Natural Product Letters, Vol. 16, No. 1, pp. 71–76

Taylor & Francis
healthsciences

EXTRACTION STUDIES OF *TABERNANTHE IBOGA* AND *VOACANGA AFRICANA*

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(Received 11 November 2000; In final form 31 July 2001)

The root bark of *Tabernanthe iboga* contains ibogaine as its predominant alkaloid and has been an important source of it. Ibogaine is used experimentally to interrupt drug addiction and allow therapeutic intervention, but is currently unaffordable to doctors in less economically developed countries. To meet this need, an extraction of alkaloids from *T. iboga* root bark was optimized and simplified to use only diluted vinegar and ammonia, and was successfully applied to related alkaloids from *Voacanga africana* bark also. The alkaloids were converted to their hydrochlorides and purified, and the minor alkaloids were recovered.

Keywords: Addiction treatment; Drug addiction; Ibogaine; Ibogaline; Voacangine; *Tabernanthe iboga*; *Voacanga africana*

INTRODUCTION

The root bark of the *Tabernanthe iboga* shrub has been used for centuries in West African ceremonies by Bwiti initiation society members entering adulthood [1]. The Bwiti believe that the initiates meet their deceased ancestors and thus form a more tangible link with their past and traditions. The principle alkaloid in the root bark is ibogaine [2], which itself possesses pharmacological effects similar to those of the root [3]. These effects, which last about 36 h in human beings after a single oral dose, may include nausea, incoordination, visual after images and closed-eye imagery, introspectiveness, and many psychological experiences which could be of psychotherapeutic value, such as the re-experiencing of past memories in an unthreatening manner [4,5].

The ability of ibogaine to interrupt addiction was discovered in 1962 by Howard Lotsof of New York [6]. Howard was addicted to heroin and took an extremely rare opportunity to ingest ibogaine due to his interest in psychedelics. After the experience he realized that both his desire for heroin and the expected symptoms of withdrawal were absent. This freedom from addiction continued over the following months, and the ability of ibogaine to interrupt addictions to heroin, methadone, cocaine, methamphetamine, and nicotine has since been demonstrated in animals as well as hundreds

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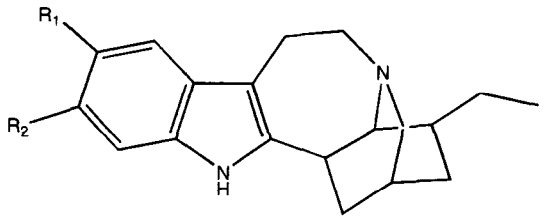
ISSN 1057-5634 print: ISSN 1029-2349 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/1057563029001/4881

of human subjects [5]. Howard Lotsof began patenting the use of ibogaine for treating drug addictions [7] in 1985 and campaigned between 1982 and 1994 to obtain FDA approval for this use. This campaign included initiating research agreements with academic institutions in Canada, Europe, the United States and Central America as well as the National Institute on Drug Abuse [8]. In spite of severe financial obstacles for researchers in this area, ibogaine continues to be the focus of continued research and experimental treatment in both animals and humans [5].

The most popular natural source of ibogaine has been the root bark of *T. iboga* [2], but the shrub only grows naturally in Africa [3] and currently requires professional training to extract. Existing procedures [2,9] use haloalkanes or alcohols for the extraction and chromatography for the purification of iboga alkaloids and are expensive and difficult because their objective was only to identify the alkaloids present. Ibogaine can also be prepared semisynthetically [10] or synthetically [11], and these methods hold great promise for future development but are currently expensive. Meanwhile affordable ibogaine is needed by researchers and doctors exploring treatment options for addiction in less economically developed countries. This article presents a convenient, inexpensive, and efficient procedure to isolate and purify the alkaloids from *T. iboga* root bark and enable affordable processing of the bark in Africa without exportation.

RESULTS AND DISCUSSION

Analysis of *T. iboga* root bark using silica TLC, eluting twice with ethyl acetate followed by staining with iodine vapor, showed ibogaine (2) as a dark brown spot ($R_f = 0.16$) with a trail (depending on concentration), a red spot ($R_f = 0.07$) belonging to ibogaline (4) below it, and a small brown spot ($R_f = 0.21$), assumed to be ibogamine (1), slightly above it. The percentages of ibogaine, ibogaline, and ibogamine appear to be 80, 15, and 5% respectively judging by the size and density of the stained spots. The spot for ibogaline gave a red stain using Keller's reagent [12], confirming its identity [9]. Occasionally a batch of root would contain ibogaine and ibogamine but little or no ibogaline, and perhaps this was a related Tabernanthe species [9]. TLC analysis of root wood, stem bark or leaves of the *T. iboga* plant showed negligible ibogaine.



(1) Ibogamine: $R_1 = R_2 = H$
(2) Ibogaine: $R_1 = CH_3O$, $R_2 = H$
(3) Tabernanthine: $R_1 = H$, $R_2 = CH_3O$
(4) Ibogaline: $R_1 = R_2 = CH_3O$

The optimized extraction method involved stirring powdered root bark with vinegar and filtering. Boiling the bark made the vinegar impossible to filter and was unnecessary. Although filter paper or coffee filters worked on a small scale, a cloth sack was more appropriate for large scale filtration. Either shredded or powdered root or root

bark were efficiently extracted using this method, although large shavings trapped some alkaloid under the bark. The yield was not improved by extracting for longer than an hour, increasing the concentration of acetic acid, or using a larger volume of acetic acid solution. Each extraction of shredded root bark removed about half as much alkaloid as the previous one, so that three extractions gave approximately 87% of the alkaloid potentially extractable from the root. Further extractions were practical only for large batches or if the extracts were then used to extract fresh root in a batch process.

Ammonia was convenient for basifying the filtered extracts, although other inorganic bases should have worked also. The resulting solid precipitate of total alkaloids (TA) was fortuitous since the expected oil would have necessitated laborious extraction. The TA took fewer hours to filter if the upper liquid was first siphoned off after the solid settled. The TA was dried at room temperature or with gentle warming. Solutions left sitting for more than a few days were contaminated by bacteria.

The TA solid showed no detectable change according to TLC even after months of exposure to indirect sunlight and air. The solidity and stability of the TA were unexpected because the evaporated acetone extract of it gives an unstable oil. The alkaloids in the TA solid were purified [2] by extraction with acetone, leaving a significant amount (50–65%) of dark, insoluble material behind. The dissolved alkaloids were precipitated as their hydrochlorides by adding concentrated hydrochloric acid (HCl) and filtered. The solid was stable during years of storage and being enriched in the major alkaloids is called purified total alkaloid hydrochlorides (PTA HCl). The relative quantities of TA and acetone were optimized for this procedure to maximize the yield of PTA HCl, but the optimum volume of HCl depended on the moles of extracted alkaloid determined by titration with HCl.

A significant quantity of ibogaine and other alkaloid hydrochlorides remained in the acetone after this procedure, and the solution darkened over time. Evaporating the acetone gave an oil which was also too unstable to store, but dissolving it in water and adding ammonia gave a solid of the residual alkaloids (RA). This powder was stable during storage, and together with the extracted TA residue and PTA HCl, weighed almost the same as the original TA.

Recrystallization of PTA HCl from 95% ethanol gave ibogaine HCl with a significant amount of ibogaline still present. Each successive recrystallization removed about half of the remaining ibogaline, but at a cost in yield. Ibogaine HCl crystals dissolved slowly in the boiling ethanol while the solution darkened. Recrystallization from water or mixtures of water and ethanol seemed to remove a larger proportion of ibogaline but also darkened. Recrystallization from 95% ethanol gave greater purification and yield for the base [2] than for the ibogaine HCl, but the base was less stable for both handling in solution and storage, unless melted and solidified into a solid chunk. Chromatography using activity III basic alumina, eluting with cyclohexane followed by benzene or toluene, separated ibogaine (490 mg) and ibogaline (109 mg) from TA, but this method was costly and laborious on a large scale.

The yield (2.0–2.2%) of PTA HCl from the acetic acid extraction of root bark shavings exceeded those of ethanol or chloroform extractions (0.2–1.1%) and left relatively little alkaloid which could be extracted by other means. The alkaloids which could be extracted using petroleum ether from the acetic acid extract which had been basified and had the TA filtered out amounted to only 1–2% of the weight of the TA.

Solutions and solid samples of TA, PTA base and PTA HCl were exposed to direct sunlight and air for 10 days to assess their relative stabilities. Only the solids remained intact in sunlight, and the hydrochloride was more stable than the base in general. The rates of decomposition for the alkaloids in different solvents were, from least to greatest: ethanol, water, acetone, chloroform, and petroleum ether.

The most promising alternative source of ibogaine was its semisynthesis from voacangine, obtained from the bark of the *Voacanga africana* tree. A patent [10] by Janot and Goutarel claims that while *T. iboga* root bark contains only 0.3% ibogaine, the more abundant and accessible trunk bark of V. africana contains 0.5% voacangine, which can be easily converted into ibogaine. Extraction of V. africana trunk bark using vinegar (see the Experimental section) was highly successful in isolating crude alkaloids. However, extensive attempts to isolate or even identify voacangine in this mixture, or to convert the mixture into ibogaine according to the patent, were completely unsuccessful. A later publication [13] found only 0.14% voacangine in the bark, and suggests that the concentration of voacangine varies.

EXPERIMENTAL SECTION

Extraction of *T. iboga* Root (TA)

One kg (2.5 L) of powdered *T. iboga* root and 5 L of 0.5% acetic acid were placed in a 6 L plastic bucket, stirred occasionally for one hour, and filtered through a cloth sack. The sack was wrung to expel all possible liquid from the root powder and the filtrate (pH = 3–4) was basified using 60 mL of 30% ammonia. The resulting flocculent, medium greenish-brown precipitate of TA was patiently gravity filtered through 30 cm filter paper and thoroughly rinsed with distilled water. This procedure was repeated twice more on the same root powder. The filter papers bearing the TA were placed on paper towels on a wire rack and left in a warm draft until successive weighings detected no more than 0.3% loss per day. The hard, dark brown solid weighed 30.037 g (3.0%) and was ground in a mortar and sifted to give a fine brown powder.

Conversion of Alkaloids to the Hydrochlorides (PTA HCl)

28.00 g of powdered TA was placed on a filter paper in a funnel and 450 mL of acetone was added in portions with gentle stirring. The funnel was removed and 2 mL of concentrated HCl was slowly added dropwise to the flask with swirling, occasionally adding a trace of PTA HCl from a previous batch to initiate precipitation. After waiting a few minutes to allow precipitation to begin, dropwise HCl (2.8 mL) was added with swirling until the liquid became acidic according to pH paper. A final 0.4 mL of HCl was added dropwise and the flask was placed in the refrigerator overnight. The yellow powder was scraped from the sides of the flask, filtered, rinsed with 84 mL of acetone, and dried at room temperature to give 9.493 g (33.9%) of PTA HCl. The black, spent TA weighed 14.521 g (51.9%) after drying.

Ibogaine HCl

9.712 g of PTA HCl was patiently dissolved in 150 mL of boiling 95% ethanol, set overnight at room temperature, refrigerated for 2 h, and the mother liquor was

decanted from the yellow crystals (4.412 g). Recrystallizing again from 80 mL of 95% ethanol gave 3.666 g of mostly pure ibogaine HCl.

Recovery of Residual Alkaloids (RA)

Most of the acetone was distilled from the filtrate from the preparation of PTA HCl and the remainder was evaporated using a stream of air. The dark residue was dissolved in 400 mL of distilled water, filtered, and basified to pH 9 using 3 mL of 30% ammonia. The medium yellow suspension was filtered through a fresh coffee filter paper and left on a warm surface to dry. The chunks of light, chalky, off-white alkaloid residue weighed 4.750 g (17.0%).

Extraction of *V. Africana* Trunk Bark (VTA)

One kg of powdered trunk bark was extracted in the same manner as the *T. iboga* root above, resulting in 59.723 g (6.0%) of crumbly brown voacanga total alkaloids (VTA).

Conversion of Alkaloids to the Hydrochlorides (VPTA HCl)

Seventy five grams of VTA was treated in a manner similar to the PTA HCl above, resulting in 35.929 g (43.6%) of medium brown VPTA HCl. The spent VTA weighed 31.534 g (42.0%).

Recovery of Residual Alkaloids

The filtrate from the preparation of VPTA HCl was treated in a manner similar to the PTA HCl filtrate above, resulting in 12.119 g (16.2%) of chalky, off-white solid.

Acknowledgments

I would like to thank my friends Karl Naeher and Eric Taub for providing encouragement, support and European housing throughout this research.

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