole itself has been isolated from the flowers of many *Jasminium* and *Citrus* species (1), from *Robinia pseudacacia* L. (2), *Cheiranthus cheiri* L. (3), *Narcissus jonquilla* L. (4), and *Chimonanthus fragrans* Lindl. (5); it appears to be an essential constituent of the perfumes of these flowers. Reports have also been made of the isolation of indole from nonfloral material, e.g., *Celtis reticulosa* Miq. (6) and *Thlaspi arvense* L. (7), but these have been criticized on the grounds that the indole was probably the result of bacterial action on a labile indole precursor (8). Numerous other claims

for the presence of indole in plants have been based solely on the color reactions given either by the plant extracts or by the volatile constituents of the oils obtained from the blossoms by enfleurage.

The origin of indole in plants is not yet established; it was earlier suggested that it might be a degradation product of tryptophan, but this possibility does not appear to have been investigated. In some plants, at least, the reverse may be true, and indole may be converted into tryptophan by combination with serine. Whether this is the principal mode of biosynthesis of tryptophan remains to be determined; it is perhaps more likely that indole and tryptophan are products of alternative pathways of metabolism of indole-3-glycerol phosphate, and that conversion of the last-named into tryptophan does not proceed by way of indole. Indole-3-glycerol phosphate may well be the vital intermediate between anthranilic acid and the naturally occurring derivatives of indole. Thus far, there is very little evidence for this route of biosynthesis in higher plants but it is well established in certain microorganisms, e.g., *Escherichia coli* and *Neurospora* (9). It would be dangerous to assume by analogy that the same route is used in the higher plants; nevertheless, it remains an attractive possibility in the absence of any evidence for an alternative. In this connection, it is of interest that methyl anthranilate accompanies indole in the flowers of the jasmine and the bitter orange (1), and in *Robinia pseudacacia* (2).

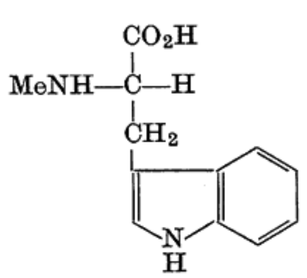
Although the natural occurrence of indole and the biosynthesis of the indole ring system are of importance and relevance to the wider question of the biosynthesis of the complex indole alkaloids, indole will not be discussed in detail here, as it is not an alkaloid. For a comprehensive and critical account of the occurrence of indole and its simple derivatives in plants, the reader is referred to the article by Stowe (8).

L-Tryptophan is the ubiquitous indole derivative in plant proteins, and similarly need not be discussed at length. However, it is satisfying to note in passing that the early assumption that tryptophan is the biogenetic precursor of all the indole alkaloids has been substantiated by the comparatively few radioactive tracer experiments that have so far been carried out, e.g., the formation of the ergot alkaloids in *Claviceps purpurea* (10), and of ajmaline, reserpine, and serpentine in *Rauwolfia serpentina* Benth. ex Kurz. (11).

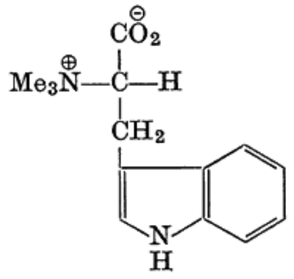
II. Abrine and Hypaphorine

Abrine (I), the N_b-methyl derivative of L-tryptophan, occurs in the seeds of the jequirity (*Abrus precatorius* L.) (12, 13); so far it has not

been obtained from any other botanical source. The amino acid abrine must not be confused with abrin, the toxic protein mixture obtained from the same seeds, which was isolated and named as early as 1884 (14).



I
Abrine



II
Hypaphorine

The constitution of abrine was proved by methylation with methyl iodide and methanolic sodium hydroxide, which gave the same methyl ester methiodide as did similar treatment of L-tryptophan (15). Since the product was almost completely racemized (16), this did not establish the configuration of the asymmetric center. The configurational identity of abrine and L-tryptophan was proved by Cahill and Jackson (16), who obtained the same optically pure methyl betaine (II) from both abrine and L-tryptophan by methylation with methyl iodide and methanolic sodium hydroxide. Under the appropriate conditions, the racemic methyl ester methiodide crystallized out, and was removed; the methyl betaine (II) which remained unesterified also escaped racemization, and was recovered from the mother liquors.

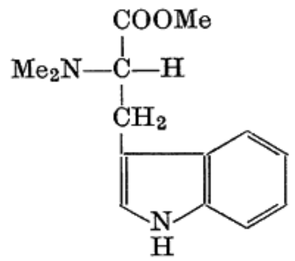
The optically active methyl betaine (II) is identical with hypaphorine (16, 17), which occurs widely in the seeds of *Erythrina* species. It was first isolated by Greshoff (18) from the seeds of *E. subumbrans* Merrill (*Hypaphorus subumbrans* Hassk.); much later, it was discovered in the seeds of *E. variegata* var. *orientalis* (L.) Merrill (*E. indica* Lam.) (19, 20) and in *E. cristagalli* L. (21). More recently, the search for the major *Erythrina* alkaloids has revealed the presence of hypaphorine in the seeds of 23 other *Erythrina* species (22–28); according to Folkers *et al.* (25), it has been found in every *Erythrina* species so far examined. Occasionally, the amount of hypaphorine in the seeds is comparatively high; in *E. acanthocarpa* E. Mey., for example, it is 5.8% (25), while in *E. pallida* Britton and Rose it is as high as 6.7% (26). Although many quaternary compounds exhibit curare-like activity, the physiological effects of *Erythrina* extracts are apparently not due to hypaphorine.

The natural occurrence of hypaphorine is probably not confined to *Erythrina* species. Von Lippmann (29) isolated from beet shoots a substance with the appropriate physical and analytical properties which,

like hypaphorine, decomposed on being heated into indole and trimethylamine. Although final identification of this substance was not achieved, it seems very probable that von Lippmann's conclusion that it was hypaphorine is correct.

The decomposition of hypaphorine into indole and trimethylamine occurs slowly in the rotting wood of *Abrus precatorius* L., and is responsible for its fecal odor. It also led van Romburgh (30) to propose the correct structure for hypaphorine, which was soon established by synthesis from L-tryptophan (17).

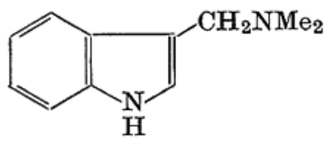
The methyl ester of N_b-dimethyl-L-tryptophan (IIa) also occurs naturally, and has recently been shown to be the major base of *Pultenaea altissima* F. Muell. ex Benth. (Leguminosae) (30a).



IIa

III. Gramine and Its Derivatives

A. Gramine, 3-Aminomethylindole, and 3-Methylaminomethylindole



III
Gramine

The simplest well-authenticated indole alkaloid is gramine (III), which was originally isolated from chlorophyll-deficient barley mutants by von Euler and Hellström (31, 32). It was at first believed that the presence of gramine in these mutants was genetically related to the chlorophyll deficiency (33), but this became untenable when gramine was shown to be a constituent of normal sprouting barley (*Hordeum vulgare* L.) (34, 35). The Graminae have not been extensively investigated, so it is not yet known whether gramine occurs widely. However, the alkaloid donaxine, from the Asiatic sedge *Arundo donax* L. (36), has

been shown to be identical with gramine (34, 37, 38); so far, this constitutes the only other recorded occurrence in the Graminae. In other families, gramine has been isolated from the winged fruit of *Acer rubrum* L. (39), from the leaves of the silver maple, *A. saccharinum* L. (40), and from *Lupinus luteus* L. (40a).

Gramine is a monoacidic tertiary base which contains two methyl groups attached to nitrogen, and gives a typical indole UV-spectrum (32); it is optically inactive and possesses one active hydrogen atom (36). It was first formulated as 2-dimethylaminomethylindole, mainly on the basis of the close similarity of its UV-spectrum with that of 2-methylindole, but this was soon disproved by comparison of synthetic 2-dimethylaminomethylindole with gramine (41). Other formulations briefly considered were 3-methyl-2-dimethylaminoindole, 2-methyl-3-dimethylaminoindole, and 2-ethylmethylaminoindole, but none of these explained the absence of *C*-methyl groups (Kuhn-Roth) and, although the first accounted for the production of skatole by zinc dust distillation, this was not accepted as indicating the presence of a substituent at position 3, owing to the drastic nature of the degradation and the poor yield of skatole obtained (38, 41, 42). The structure of gramine was then revealed fortuitously by Wieland and Hsing in an attempt to synthesize 3-dimethylaminoacetylindole by reaction of indole magnesium iodide with dimethylaminoacetonitrile. Unexpectedly, the product, mp 134°, had the composition $C_{11}H_{14}N_2$, and was identified as gramine (43). A second synthesis was later reported by Kühn and Stein, who obtained a quantitative yield of gramine by the Mannich condensation of indole with formaldehyde and dimethylamine (44).

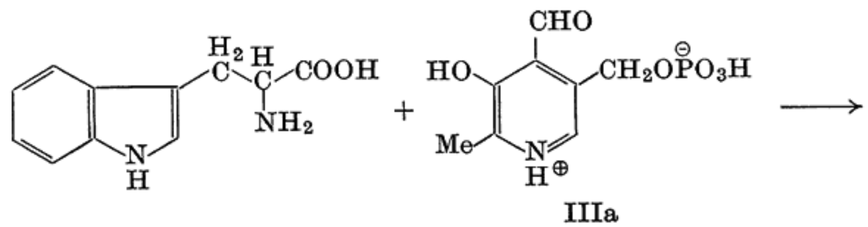
As a Mannich base, gramine finds extensive application in preparative indole chemistry. Indeed, gramine is one of the few alkaloids which are more familiar as intermediates in organic synthesis, and which are readily accessible in high yield from cheap starting materials. In alkaline media, gramine methiodide behaves as an effective alkylating agent, particularly in reactions with compounds containing an active methine or methylene group. For example, reaction of gramine methiodide with potassium cyanide gives indoleacetonitrile (45–47), which affords convenient preparations of indoleacetic acid (45, 47, 48, 49) and tryptamine (45). Condensation of gramine or its methiodide with the sodium derivative of acetamidomalonic ester yields ethyl α-acetamido-α-carbethoxy-β-(3-indolyl)-propionate, which on hydrolysis and decarboxylation provides a valuable synthesis of (±)-tryptophan (50, 51). Alternatively, gramine will condense with ethyl nitroacetate at 100° to give an intermediate which can also be converted readily into (±)-tryptophan by appropriate transformations (52).

The biogenesis of gramine in barley has provided the subject for an interesting study using radioactive tracer techniques. Administration of (±)-tryptophan-β-C^{14} to sprouting barley led to the formation, in the leaves, of radioactive gramine, in which the activity resided specifically on the carbon atom of the methylene group, corresponding to the one originally labeled (53). When a mixture of (±)-tryptophan-2-C^{14} and (±)-tryptophan-β-C^{14} was fed to sprouting barley, the gramine isolated contained radioactivity at the methylene group and the 2-position only. Further, the ratio of these activities was the same as in the original tryptophan administered to the plant (54). These results establish beyond doubt that tryptophan is converted into gramine in barley by a process which does not involve fission of the indole-β-carbon linkage. Instead, fission must occur between the α and β carbon atoms of the tryptophan. The intermediates in this conversion have not yet been identified with certainty. Both 3-indolyl-β-C^{14}-pyruvic acid and 3-indolyl-β-C^{14}-acrylic acid are converted in sprouting barley into radioactive gramine specifically labeled on the carbon atom attached to the ring (55); however, the incorporation is very low, hence, these substances may not be direct intermediates. It may even be that they are first converted in the intact plant into tryptophan by enzymatic amination (56). This is consistent with the observation that the incorporation of 3-indolyl-β-acrylic acid and its conversion into gramine in excised barley shoots is much lower still (57), which suggests that the appropriate enzyme is not present in effective amounts except in the intact plant (56). Indole-3-glyoxylic acid, indole-3-aldehyde, and (perhaps surprisingly) indole-3-acetic acid are not converted by sprouting barley into gramine; however, the failure to incorporate indole-3-acetic acid was attributed to destruction of this compound before it reached the site of gramine synthesis (55).

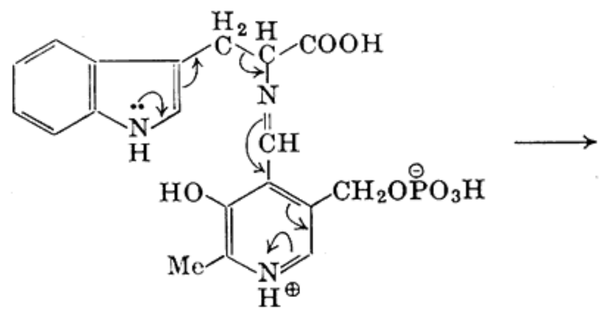
These studies have been taken a stage further by O'Donovan and Leete, who administered a mixture of (±)-tryptophan-β-C^{14} and (±)-tryptophan-β-H^3 to intact barley seedlings (56). The radioactive gramine thus obtained was shown to contain the same ratio of C^{14} to tritium as the original tryptophan mixture, and it was further established that the radioactivity was present only in the methylene group of the side chain. These results prove very convincingly that the methylene group of tryptophan remains intact during its conversion into gramine under these conditions. Hence, 3-indolyl-β-acrylic acid, indole-3-aldehyde, and indole-3-glyoxylic acid cannot be precursors of gramine, since the intermediacy of these compounds would necessarily involve the loss of a part or the whole of the tritium attached to the β-carbon atom of the tryptophan side chain. Other conceivable intermediates, such as 3-indolyl-β-pyruvic acid and indole-3-acetic acid, can also be eliminated,

since the methylene hydrogen atoms in these compounds are located on carbon atoms attached to a carbonyl function, and would therefore be labile.

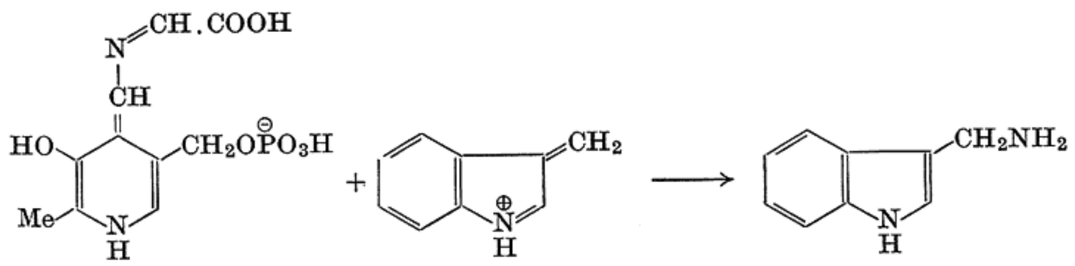
All the above results are consistent with Wenkert's recent suggestion (57a) that the biological conversion of tryptophan into gramine proceeds by condensation with pyridoxal phosphate (IIIa) with formation of a



IIIa



IIIb



IIIc

III

Schiff's base (IIIb), which is then degraded by a reverse Michael reaction to the protonated 3-methyleneindolenine (IIIc). Addition of ammonia then yields 3-aminomethylindole, which on methylation affords gramine (III). This attractive hypothesis finds support in the recent isolation from barley seedlings of both 3-aminomethylindole and 3-methylaminomethylindole (57b). It is also supported by the demonstration that 3-aminomethylindole can be methylated to 3-methylaminomethylindole

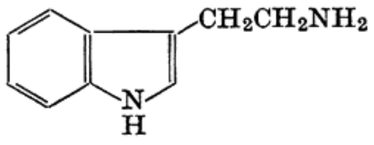
by (−)-*S*-adenosyl-L-methionine in the presence of an enzyme preparation from barley shoots, and that the same system converts 3-methylaminomethylindole into gramine (57b).

In retrospect, the report that phenylalanine is not a precursor of tryptophan and therefore of gramine in barley is not surprising; it seems more probable that anthranilic acid is a precursor (57c).

B. Donaxarine

Donaxarine, $C_{13}H_{16}N_2O_2$, the minor alkaloid of *Arundo donax*, has been described on only one occasion, and little information is available concerning its structure. Apart from a positive pine splinter reaction and the fact that it occurs in the same plant as gramine, there seems little justification for its inclusion with the indole alkaloids. Donaxarine contains an *N*-methyl group and one active hydrogen atom, and is optically inactive. The function of the oxygen atoms is unknown, but they are not contained in phenolic hydroxyl groups or methoxyl groups (58, 59).

IV. Tryptamine and Its Derivatives



IIId
Tryptamine

The occurrence of tryptamine (IIId) in plants was first discovered by White, who isolated it from *Acacia floribunda* Sieb. and *A. pruinosa* Cunn. (60). Since that time it has been obtained from other *Acacia* species, namely, *A. cultriformis* Cunn., *A. longifolia* Willd., *A. podalyriaefolia* Cunn. (61), *A. acuminata* Benth., *A. cardiophylla* Cunn., and *A. vestita* Ker. (62). Its presence has also been revealed in the inkcap fungus, *Coprinus micaceus* Fr. (63), and in another fungus, *Panaeolus foenisicii* Pers. (63a). More recently, it has been discovered to be present in several edible fruits, namely, the tomato (64, 64a), plum, and eggplant, and also in traces in the orange (64a). There are also reports of its occurrence in mesquite (*Prosopsis juliflora* DC.) (65) and in lentils (*Lens esculenta* Moench., syn. *L. culinare*) (65a).

Like gramine, tryptamine is more familiar as an intermediate in preparative indole chemistry than as an alkaloid. It was first synthesized

by Ewins, who obtained it by Fischer cyclization of the phenylhydrazone of γ-aminobutyraldehyde (66). It was later prepared by Majima and Hoshino by reaction of indole magnesium iodide with chloroacetonitrile, and reduction of the indoleacetonitrile so obtained (67). These preparations are now mainly of historical interest, having been superseded first by the preparative sequence involving gramine methiodide (45), and more recently by Speeter and Anthony's method, from indole via indole 3-glyoxylyl chloride and the corresponding amide (68, 69). This last method is of particular value, as with appropriate modifications it affords a convenient preparation of pure N_b-substituted tryptamines using the same number of stages. A fifth method of synthesis of tryptamine involves the lithium aluminum hydride reduction of 3-β-nitroethylindole, prepared by the reaction of indole or indole magnesium bromide with nitroethylene (70). A related method utilizes the catalytic or electrolytic reduction of 3-β-nitrovinylindole, prepared by condensation of indole 3-aldehyde with nitromethane (70a). Finally, tryptamine may be obtained directly from indole by reaction of indolyl magnesium bromide with ethyleneimine (70b).

Dipterine, the N_b-methyl derivative of tryptamine, occurs in two Asiatic members of the family Chenopodiaceae, *Girgensohnia diptera* Bge. (71, 72) and *Arthrophytum leptocladum* Popov (73), and also in the bark of *Piptadenia peregrina* Benth. (73a). *Arthrophytum leptocladum* also contains a closely related base, leptocladine (74), identified as N_b-methyltetrahydroharman by synthesis from dipterine and acetaldehyde (73).

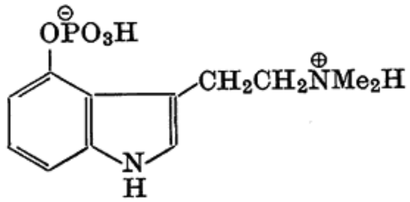
N,*N*-Dimethyltryptamine occurs more widely in nature, and is the simplest of several naturally occurring tryptamine derivatives which exhibit psychotomimetic activity. It was first identified as a constituent of the seeds and pods of *P. peregrina* and *P. macrocarpa* Benth. (Leguminosae) during an attempt to isolate the hallucinogenic principles present in the narcotic snuff prepared from these plants by certain American Indian tribes (75). The physiological activity of this snuff is only partly owing to dimethyltryptamine; bufotenine is a second active constituent. Another plant which is used for a similar purpose is *Prestonia amazonica* (Benth.) Macbride (*Haemadictyon amazonicum* Benth.) (Apocyanaceae). A concoction from the leaves is consumed by some Colombian and Peruvian Indians for its hallucinogenic properties. Although the plant was earlier reported to contain two alkaloids (76), it seems probable that this was the result of botanical confusion with *Banisteria caapi* Spruce, which is used by the natives for the same purpose, often alone but sometimes mixed with *Prestonia amazonica* (77). In later investigations using carefully identified *P. amazonica*, only

N,*N*-dimethyltryptamine was isolated (77). *N*,*N*-Dimethyltryptamine also occurs in the leaves of *Lespedeza bicolor* var. *japonica* (Leguminosae) (78), and in the roots of *Mimosa hostilis* Benth. (40, 79). The latter plant is also the source of an extract used by the local (Brazilian) Indians in their mysticoreligious ceremonies for its hallucinogenic properties. These rituals have been described by Gonçalves de Lima, who recorded the extraction of nigerine from *Mimosa hostilis*, but did not identify it as *N*,*N*-dimethyltryptamine (79).

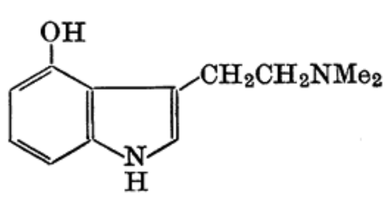
On account of the activity of these plant extracts and the isolation from them of *N*,*N*-dimethyltryptamine, the physiological activity of this base in humans is of interest. When injected intramuscularly, it causes hallucinations and illusions, which are characterized by their rapid appearance and brief duration (80). Apparently, dimethyltryptamine is rapidly metabolized and excreted mainly as indoleacetic acid, although the urine is enriched with 5-hydroxyindoleacetic acid; whether this is the result of oxidation at the 5-position or stimulation of the metabolism of serotonin in the brain is not yet known (80).

The seeds of *Piptadenia peregrina* and *P. macrocarpa* also contain *N*,*N*-dimethyltryptamine oxide (75). Since *N*,*N*-dimethyltryptamine is readily oxidized on exposure to air, the oxide of this base may be an artifact.

V. Psilocin and Psilocybin



IV
Psilocybin

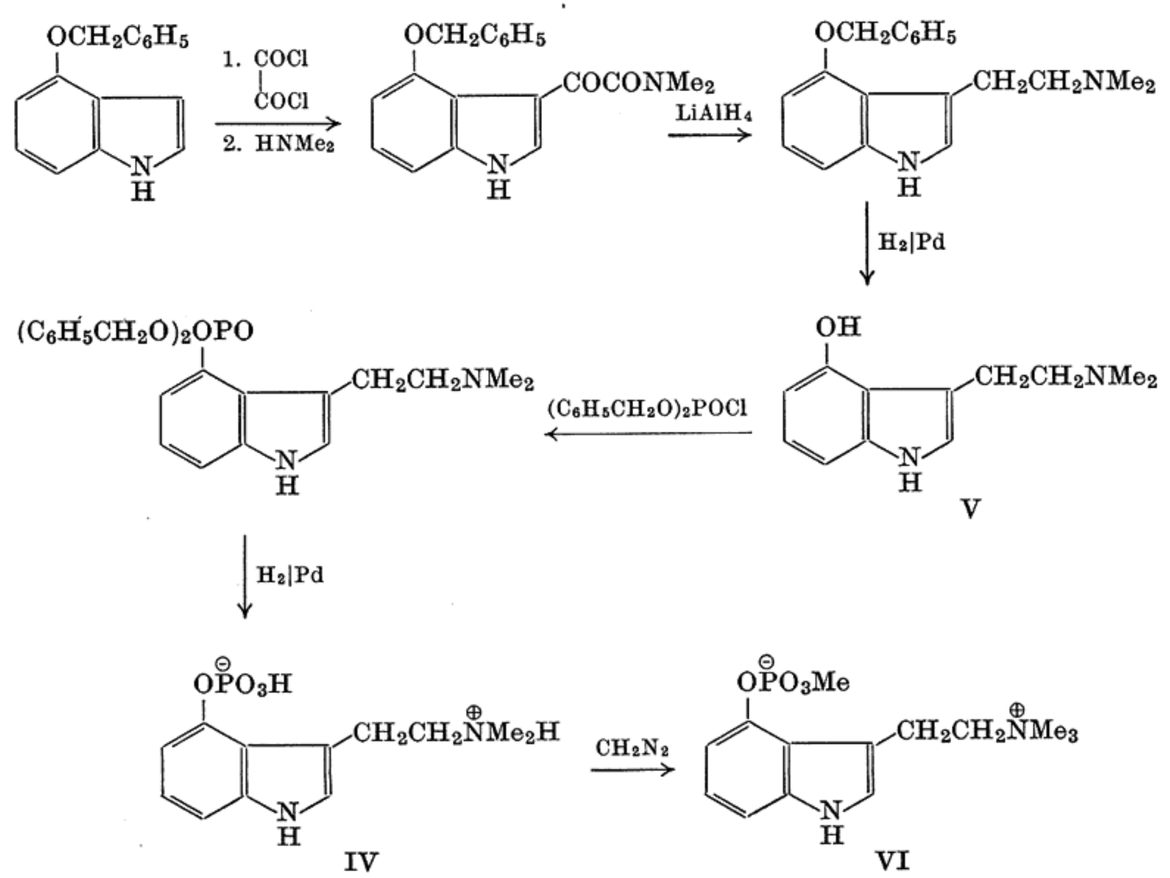


V
Psilocin

Psilocybin (IV) and psilocin (V) occur in several Mexican fungi, and, aside from mitragynine, represent the only derivatives of 4-hydroxyindole hitherto found in plants. Psilocybin was first isolated from *Psilocybe mexicana* Heim (81), and has since been obtained from *P. caerulescens* Murr. var. *mazatecorum* Heim, *P. semperviva* Heim et Cailleux, *P. zapatecorum* Heim, *P. aztecorum* Heim, and in *Stropharia cubensis* Earle (82, 83) and *Panaeolus sphinctrinus* (83a). All these fungi were of Mexican origin, but it is interesting that specimens of *Stropharia cubensis* procured from Thailand and Cambodia also contained psilocybin (82, 83). Psilocin occurs in very much smaller proportions, but has been detected in *P. mexicana* (81), *P. semperviva*, *P. aztecorum*, and *Stropharia cubensis*

(82). Other North American fungi which have recently been shown to contain psilocybin and psilocin are *Psilocybe cyanescens* and *P. baeocystis* Singer and Smith (83b, 83c); psilocybin also occurs in *Conocybe cyanopus* (83b). Curiously, psilocin appears to be present in much larger amounts than psilocybin in *P. baeocystis* (83c).

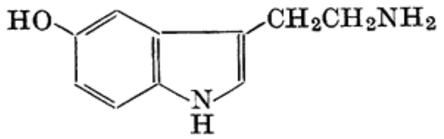
Both psilocybin, $C_{12}H_{17}N_2O_4P$, and psilocin are optically inactive, amphoteric substances, which exhibit UV-spectra closely similar to those of 4-hydroxyindole derivatives. Hydrolysis of psilocybin gives psilocin and one equivalent of phosphoric acid. Reaction of psilocybin with diazomethane gives dimethylpsilocybin, a neutral betaine which contains one saponifiable methoxyl group. The second methyl group introduced in the methylation is attached to nitrogen, since pyrolysis of dimethylpsilocybin gives trimethylamine; psilocybin itself does not give trimethylamine on pyrolysis, and hence presumably contains a dimethylamino group (83, 84). The two carbon atoms which remain to be located were presumed to be present in an ethanamine side chain. Psilocin was therefore formulated as 4-hydroxy-*N*,*N*-dimethyltryptamine (V), and psilocybin as its *O*-phosphoryl derivative (IV) (85); dimethylpsilocybin must accordingly be the betaine (VI). These formulations were substantiated by the synthesis of psilocin and psilocybin according to the illustrated sequence of reactions (83, 84, 85).



Since pre-Columbian times, many Mexican Indians have used narcotic and hallucinogenic drugs in their rituals; in some remote parts of Mexico such drugs are apparently still used. In recent years, it has been established that these drugs are prepared from various fungi, notably those belonging to the *Psilocybe* and *Stropharia* genera (83, 86, 87, 88, 89). This discovery stimulated interest in the hallucinogenic constituents of these fungi, as a result of which psilocybin and psilocin were isolated. Ingestion of these fungi results in hallucinations and a state of intoxication (83, 86, 90); qualitatively, the effects are similar to those of mescaline and lysergic acid diethylamide (86, 91). The psychotomimetic activity of pure psilocybin is remarkably similar to that of *Psilocybe mexicana* extracts, and it is probable that the total activity of the Mexican drug prepared from this species can be ascribed to psilocybin (83, 92). This is not necessarily true of extracts of other fungi, however; for example, *P. yungensis* is reported to be hallucinogenic, but it has been established that it does not contain psilocybin (93).

In *P. semperviva* it has been demonstrated that tryptophan is a precursor of psilocybin (93a). It was simultaneously suggested that a similar oxidation of tryptophan or a tryptophan metabolite at the 4-position constitutes an important intermediate stage in the biosynthesis of the ergot alkaloids from tryptophan.

VI. 5-Hydroxytryptamine and Its Derivatives



VII
5-Hydroxytryptamine

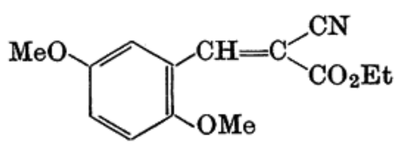
A. 5-Hydroxytryptamine

Since the discovery of 5-hydroxytryptamine (serotonin, enteramine, thrombocytin) (VII), and the demonstration of its physiological activity and its important function as a neurohormone, the possibility of its occurrence in plants has attracted much attention. It was first shown to be present in *Mucuna pruriens* DC. (cowhage), and is probably responsible for the intense irritation which results when cowhage comes into contact with the skin (94). This irritation could be a mechanical effect due to the trichomes, but it is more likely to be the result of liberation of

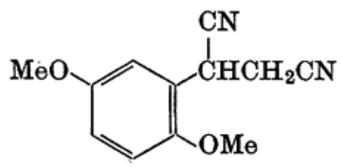
histamine. 5-Hydroxytryptamine is probably also the active irritant of *Urtica dioica* L. (stinging nettle) (95), since it occurs to the extent of 0.02% in this species. It also occurs in *Prosopsis juliflora* DC. (65), *Gossypium hirsutum* L., and *Symplocarpus foetidus* Nutt. (96), in the bark of *Hippophae rhamnoides* L. (96a), and in several fungi belonging to the genus *Panaeolus*, namely, *P. campanulatus* (Fr.) Quélet (*P. linnaenus* Imai) (83a, 97), *P. acuminatus* (Schff. ex. Fr.) Quélet, *P. foenisicii* Pers., *P. semiovatus* Fr., and *P. subalteatus* (Berk. et Br.) Sacc. (63a). Of much greater interest, however, are the reports of the presence of 5-hydroxytryptamine in several edible fruits, namely, the banana (64, 64a, 64b, 98, 99), tomato (64, 64a, 64b), pineapple (100), plum, avocado, eggplant (64a), plantain (64a, 100a) and "Matoke" banana (both of which are varieties of *Musa paradisiaca* L.) (100b), papaw (*Carica papaya* L.), passion fruit (*Passiflora foetida* L.) (100a), and the walnut (100c).

The preparation of 5-hydroxytryptamine has been repeatedly investigated, and several convenient syntheses have been described; in fact, virtually all the known routes to tryptamine derivatives have been employed. The first synthesis was an adaptation of the gramine route, starting from 5-benzyloxyindole and proceeding via 5-benzyloxygramine, 5-benzyloxyindoleacetonitrile, and 5-benzyloxytryptamine (101). In common with all the other preparations involving 5-benzyloxytryptamine, the final stage, namely, debenzylation, was achieved by catalytic hydrogenation. Almost contemporaneously, a second synthesis of 5-hydroxytryptamine was reported via 5-benzyloxyindoleacetonitrile, prepared by the reaction of 5-benzyloxyindole magnesium iodide with chloroacetonitrile (102). An analogous route using 5-methoxyindole gave 5-methoxytryptamine, which was demethylated by means of aluminum chloride (103). The method of Speeter and Anthony (68) from 5-benzyloxyindole via 5-benzyloxyindoleglyoxylyl chloride and the related dibenzylamide affords a valuable preparation which proceeds in high over-all yield. A later synthesis involved the condensation of 5-benzyloxyindole-3-aldehyde, prepared by Vilsmeier-Haack formylation of 5-benzyloxyindole, with nitromethane; reduction of the product with lithium aluminum hydride then afforded 5-benzyloxytryptamine (104, 105). A somewhat shorter method uses the reaction of 5-benzyloxyindole with nitroethylene at 100°, which yields 3-(2-nitroethyl)-5-benzyloxyindole; reduction with lithium aluminum hydride provides yet another route to 5-benzyloxytryptamine (106). Finally, in this series of preparations from 5-benzyloxyindole, a patented method describes the briefest synthesis hitherto reported, namely, the reaction of 5-benzyloxyindole magnesium bromide with ethyleneimine, which gives 5-benzyloxytryptamine directly (70a).

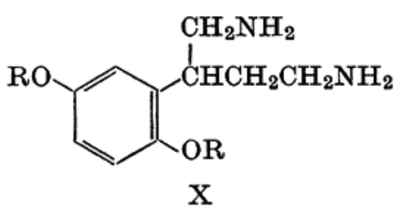
Several syntheses are on record which avoid the preparation of 5-benzyloxyindole; in these procedures, the indole ring is usually formed after provision is made for the introduction of the ethanamine side chain. The first of these (107, 108) was an adaptation of Ewins' original tryptamine synthesis. A subsequent route (109) started from ethyl α-cyano-2,5-dimethoxycinnamate (VIII), which was prepared by condensation of 2,5-dimethoxybenzaldehyde with ethyl cyanoacetate. When this was boiled with potassium cyanide solution, addition of the elements of hydrogen cyanide was accompanied by hydrolysis of the ester function and decarboxylation, to give 2,5-dimethoxyphenylsuccinonitrile (IX).



VIII



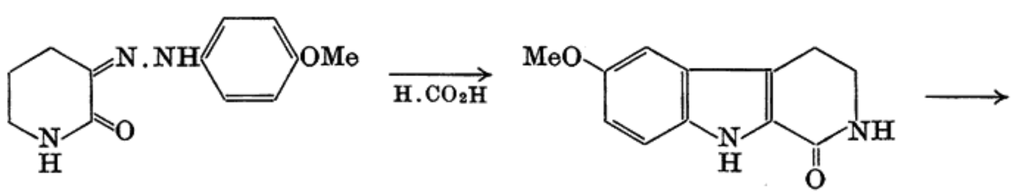
IX



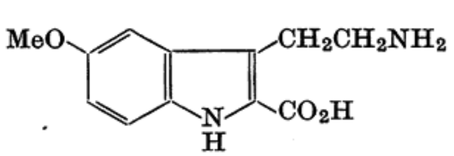
X

Hydrogenation of the latter gave the corresponding diprimary amine (X; R = Me), which on demethylation gave the phenol (X; R = H). Ferricyanide oxidation then gave 5-hydroxytryptamine in 25% over-all yield from 2,5-dimethoxybenzaldehyde (109).

The synthesis developed by Abramovitch and Shapiro (110) utilizes the formation of 6-methoxy-1-keto-1,2,3,4-tetrahydro-β-carboline (XII) by the Fischer cyclization of the *p*-methoxyphenylhydrazone (XI) of 2,3-dioxopiperidine. Alkaline hydrolysis of XII and decarboxylation of the product (XIII) gave 5-methoxytryptamine (110), demethylation of which had previously been reported (103).

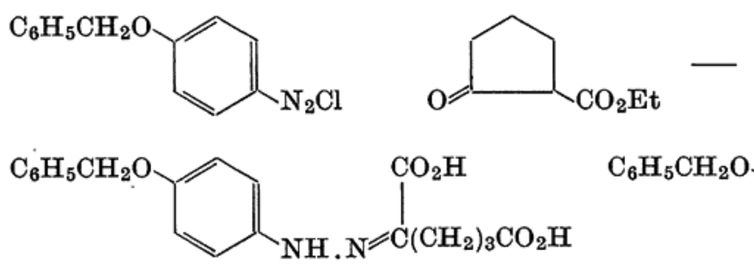


XI XII



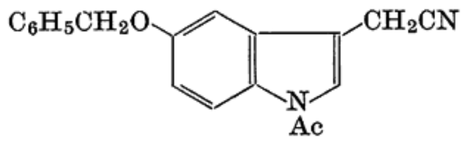
XIII

A different approach was adopted in the synthesis by Justoni and Pessina (111). The Japp-Klingemann reaction of *p*-benzyloxyphenylhydrazine with cyclopentanone carboxylic ester gave the *p*-benzyloxyphenylhydrazone of α-ketoadipic acid (XIV); Fischer cyclization of the corresponding dimethyl ester then yielded 5-benzyloxyindole-2-carboxylic-3-β-propionic acid (XV). Decarboxylation of XV followed by Curtius degradation and debenzylation eventually afforded 5-hydroxytryptamine.

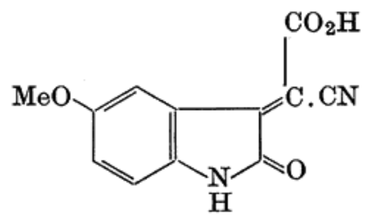


XIV XV

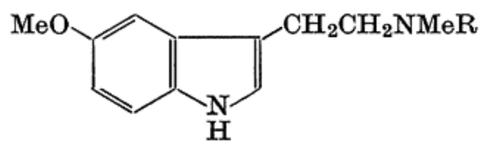
Finally, mention may be made of two further syntheses, which employ as crucial stages the condensation of *N*-acetyl-5-benzyloxyindoxyl (112) or 5-methoxyisatin (113) with cyanacetic acid to give the intermediates XVI and XVII, respectively; these were then converted into 5-hydroxytryptamine by standard procedures.



XVI



XVII



XVIII

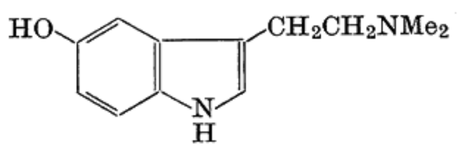
In mammals 5-hydroxytryptamine is found in the brain, in the blood, and in the tissues of the stomach, intestines, and lungs; its function in all these sites has not yet been fully elucidated. However, there is little doubt that it plays an extremely important role in the central nervous system, and, in particular, in the brain. The psychotomimetic activity of some drugs appears to be due to interference with the function of 5-hydroxytryptamine in the brain. It is also implicated in certain

abnormal pathological conditions; some intestinal tumors contain appreciable amounts of 5-hydroxytryptamine, which is excreted as 5-hydroxyindoleacetic acid. The appearance of this acid in inordinate amounts in the urine is used in the diagnosis of such tumors. The biochemistry and pharmacology of 5-hydroxytryptamine have been repeatedly discussed (see, for example, Ref. 114 and 115).

B. 5-Methoxy-*N*-methyltryptamine and 5-Methoxy-*N*,*N*-dimethyltryptamine

A report that sheep fed on a perennial grass, *Phalaris tuberosa* L., developed a condition known as "staggers" led to the investigation of a related species, *P. arundinacea* L., and the subsequent isolation from it of 5-methoxy-*N*-methyltryptamine (XVIII; R = H) (116). 5-Methoxy-*N*,*N*-dimethyltryptamine (XVIII; R = Me) also occurs naturally, and has been isolated from *Dictyoloma incanescens* DC. (40). Both bases have recently been shown to be present in the bark of *Piptadenia peregrina* Benth. (73a).

C. Bufotenine



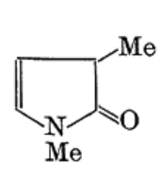
XIX
Bufotenine

Bufotenine, 5-hydroxy-*N*,*N*-dimethyltryptamine (XIX) occurs in the leguminous shrubs, *Piptadenia peregrina* (75, 117), *P. macrocarpa* Benth. (75), and *P. colubrina* Benth. (40). The seeds of the first two species have been used for centuries by certain Indian tribes of South America and the Caribbean islands as the source of a ceremonial, narcotic snuff, called cohoba, which is inhaled through a bifurcated tube. Some Brazilian Indians use the roasted seeds of *P. colubrina* for a similar purpose. Small doses of this snuff produce hallucinations and a kind of intoxication; excessive doses cause a violet temporary derangement. Whether bufotenine is the principal hallucinogen in these preparations has not yet been established, but it is certainly present in significant proportions; *P. peregrina* seeds contain 0.94% and *P. colubrina* seeds as much as 2.1% of bufotenine. Intravenous injection of bufotenine is reported to cause hallucinations (118), but the possibility that inhalation of *Piptadenia*

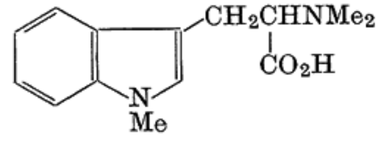
extracts can result in the absorption of sufficient bufotenine to cause these hallucinations has been refuted (119). It is therefore suggested that the hallucinogenic activity of the ancient Indian snuff was due to some more potent extraneous material introduced, or generated chemically, during preparation (119).

The isolation of bufotenine from vegetable sources demonstrates its ubiquitous nature. It also occurs in the secretion of the parotid gland of the toad (*Bufo vulgaris* Laur.) and several other *Bufo* species (120–125), in certain fungi [*Amanita mappa* Batsch., *A. muscaria* L., *A. pantherina* DC. (126), *A. porphyria* (126a), *A. tomentella*, and *A. citrina* Pers. (126b)], and in human urine (127).

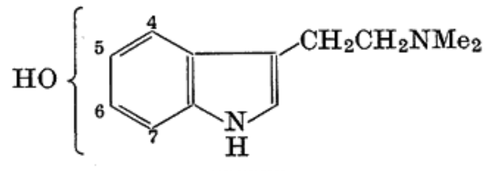
Bufotenine was first isolated from *Bufo vulgaris* in 1893 by Phisalix and Bertrand (120), but it was not fully characterized. Handovsky (128) later isolated the same oil, and obtained a crystalline oxalate, among other salts, which appeared to have the formula, $C_{14}H_{18}N_2O_6$, and from which he deduced that the base had the composition C_6H_9NO. Since the base gave a pine splinter color test, it was assigned a structure (XX) based on pyrrole (128). Wieland *et al.* reinvestigated these toad secretions, and from the basic fraction isolated two interconvertible, crystalline picrates, mp 178°, which were formulated as derivatives of a base, $C_{14}H_{18}O_2N_2$. The free base was not obtained crystalline, but since a relationship with hypaphorine was suspected from its general properties,



XX



XXI



XXII

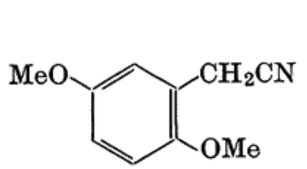
the structure XXI was tentatively proposed (129). However, this hypothesis was considerably weakened by comparison of bufotenine with *ind*-*N*-methyltryptophan, and was completely invalidated by its eventual crystallization and purification, when the molecular formula $C_{12}H_{16}ON_2$ was established (121). Bufotenine was known to contain a 3-substituted indole nucleus and a tertiary amino group; the weakly acidic properties were now shown to be due to a phenolic hydroxyl group. A free imino group was also present, since the base contained two active hydrogens and yielded a diacetate. These data were combined in the formula XXII, in which the position of the phenolic group was unspecified; however, positions 4 and 7 were provisionally eliminated, since at that time no derivatives of 4- or 7-hydroxyindole had been found among natural products. The synthesis of the two remaining

isomers was therefore undertaken. Methylation of 6-methoxytryptamine, already known in connection with investigations in the harmine series, with methyl iodide and thallium hydroxide, gave a quaternary iodide which coincided in melting point (182°–183°) with *O*-methylbufotenine methiodide (mp 183°–184°), and corresponded closely in physical and chemical properties, but which gave a depression of almost 40° of melting point on admixture. 5-Methoxy-*N*,*N*-dimethyltryptamine, mp 183°, was subsequently synthesized from 5-methoxyindole by condensation of the Grignard derivative with chloroacetonitrile, followed by reduction with sodium and alcohol and methylation of the 5-methoxytryptamine with methyl iodide and thallium ethoxide. The product was shown to be identical with *O*-methylbufotenine methiodide in all respects (121).

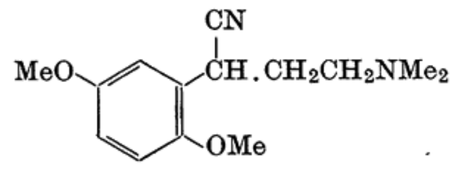
The synthesis of bufotenine itself followed closely upon the proof of its structure. Hoshino and Shimodaira reduced the ethyl ester of 5-ethoxyindole-3-acetic acid by the Bouveault-Blanc procedure to the corresponding primary alcohol, which was treated with phosphorus tribromide and then dimethylamine, to give the ethyl ether of bufotenine, which was demethylated with aluminum chloride (130). In a later synthesis, 2,5-dimethoxybenzyl cyanide (XXIII) was alkylated by Eisleb's method with dimethylaminoethyl chloride in the presence of sodamide to give 1-(2,5-dimethoxyphenyl)-3-dimethylaminopropyl cyanide (XXIV), which was then hydrogenated over Raney nickel to yield 2-(2,5-dimethoxyphenyl)-4-dimethylaminobutylamine (XXV; R = Me). Demethylation of this with hydrobromic acid, followed by oxidation of the product (XXV; R = H) with potassium ferricyanide yielded bufotenine (XIX) via the related quinone (109).

Two further syntheses of bufotenine have since been reported. In the first of these, 5-benzyloxyindole was treated with oxalyl chloride to give 5-benzyloxy-3-indoleglyoxylyl chloride, which was converted by reaction with dimethylamine into 5-benzyloxy-*N*,*N*-dimethyl-3-indoleglyoxylamide. Reduction of this with an excess of lithium aluminum hydride yielded *O*-benzylbufotenine, which was subsequently debenzylated (68). The fourth synthesis uses the gramine route (131). 5-Benzyloxyindole was converted into 5-benzyloxygramine, and thence into 5-benzyloxyindole-3-acetic acid, by standard procedures. *O*-Benzylbufotenine was prepared from this by conversion into the related acid azide, reaction with dimethylamine, and reduction of the amide with lithium aluminum hydride. Catalytic debenzylation over a palladium catalyst gave bufotenine, identical with that from *Amanita mappa* in all respects except melting point. Whereas bufotenine has been reported in several instances to have mp 146°–147° (68, 117, 121), Stoll *et al.* (131) found that

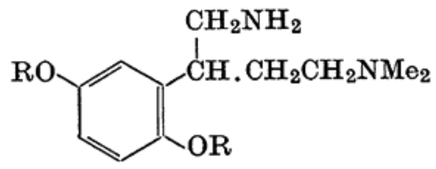
their sample melted at 138°–140° in spite of the most diverse and careful methods of purification. This recalls the behavior of tryptamine, which has been reported to exist in two forms, of mp 118° (132) and 145° (66).



XXIII



XXIV



XXV

The seeds of *Piptadenia peregrina* and *P. macrocarpa* also contain bufotenine *N*-oxide (75). Since some tertiary derivatives of tryptamine, e.g., *N*,*N*-dimethyltryptamine, are readily converted by aerial oxidation into the *N*-oxide, it is possible that bufotenine oxide may be an artifact, generated during the extraction procedure or chromatographic separation. However, the formation of bufotenine oxide from bufotenine has never been observed in the absence of a specific oxidizing agent; hence, it may be a genuine constituent of the seeds.

VII. Cryptolepine

Extracts of the *Cryptolepis* genus (Asclepiadaceae), which are shrubs indigenous to tropical Africa, have found application as stomachics and in the dyeing of textiles and leather. The sap is extremely bitter, and is characterized by the rapidity with which it turns deep red on exposure to air.

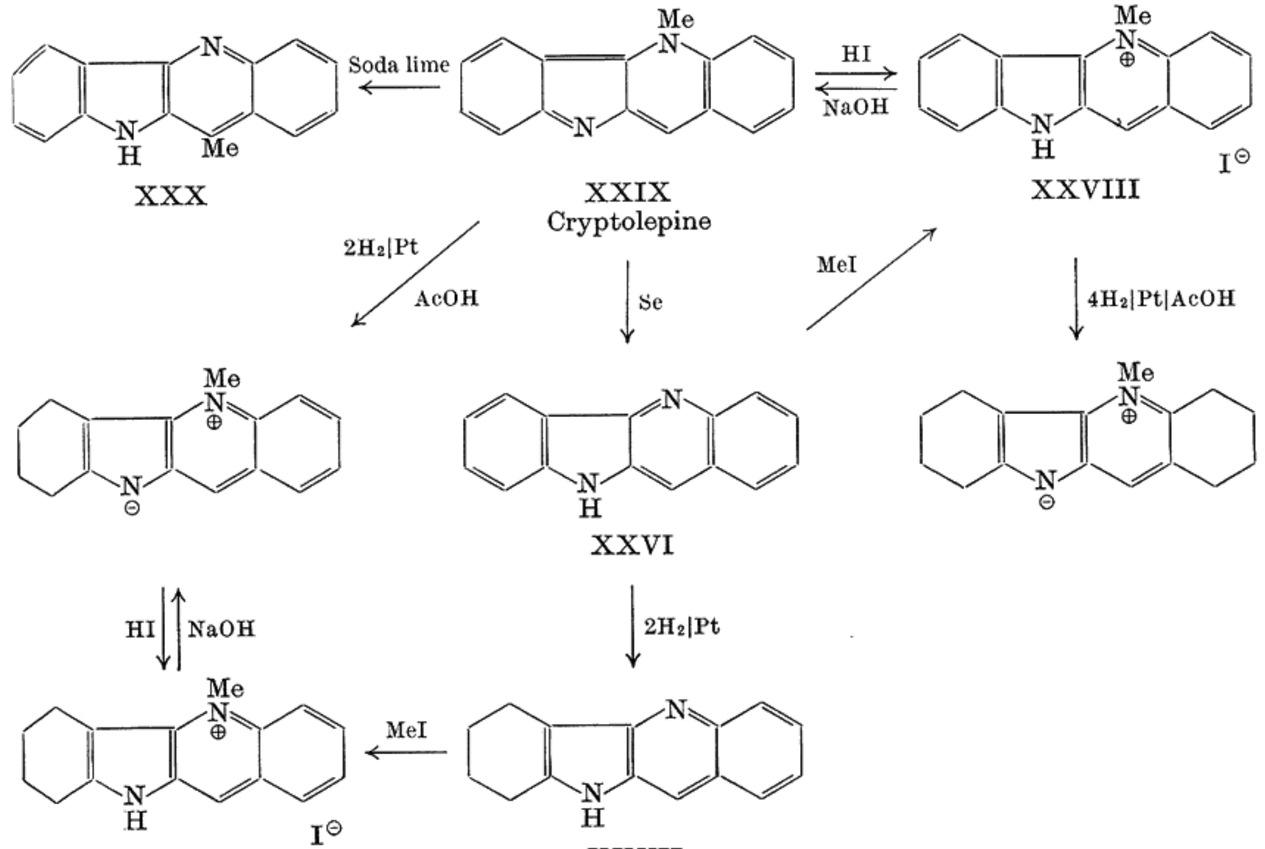
The alkaloid cryptolepine was first isolated from the roots of *Cryptolepis triangularis* N.E.Br., from the Belgian Congo, by Clinquart (133), and later by Delvaux (134), who obtained a base, mp 193°–194°, analysis of which corresponded to the formula $C_{17}H_{16}ON_2$. Dry distillation of cryptolepine with quicklime gave a colorless sublimate, $C_{13}H_{10-12}N_2$, mp 242°–243°, and a yellow sublimate, mp 225°, which were not further investigated. Cryptolepine was later isolated from Nigerian *Cryptolepis sanguinolenta* (Lindl.) Schlechter, and differs from all known alkaloids in that it forms deep violet needles, which give rise to solutions which are violet to red, according to the solvent (135). Analysis of the base (mp of

hydrate, 166°–169°), and several of its salts, which are yellow, indicated the molecular formula, $C_{16}H_{12}N_2$. The earlier formula of Delvaux is understandable in view of the tendency of cryptolepine to form solvates, particularly with water and alcohols.

The alcohol-free base, which can be obtained as a hemihydrate after being dried at 120°/0.01 mm, does not contain any *C*-methyl groups, but has one methylimino group. Selenium dehydrogenation gives a colorless base, base A, $C_{15}H_{10}N_2$, mp 249°–251°, which forms a yellow methiodide, identical with cryptolepine hydriodide. Hydrogenation of base A affords a tetrahydro derivative which can be converted, via its methiodide, into the corresponding methonitrate, identical with tetrahydrocryptolepine nitrate. Distillation of the alkaloid over soda lime gives a pale yellow base, base B, $C_{16}H_{12}N_2$, mp 264°–265°, which possesses a *C*-methyl group, and which presumably arises from cryptolepine by migration of the methyl group from nitrogen to carbon.

Hydrogenation of cryptolepine can proceed in three ways, according to the conditions employed. In methanol solution, using a platinum oxide catalyst, a yellow dihydro derivative is rapidly formed. When the resulting methanol solution is shaken with air, the violet color of cryptolepine reappears in a few seconds, thus rendering impracticable the isolation of the reduction product. This reduction can also be accomplished using sodium hydrosulfite, and is assumed to involve the reduction of a pyridine ring to a dihydro derivative. More vigorous hydrogenation of the base in acetic acid using a platinum catalyst yields tetrahydrocryptolepine, whereas hydrogenation of the hydrochloride under the same conditions leads to the slow formation of octahydrocryptolepine.

The absorption spectra of cryptolepine and the two hydrogenation products show, in common, a shift toward longer wavelengths in alkaline solution. It can therefore be inferred that the chromophore, which probably consists of the two nitrogen atoms linked by a system of conjugated double bonds, remains essentially unaffected by the hydrogenation, which involves the saturation of carbon rings. Cryptolepine must be tetracyclic, and a consideration of its UV-spectrum suggests that these four rings are linearly arranged. One of the few ring systems capable of meeting all these requirements is contained in the known base, quindoline (XXVI). This was shown by direct comparison to be identical with base A; tetrahydroquindoline and quindoline methiodide were identified with tetrahydrobase A (XXVII) and cryptolepine hydriodide (XXVIII), respectively (135). Cryptolepine (XXIX) is therefore the anhydronium base corresponding to quindoline methiodide, and it is of interest that it had been synthesized more than 20 years before its first isolation from *Cryptolepis triangularis* (136, 137, 138).



XXX XXIX Cryptolepine XXVIII

XXVI

XXVII

The structure of the isomer obtained on soda lime distillation is uncertain, but it is probably best formulated as XXX, since its spectrum is closely similar to that of quindoline. Cryptolepine has a significant hypotensive activity, and has been reported to cause a marked and prolonged fall in blood pressure in dogs (139, 140).

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