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Review Article

Ibogaine: A Historical Journey through Pharmacology, Total Synthesis, and Evolution Towards Iboga Alkaloid Analogs

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Abstract

Ibogaine, a powerful psychedelic, has been used throughout the world for much of human history. Its diverse usage has led to a unique outlook of the indole alkaloid as both an integral part of life and a concerning psychedelic. The pharmacologic community showed initial interest in utilizing ibogaine for the treatment of a number of substance use disorders; however, difficulty in synthesis has largely hindered therapeutic development. This work aims to examine the history of ibogaine, including its pharmacological properties and total syntheses, as well as potential applications of structurally similar chemicals which are simpler to make in a laboratory and do not cause heart problems, ibogalogs, particularly ibogainalog and tabernanthalog.

Keywords: Ibogaine; Ibogalogs; Total Syntheses; Psychedelics

Introduction

Ibogaine, an indole alkaloid, is considered a controversial compound due to its effects on the central nervous system and the cardiovascular actions thus the pursuit of therapeutic applications has historically not been vigorous. As a natural product of the *Tabernanthe iboga (T. iboga)*, traditional medicinal plant native to central Africa, it is an integral part of life there and a substance necessary for religious rituals and rites of passage [1]. In the 1960's, the beneficial effects as an addiction treatment suggested that single oral doses of ibogaine rapidly alleviated opioid withdrawal symptoms. While, in some countries (i.e., France), ibogaine-containing products (tradename Lambarene; used as a mental and physical stimulant) have been deemed illegal, use of ibogaine is unregulated in several countries (e.g. Mexico, Costa Rica, Panama, the Netherlands and Portugal [2]. The route of administration and the dose of the compound have a significant impact on both the rate and magnitude of bioavailability. To date, dissociative psychedelic with dreamlike properties, exerting multiple anti-addictive effects by targeting various stages of the addiction cycle, including the withdrawal and negative emotional states, continue to interest researchers.

As a natural product of the *Tabernanthe iboga (T. iboga)* plant, it sits in an interesting middle ground for both the synthetic and pharmacological communities. Despite an apparent lack of an economic base due to the mentioned regulatory issues in some countries and inability to patent the structure of ibogaine in addition to inefficiencies in extracting the substance from the plant, there is significant interest in exploring pharmaceutical effects of this class of compounds [3]. The synthetic community has produced useful semi- and total syntheses [3]. The history of ibogaine in western chemistry began in 1901 when it was first extracted and crystallized from the Tabernanthe iboga root bark [1]. The structure was elucidated in 1957, and the absolute stereochemistry confirmed by crystallography in 1960. Ibogaine possess a complex fused ring system that is prominent in both the parent compound, its metabolites, and numerous other indole alkaloids that have been extracted from *T. iboga* [4] (Figure1).

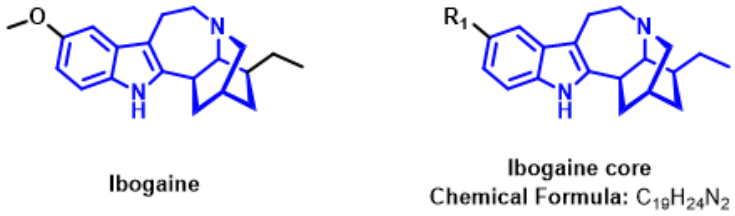


Figure 1: The structure of Ibogaine with the ibogaine core highlighted.

Ibogaine is the most abundant alkaloid within the *T. iboga* plant, while the percentage of it in the entire plant is relatively low. In the dried root bark, the percentage of ibogaine is 5-6% [5]. However, the extraction of ibogaine for research purposes is expensive and largely inefficient.

Ibogaine has a complex pharmacological profile, wherein it has several receptor interactions including serotonin receptor modulation, NMDA receptor agonism, kappa- and mu-opioid receptors, and dopamine regulation [1]. Ibogaine has also exhibited anti-addictive properties that are of interest to researchers. Ibogaine's primary metabolite, noribogaine, has a longer half-life and may be attributed to its anti-additive effects. The use of ibogaine is not without safety concerns including cardiac risk, neurotoxicity, additional psychological risks (hallucinations), ataxia and seizures [6].

History of Ibogaine Usage and Pharmacology

Use of ibogaine is often associated with the Punu, Mitsogo, and Fang peoples of Gabon and Cameroon, where the Bwiti religion is prominent. Within Bwiti practices, high doses are used for religious practices, acting as a hallucinogen to achieve visionary states, and lower doses are used for their stimulating effects to aid in staying alert for long periods of time, often for hunting. Bwiti healers use iboga to treat several ailments including pain and fever [2]. The cultural context of ibogaine's usage is deeply intertwined with such spiritual and healing practices [7]. In Western Europe, following the isolation of ibogaine, researchers identified it as the primary psychoactive compound. French researchers examined ibogaine's effects on the central nervous system (CNS). Simultaneously, ibogaine was sold from the 1930s to the mid-1960s as Lambarene in France. Lambarene, an ibogaine containing extract of *Tabernanthe manii* plant was a purified ibogaine hydrochloride salt sold as an antidepressant and stimulant. It was removed/withdrawn in 1966, when all ibogaine containing products became illegal in France [5].

In the United States, ibogaine gained interest through the experimental use of a teenage heroin addict, Howard Lotsof. In 1962, while dealing with heroin addiction, Lotsof accidentally discovered its anti-addiction properties. During recreational experimentation with ibogaine, he noticed alleviation of withdrawal symptoms from heroin. Lotsof used additional experiments as evidence to raise awareness about ibogaine's potential as an addiction treatment. These results were patented in 1985 [8] initially for heroin, wherein oral administration of ibogaine or its salts "disrupt the heroin addiction syndrome." A single dose of ibogaine or an ibogaine salt at a dose ranging from 6 mg/kg to 19 mg/kg showed disruption of addiction for approximately 6 months. Later patents included the same treatment for cocaine, heroin, and poly-substance use disorder [9].

While initial animal studies supported Lotsof's claims of decreased opiate dependence and withdrawal symptoms, The *Lots of Procedure* [10] has not been admitted as a clinical procedure, due to the side effects. Concurrent to Lots of's patents, several academic groups began examining ibogaine's anti-addictive potential in rats. While ibogaine showed a reduction in self-administration of morphine and cocaine [11,12], it also presented tremorgenic and neurotoxic effects. O'Hearn and Molliver presented work displaying a degradation of Purkinje cells followed by ataxia following a dose of 100mg/kg [13]. However, later studies showed that this degradation is dependent on dose, wherein a dose of 40mg/kg showed no degradation and retained reduced morphine or cocaine self-administration.

In humans, potential cardiotoxic side effects have hampered therapeutic development strategies. These affect predominantly the heart's electrophysiology, causing arrhythmias, prolonged QT intervals, and in rare cases cardiac arrest. The exact mechanism is not known but is believed to be due to ibogaine's interaction with potassium channels.4 These cardiotoxic effects have been implicated ibogaine related deaths, prompting USFDA to identify ibogaine as a Schedule I classification in 1975 [14].

Human CNS effects of ibogaine have been theoretically linked to biogenic amine levels in selected brain regions. Biogenic amine levels in the brain vary significantly across different regions, with the most prominent ones being dopamine (DA) concentrated in the substantia nigra and ventral tegmental area, norepinephrine (NE) in the locus coeruleus, serotonin (5-HT) in the raphe nuclei, and histamine (HA) in the tuberomammillary nucleus. Given the involvement of these neurotransmitters in drug addiction, the effects of ibogaine on biogenic amine transport may contribute to the potential anti-addictive properties of ibogaine. With rat brain synaptosomes as our experimental system, we measured the effects of ibogaine on the uptake and release of DA and 5-HT. Ibogaine competitively blocked both DA and 5-HT uptake with IC50 values of 20 mM at 75 nM 3H-DA and 2.6 mM at 10 nM 3H-5-HT. Ibogaine had no effect on K1-induced release of 3H-DA from preloaded synaptosomes, but 20 mM and 50 mM ibogaine inhibited roughly 40% and 60%, respectively, of the K1-induced release of 3H-5-HT from preloaded synaptosomes. In the absence of a depolarizing

stimulus, ibogaine evoked a small release of 3H-DA but not 3H-5-HT. These relatively low-potency effects of ibogaine on DA and 5-HT uptake in synaptosomes are consistent with the low binding affinity of ibogaine that has been previously reported for DA and 5-HT transporters. Our results suggest that ibogaine modulates DA and 5-HT levels in the brain by directly blocking their uptake, and plausibly that a concentration of ibogaine in the micromolar range is required. Furthermore, if the anti-addictive effects of ibogaine require this concentration, then ibogaine likely exerts these effects through a combination of neurotransmitter pathways. Binding affinities and functional potencies of ibogaine in the micromolar range have been reported for a variety of neuronal receptors and transporters [9].

Pharmacology of Ibogaine

Ibogaine presents complex pharmacological relationship with several neurotransmitters. Its predominant mechanisms of action include interactions with dopamine, serotonin, opioid, and NMDA receptors. The latter involves neuroplasticity and neurotransmission [1]. It works as a weak dopamine reuptake inhibitor, causing an increase in dopamine levels. Dopamine transporter IC50 values range from 1.5 to 20 μM [15]. This can lead to improved emotional states and may also be attributed to ibogaine's ability to reduce cravings in addiction treatment (Figure 2).

Figure 2: The structures of ibogaine and serotonin, which contain a tryptamine core, compared to the catecholamine core seen in dopamine.

The complex psychedelic effects are believed to result from multi-receptor activity, causing both dissociative and hallucinogenic effects, presenting ibogaine as an unparalleled substance compared to other more common psychedelics. Ibogaine's effectiveness in addiction treatment is believed to act by resetting neural pathways, evidence includes small-scale trials, where ibogaine continued to show alleviation in withdrawal symptoms, and interruption in addiction cycles such as cravings for narcotics. As described above, the psychedelic effects of ibogaine are attributed to multiple neurotransmitters within the brain; however, the exact mechanisms behind the psychedelic properties are not well understood. Like most other psychedelic molecules (Lysergic Acid Diethylamide (LSD), psilocin), ibogaine binds to the 5-HT2A receptor as a partial agonist, which plays a role in producing classic psychedelic effects such as auditory and visual hallucinations, altered sense of time, and changes in thought processes [9, 12,16] (Figure 3).

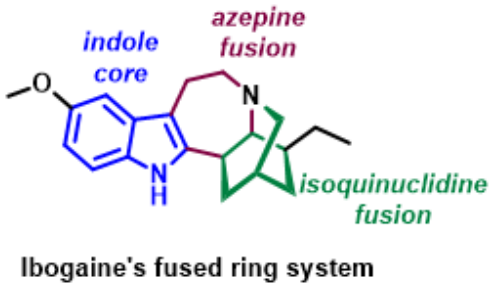


Figure 3: Ibogaine with indole, azepine, and isoquinuclidine rings specified.

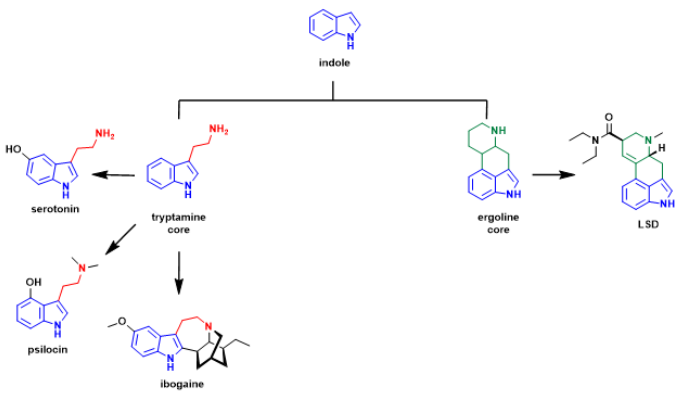
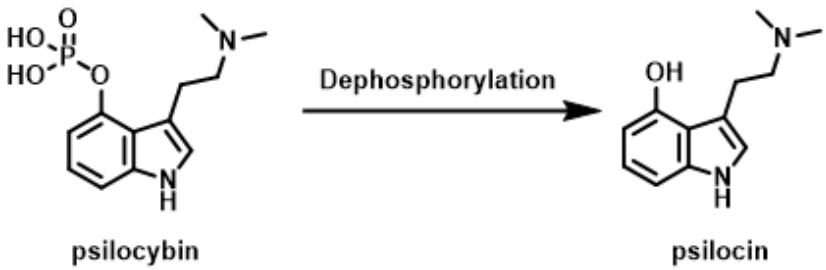


Figure 4 : examination of how a simple indole core is present in other cores of known psychedelics, like tryptamines and ergoline. The indole core is highlighted in blue, the substituents highlighted in red represent the tryptamine core, and those highlighted in green represent part of an ergoline core.

Ibogaine, LSD, and psilocin are similar, most notably in their interactions with serotonin receptors, especially 5-HT2A, but also structurally. Ibogaine is an indole alkaloid, containing a distinct tricyclic ring system built off an indole core. Indoles are ubiquitous in both natural products and pharmaceuticals. The tricyclic ring system utilizes the indole core as a base that is fused to an azepine moiety (7-membered nitrogen containing heterocycle). The final fused ring, the isoquinuclidine, is formed via a fusion through the azepine's nitrogen [17]. Ibogaine contains additional substituents including a methoxy group attached to the indole ring and an ethyl group attached to the isoquinuclidine ring. The azepine ring in ibogaine makes it unique among other psychedelic compounds (Figure 4).

LSD contains a tetracyclic ring system utilizing an ergoline backbone. Ergoline backbones are also indole-based and fused to three additional rings. The resulting ring system is highly conjugated, assisting in the rigidity of the complex structure. LSD's substituents include a N,N-diethylamide attached to the ring system at position 8 and a methyl group attached through the nitrogen of the tetrahydropyridine, part of the ergoline skeleton. Psilocin, a tryptamine, has the simplest structure of the three containing an indole core and an ethylamine side chain. In psilocin's case, the ethylamine side chain contains an N,N-dimethyl substituent, increasing its lipophilic character. It also contains a hydroxy group at the 4-position of the indole ring.

The structural similarities are attributed to the psychedelic effects; however, neither psilocin nor LSD have exhibited any anti-addictive properties. Ibogaine and psilocin are further comparable due to respective metabolites being the primary compound to cause pharmacological effects as compared to the parent molecule. In this case, psilocin is the primary metabolite of psilocybin, a substitute tryptamine that contains a phosphorylated indole. This moiety is rapidly dephosphorylated to form psilocin (Scheme 1).



Scheme 1: conversion of psilocybin to psilocin.

Ibogaine's primary metabolite, noribogaine, has been equally attributed to several pharmacological effects such as its namesake. Ibogaine has a short half-life of 7 hours in humans, contrary to the psychoactive effects acting for 24 hours or longer. This contributed to an active metabolite, known as noribogaine. The O-demethylation of ibogaine to noribogaine is catalyzed primarily in the liver by CYP2D6, with some reactivity with CYP2C19 and CYP3A4 [18]. The half-life of noribogaine is 28 - 50 hours in humans. In studies, by Glue et al the half-lives were calculated based on data from healthy volunteers [19] (Scheme 2).

Scheme 2: Ibogaine metabolites conversion of ibogaine to noribogaine metabolite.

Both ibogaine and noribogaine are known to have a high affinity for serotonin transporters (SERT) which inhibits the reuptake of serotonin. The indole ring exhibited in all three compounds is key to their respective activity towards serotonin receptors (5-HT). The indole core allows them to mimic serotonin, whose tryptamine core assists in binding to the same receptors. The blockage of SERT increases the amount of serotonin in the synaptic space. In serotonin transport, Tanaka *et al* presented IC50 for ibogaine to range from 0.55 – 10 μM [12, 20]. This antidepressant-like effect is similar to those seen in SSRIs, but less effective due to ibogaine's

lower affinity to bind to SERT. When comparing ibogaine to the most prescribed SSRI in the United States, Sertraline (Zoloft) has a SERT inhibition IC50 value of 0.29 μM. Ibogaine's primary metabolite, noribogaine, has a longer half-life and it is therefore considered a more potent SERT inhibitor. Mash et al showed that noribogaine serotonin transport IC50 values were 10-fold stronger compared to dopamine [17]. The extended activity may also contribute to a reduction in cravings and withdrawal symptoms. When comparing ibogaine's dopamine and serotonin IC50 values, it has been reported to exhibit 10 - 50 times stronger for dopamine [17].

Ibogaine acts as a partial agonist for both 5-HT2B and 5-HT2C receptors. 5-HT2B receptor can affect mood and cognition, but prolonged activation of this receptor has been linked to cardiac risks. Though this receptor can cause safety concerns, it is unlikely that it acts as a pathway for ibogaine's anti-addiction properties. The 5-HT2C receptor is responsible for mood, anxiety, and appetite. When activated these receptors cause a decrease in dopamine, and in turn affect the reward/addiction pathway. This pathway is linked to dopaminergic and serotonergic symptoms. Ibogaine induced modulation of this receptor helps to suppress the overexpression of dopamine seen in response to various drugs, including opioids and stimulants [13].

Regarding NMDA (N-methyl-D-aspartate) receptor, not ibogaine itself, but its primary metabolite, noribogaine acts as a weak antagonist inhibiting these receptors by altering neural communication, leading to altered stages of consciousness and dissociation from reality. In this case, the modulated activity of the NMDA receptors by noribogaine is comparable to ketamine, another dissociative psychedelic medication. Noribogaine modulates glutamate release, decreasing the potential for overstimulation. Modulation of this system is believed to play a role in addiction and withdrawal processes due to the neural changes that occur with chronic drug use. Regulation of the glutamate systems in addiction potentially reduces withdrawal symptoms and cravings.

Both kappa- and mu-opioid receptors are affected by ibogaine. With kappa opioid receptors (KORs), ibogaine acts as a partial agonist, which may contribute to some of its psychoactive effects. KORs traditionally produce hallucinogenic and dysphoric effects while reducing dopamine release. When activated, KORs are known to reduce the reward pathway. This would play a crucial role in the treatment of drug addiction by making drugs less rewarding. In mu-opioid receptors, ibogaine does not directly bind with high affinity receptors, but is still attributed to anti-addictive properties. This indirect modulation helps in reducing the rewarding effects of opioids.

Total Synthesis of Ibogaine

Ibogaine was first isolated in 1901, while the structure was presented in 1957 [21]. Absolute stereochemistry was determined via X-ray crystallography by Jeffery *et al* in 1960 [22]. All members of this family exhibit an indole core, like serotonin and other tryptamine-based psychedelics [14]. Ibogaine contains additional functional groups that are thought to contribute to complex pharmacological activity. This includes a methoxy group attached to the aromatic indole ring, and a bridging methyl group that fuses the azepine ring to the is quinuclidine ring. The rigidity of a multi-fused ring structure makes ibogaine distinguishable from other tryptamine and erogoline-based structures seen in psilocin and LSD, respectively.

Extracting natural ibogaine from the *Tabernanthe iboga* plant is a challenging and laborious process. The root composition of the iboga plant is approximately 6% indole alkaloids. The concentration of ibogaine in the entire plant is relatively low but is most abundant in the roots. This makes large scale extraction of ibogaine difficult and therefore inefficient. The plant also contains numerous other alkaloids. Similar chemical characteristics of these compounds further complicate the extraction and purification processes. Separation of ibogaine from structurally similar alkaloids requires advanced separation techniques (Figure 5).

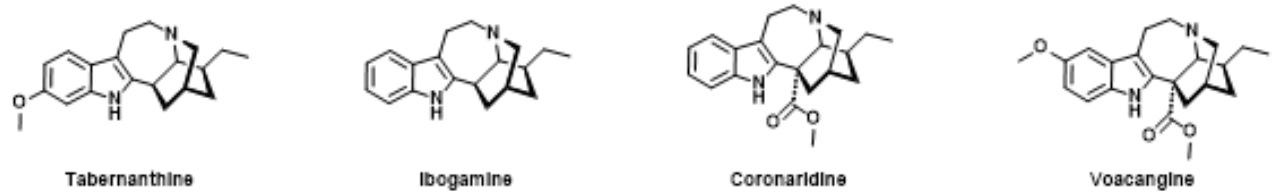


Figure 5: various examples of indole alkaloids extracted from *T. Iboga*.

The exact structure with all stereocenters specified, specifically that of the ethyl group was debated until the seminal crystal structure by Jefferey. This structure of ibogaine showed the substituent ethyl group was cis to the isoquinuclidine nitrogen in the crystalline structure [19]. Due to ibogaine's complex structure, it requires several steps that are often low yielding and produce delicate intermediates. The complex synthetic methodologies make scale-up difficult and not economically viable.

Aside from the difficulties in isolation and purification, there are also environmental issues and legal challenges. *Tabernanthe iboga* is naturally slow growing, thus harvesting for illegal or medicinal uses threatens local populations. From a legal perspective, the

plant is a protected species in several countries, further restricting harvest and exportation of the plant for ibogaine isolation. These challenges led to an increased interest in synthesizing ibogaine and its analogs, leading to more scalable and sustainable approaches for uses in medicine (Figures 6,7).

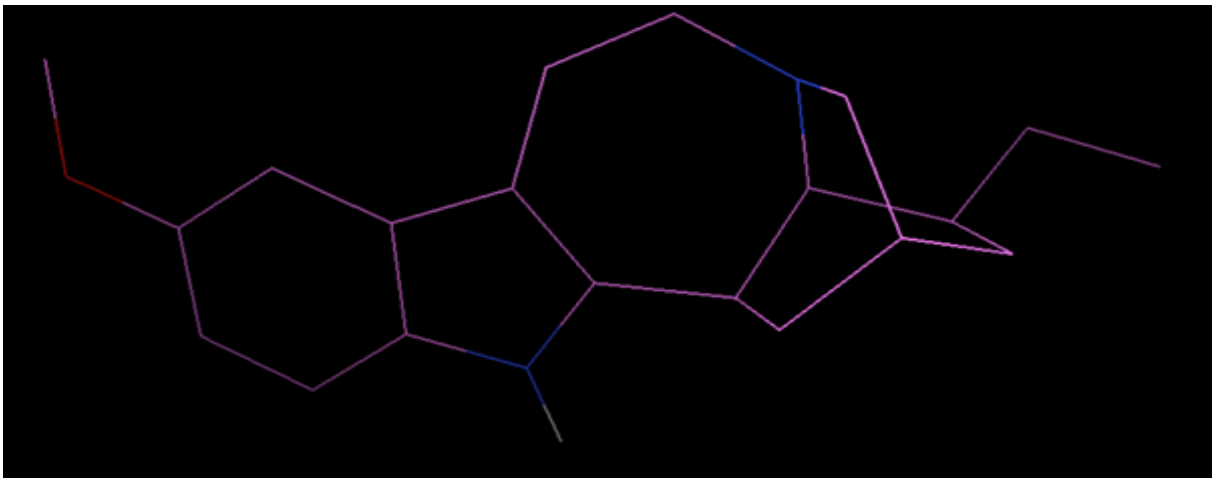
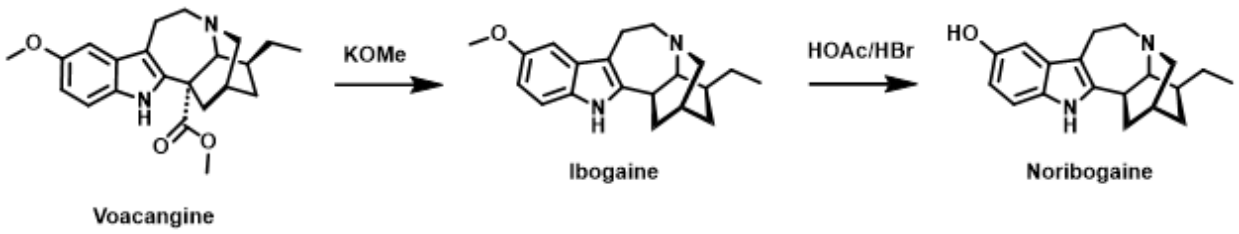
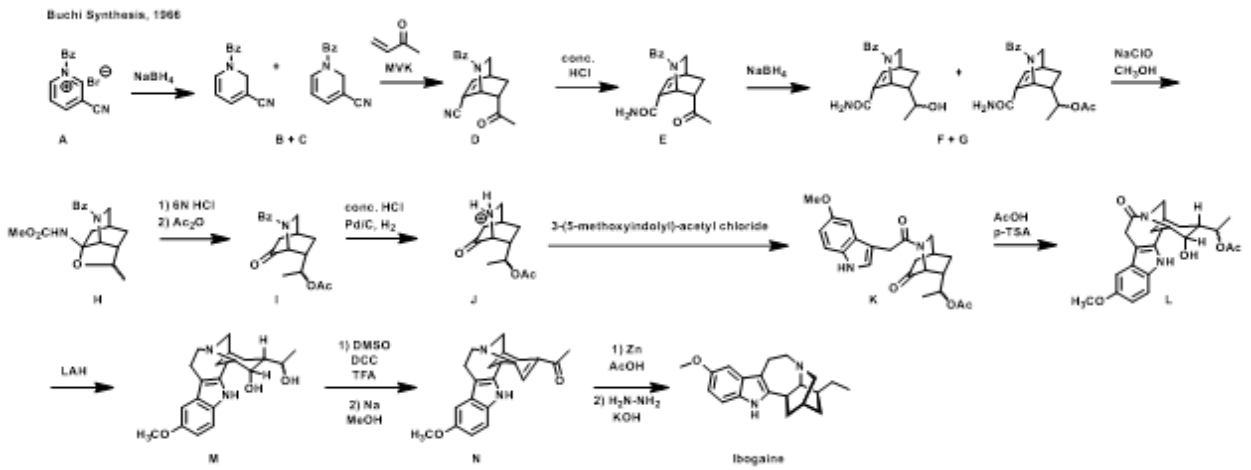


Figure 7: A 3D representation of ibogaine exhibiting the cis conformation of the isoquinuclidine and ethyl moiety. The pink scaffold represents carbon atoms, blue represents nitrogen, red represents oxygen, and grey represents hydrogen. The sdf file for ibogaine was downloaded from the NIH and visualized in *AutoDock*.

An early synthesis of ibogaine was patented in 1957 (US Patent 2813873). However, this can be deemed a semi-synthesis as this method converts voacangine to ibogaine in one step and further conversion to noribogaine in an additional step to achieve their desired product. The voacangine can be readily extracted from Voacanga Africana bark at a concentration of 5g/kg. Extraction of ibogaine from Tabernanthe iboga requires use of the root and has an approximate concentration of 3g/kg. Removal of the bark is argued to be more environmentally friendly and efficient than the destruction of the iboga plant (Scheme 3,4).



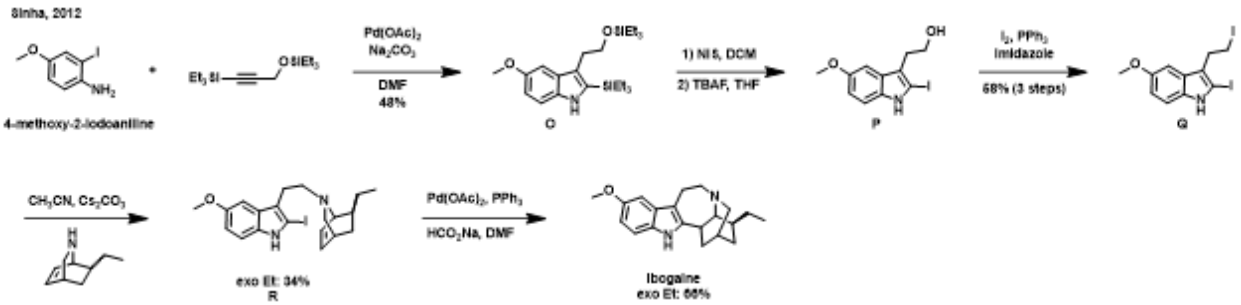
Scheme 3: The semi-synthesis of ibogaine and noribogaine from voacangine.



Scheme 4: Buchi's total synthesis of ibogaine.

A seminal total synthesis was published by Buchi et al in 1966 [23]. Buchi's method utilized a reduction of a pyridinium bromide complex (A) to a mixture of 1,2-dihydrpyridines (B +C). Either isomer can proceed to the next step and does not require purification. The crude mixture of dihydropyridines is condensed with methyl vinyl ketone, proceeding through a Diels-Alder cycloaddition to yield an isoquinuclidine (D) in a 16% yield. This intermediate is then subjected to hydrolysis by concentrated acids to form a primary amide (E). Sodium Borohydride is used to reduce the ketone to a mixture of alcohol and acetate products (F + G), either of which can be subjected to oxidation to form a tricyclic urethane core (H). This proceeds through a variation of the Hofmann rearrangement. The tricyclic urethane core is subjected to acid mediated hydrolysis followed by acetylation to produce an acetoxy ketone (I). Hydrogenolysis then forms amine salt (J), the subsequent amine condensation installs the indole groups forming a tertiary amide (K) followed by cyclization to a lactam (L). Utilizing lithium aluminum hydride, a dual reduction proceeds on both the ketone and acetoxy group (M), subsequent oxidation/dehydration forms an unsaturated alpha, beta-ketone (N). This is followed by an alkene reduction and Wolff-Krishner reduction of the unsaturated ketone producing both ibogaine and its C4-epimer (not pictured), which are readily separable [5,20].

Though this was a seminal synthesis, variation between their products and naturally occurring ibogaine. The synthesized material showed discrepancy in the stereochemistry of the ethyl group compared to prior crystallographic results. Notably, the ethyl group in this synthesis appears to be trans (endo) to the isoquinuclidine ring where the crystalline structure shows the ethyl group to be cis (exo) with the isoquinuclidine. This represents the ethyl group as extending outward, above the plane of the ring system. However, the mass and infrared spectroscopic results were identical to that of the natural product [5,20] (Scheme 5).

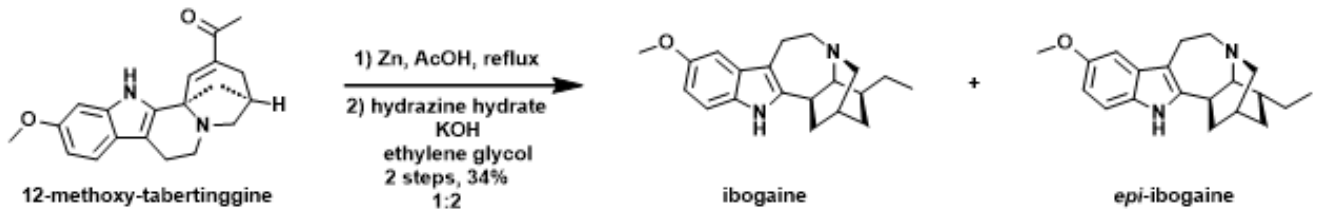


Scheme 5: Sinha's simplified total synthesis of ibogaine.

In 2012, a simplified total synthesis of ibogaine was published by Sinha et al [14]. This work began with 4-methoxy-2-iodoaniline, proceeding through the Larock indole synthesis. This is a palladium-catalyzed heteroannulation with an alkyne. The subsequent annulation forms a disilylated indole core (O). This is followed by an iodination and silyl deprotection to form intermediate P. A second iodination proceeds to form intermediate Q. The three preceding steps lead to an overall yield of 58%. Intermediate Q is then subjected to an iodine-mediated α-amination with tropane. The reaction results in two products, with both an exo-ethyl group and an endo-ethyl group. Intermediate R shows the exo variation with a 34% yield. The final step of the synthesis is a reductive Heck

coupling to yield ibogaine, with proper stereochemistry of the ethyl moiety (exo) in a 66% yield. The overall yield for the entire reaction sequence is 9.8% [14,20].

Additional syntheses have shown ibogaine to be produced from various intermediates during the syntheses of other alkaloids, such as tabertinggine. In this case, tabertinggine and its variants serve as iboga precursors. In this case, She and coworkers utilized 12-methoxy-tabertinggine as the iboga precursor to synthesize ibogaine and epi-ibogaine in 2 steps (34% yield) and a 1:2 ratio [24]. The synthesis of 12-methoxy-tabertinggine itself is ten steps from 2-(5-methoxy-1H-indol-3-yl)ethan-1-amine [24] (Figure 8)(Scheme 6).



Scheme 6: Synthesis of ibogaine and epi-ibogaine from 12-methoxy-tabertinggine.

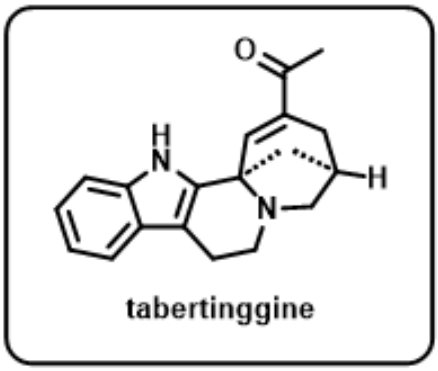


Figure 8: Structure of tabertinggine

Aside from the seminal synthesis by Buchi et al [20] and the subsequent total synthesis by Sinha14 the synthetic community has not explored additional total syntheses for ibogaine. However, as exhibited by Shi and several others, the interest in ibogalogs and semi-syntheses have remained prevalent. The synthetic difficulties of producing this unique psychedelic remain a challenge. The rigid, polycyclic structure is difficult to construct while retaining necessary stereoselectivity. This can be noted in the C-C bond formation to attach the indole core to that of the isoquinuclide which can be challenging to achieve in high yield and proper stereochemistry. As exhibited in Buchi's work, the chiral quaternary ethyl moiety is particularly difficult to construct with proper configuration [20]. Further synthetic difficulties include ibogaine's sensitive functional groups, like indole nitrogen, which can undergo degradation and be prone to overreaction. Due to the complexity of the synthesis, scalability and reproducibility at scale is also difficult.

Development of Iboga Alkaloid Analogs

Synthetic alternatives offer an alternative to synthesis and the health challenges of the original Iboga alkaloid analogs also referred to as ibogalogs, offering the potential for benefit without adverse side effects, provide a novel potential therapeutic approach. Synthesizing ibogaine and analogs promotes enhanced safety and efficacy applications. Systematic modification of the analogs has the potential for improving therapeutic effects and reducing side effects and toxicity.

Ibogalog variations can also augment pharmacological avenues of therapy The effects across multiple biological targets can be leveraged for optimization of specific effects and target selection.

While there have been numerous examples of ibogalogs and iboga precursors presented in the literature in recent years, perhaps the most notable is 18-methoxycoronaridine (18-MC), also known as zolunicant. 18-MC was first synthesized in 1996 by Glick and colleagues. In animal studies it has shown reduction in self-administration of morphine, methamphetamine, and nicotine [11,17]. Compared to ibogaine, 18-MC has shown no affinity for NMDA or 5HT transporters while maintaining agonist effects for μ-opioid receptors [11,25].

18-MC was synthesized as a variation of albiforanine isolated from the bark of Tabernaemontana albiflora. Beginning with a benzylated indoloazepine a condensation reaction with 4-(1,3-dioxolan-2-yl)-6-methoxyhexanal gave a mixture of diastereomers which were readily separable. The major isomer is represented in the scheme below only. Sodium borohydride was used to cleave the C3 and C7 to give the major diastereomer and forming a 7-membered ring. This product was then subjected to hydogenolysis to remove the benzyl protecting group. The acetal function group was removed via hydrolysis which subsequently caused a spontaneous cyclization to form an enamine. Upon reflux in toluene, the enamine was converted into the final product (Figure 9) (Scheme 7).

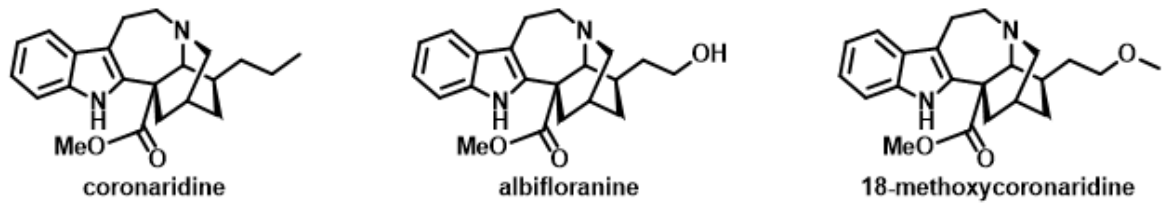
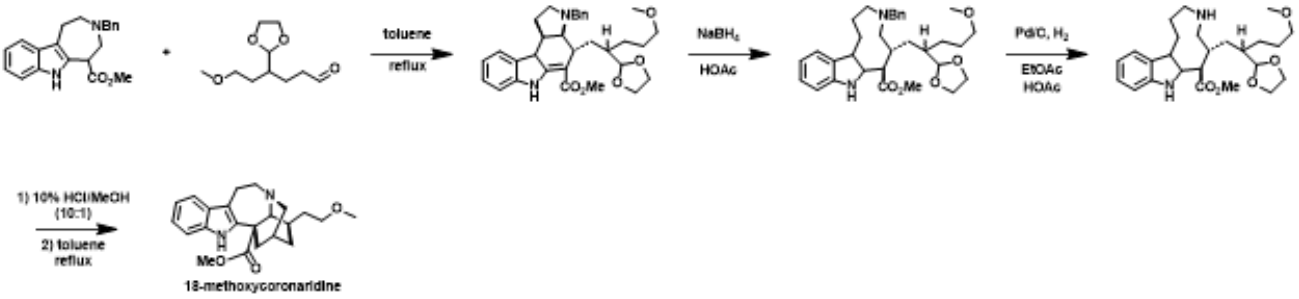


Figure 9: Structures of coronaridine, albiforanine, and 18-MC.



Scheme 7: Synthesis of 18-MC.

Conclusion

The long and convoluted history of ibogaine suggests that there is potential for pharmacologic improvement. Its diverse therapeutic potential has become a focal point to research both ibogaine itself and other iboga alkaloids. The interaction with multiple receptor systems provides a unique pharmacological profile, showing precedence for treating a variety of ailments including addiction and other neurological disorders. Its promises do not outweigh the challenges of this controversial molecule including its inherent toxicity and strong psychedelic effects. Advancements in synthesis to construct ibogaine's intricate structure has allowed for the development of novel iboga alkaloid analogs. These variants aim to retain the therapeutic potential of ibogaine while mitigating some of the limitations including toxicity, complex syntheses, and scalability complications. The evolution of ibogaine and iboga alkaloids remain a powerful source of potential therapeutics.

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