Phase II: Separation of voacangine from more basic alkaloids

Theory

Since the isolation of VTA in Phase I just reused the procedure for the isolation of iboga alkaloids, and Phase IV is based on published work, the phases that required the most research to make this manufacturing process possible were phases II and III, particularly phase II. The way this phase was discovered was that I was looking at the silica TLC of ibogaine and voacangine, noticing that the retention factor for voacangine is much higher than that for ibogaine. I had been trained to think that this meant that voacangine is much less polar than ibogaine, but this doesn't make sense because voacangine differs from ibogaine by the addition of a polar methyl ester group. But going on this “difference in polarity” idea I did some experiments to see how voacangine and the other Voacanga alkaloids would distribute themselves between methanol and petroleum, which happen not to be fully miscible. I didn't find this separation very promising.

But then I had the key insight, which should have been obvious, that voacangine has a higher retention factor not due to lower polarity, but due to lower basicity, since silica is slightly acidic as well as polar. The ester group which characterizes voacangine is close enough to the amine group to make this alkaloid significantly less basic than ibogaine. This means that in a two-phase system in the presence of a weak or limited amount of acid, that ibogaine will combine with the acid to a greater extent than voacangine will. Or course, the goal of phase II is not to separate voacangine from ibogaine, but to separate it from a large excess of other alkaloids. Fortunately, these other alkaloids seem to be more basic than voacangine is, and separable using a weak acid in a two-phase system.

The key to phase II depends on the observation that, when the Voacanga alkaloids are distributed between toluene and dilute acetic acid, the composition of the alkaloid mixture is enriched in voacangine in the toluene layer. The formation of an intractable emulsion would normally be an unacceptable obstacle – a disaster if not resolved – if the emulsion did not float and coalesce into a reasonably small volume as it does in this case. So tolerating and reusing this emulsion is another unusual feature of this procedure, where it is almost always standard practice to work only with pure phases.

Toluene was selected over other possible solvents such as ethyl acetate, diethyl ether or chloroform due to its lower volatility and lower solubility in water, and over petroleum naphtha due to its greater ability to dissolve voacangine. Toluene was preferred over benzene due to lower toxicity. It also has the advantage of being inexpensive and widely available.

Acetic acid (as white vinegar) was used out of convenience and due to familiarity with its use in extracting iboga root. However, extraction of iboga root with acetic acid was found to be less efficient (give a lower yield for a given number of extractions) than extraction with a stronger acid like hydrochloric acid, and thus the latter has been recommended. So while it may be possible to extract Voacanga bark with dilute acetic acid and directly extract this acetic acid with toluene without having to produce the intermediate VTA, this method would be expected to leave behind much more voacangine than extracting the Voacanga bark with a strong acid would, especially considering that voacangine is a weak base.

Making sure to get all the voacangine is the reason for some of the recycling steps, such as steps 18 – 20 in which the VTA is extracted with strong acid after being extracted with vinegar – to ensure that all the voacangine has been removed before it is discarded. These recycled portions can be combined with the next batch of Voacanga bark to reclaim their content of voacangine, making this process highly efficient. In this phase the only ways that voacangine can be lost are in the spent VTA and in the recovered VTA. The recovered VTA is the alkaloids left in the vinegar after it has been extracted three times with toluene. It will contain a little voacangine and even a little ibogaine. The amount of additional voacangine obtained from a fourth or fifth extraction was not found to be worth the labor, but may be worthwhile if the scale is increased and the process automated.

Once the VTA has been extracted with hot vinegar and the vinegar has been extracted with toluene, the toluene is washed (shaken) with water. The reason for this is that the toluene emulsion is trapping a significant amount of the vinegar extract. Mixing it with a large excess of water helps remove this extract and all the non-voacangine alkaloids it contains. Any voacangine it does contain gets recycled.

The toluene emulsion is then extracted with dilute hydrochloric acid. This acid is strong enough to pull even weak bases like voacangine into the water layer, allowing the voacangine to be isolated by precipitating it from the acid solution. The toluene emulsion, stripped of alkaloids, can then be reused to extract the vinegar. However, since it traps a little of the hydrochloric acid, this would make the vinegar extract increasingly acidic with each extraction – if not for the sodium acetate added in step 16 which converts the hydrochloric acid into acetic acid.

The purpose of shaking the hydrochloric acid extract with petroleum ether before precipitating the PVTA is to rid it of traces of dissolved and suspended toluene which would otherwise cause a non-solid precipitate to form. Thus the petroleum ether needs to be replaced periodically to keep its content of toluene low.

As with all phases on this manual, note that the amounts in the procedure can be scaled to the amounts on hand, and the size of the equipment adjusted accordingly. The times and temperatures should not be scaled.

Instructions for Phase II of the process for producing ibogaine from Voacanga:

Separation of voacangine from more basic alkaloids

Last revised: July 27, 2015

1. Accurately weigh out approximately 500 grams of Voacanga TA (Illustration 1), recording the measured weight on the Data Collection Sheet, and pour the VTA into a labeled 25 liter bucket. Cover the bucket until the dust settles (Illustration 2).


Illustration 1: Weigh the VTA


Illustration 2: Cover the bucket

2. Fill a 4 liter Erlenmeyer flask with four liters of clear vinegar (5% acetic acid) (Illustration 5) and add a stir bar. Heat it until hot but not painful to the touch (~60°C) (Illustration 3) and remove the stir bar (Illustration 4).


Illustration 5: Pour the vinegar


Illustration 3: Heat to 60°C


Illustration 4: Remove the stir bar

3. Pour the hot vinegar into the bucket (Illustration 6) and stir thoroughly with a stick (Illustration 7) until the mixture is homogeneous. Stir occasionally and leave overnight to cool and settle.


Illustration 6: Pour the hot vinegar


Illustration 7: Stir thoroughly with a stick

4. Weigh a coffee filter paper and write the weight, the date, the PVTA batch number and “Spent VTA” on the paper in pencil. Line the inside of a 50 cm plastic funnel with a plastic net and lay the filter paper over it. Place the filter on a labeled 25 liter plastic bucket and ensure that it is level.

5. Pour the VTA mixture into the filter and wait for it to drain into the bucket (Illustration 8). When most of the liquid has drained it may facilitate the filtration to tip the funnel so the remaining liquid is over the relatively clean paper near the edge. Proceed to step 18 while also continuing with the next step.

Illustration 8: VTA mixture after draining

6. If emulsions of toluene and/or petroleum ether are being reused, top them up with fresh toluene (Illustration 9) or petroleum ether (Illustration 10) to restore the initial 500 mL or 100 mL volumes. This will take about 50 mL of toluene and 25 mL of petroleum ether per run. Every few runs or after an especially dirty run the petroleum ether should be replaced with 100 mL of fresh petroleum ether and the old petroleum ether stored for later recycling by distillation (Illustration 11).

Illustration 9: Topping up the toluene emulsion

Illustration 10: Topping up the petroleum ether

Illustration 11: Used petroleum ether to be recycled

7. Pour the filtrate (Illustration 12) from the VTA into a 5 liter separatory funnel (Illustration 13) containing 500 mL of toluene or a reused emulsion containing a similar amount of toluene (Illustration 14).

Illustration 12: The filtrate from the VTA

Illustration 13: Pour the filtrate

Illustration 14: The toluene emulsion before settling

8. Pick up (Illustration 15) and shake (Illustration 16) the stoppered funnel and let the layers separate for at least one hour. Since this separation is the least efficient of the emulsion separations, this is the best point to stop work for the day if the extraction cycles cannot be completed.

Illustration 15: Lift the separatory funnel by the top

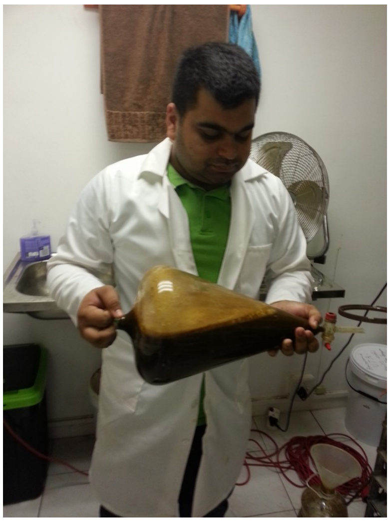

Illustration 16: Shake the funnel thoroughly

9. Once the yellow toluene emulsion has separated as much as it will (Illustration 17), remove the stopper and drain the darker lower layer of VTA extract from the separatory funnel through the stopcock (Illustration 18) and set it aside. Try to avoid dispensing any of the toluene emulsion (Illustration 19).


Illustration 17: Settled toluene emulsion before separation


Illustration 18: Extract being separated from toluene


Illustration 19: Stopcock closed to keep the toluene emulsion in

10. Add 4 liters of water to the separatory funnel (Illustration 20), shake it (Illustration 21) and wait one hour for the layers to separate (Illustration 22).


Illustration 20: Add four liters of water


Illustration 21: Shake the funnel thoroughly


Illustration 22: The emulsion settled from the water wash

11. Remove the dark, clear lower layer of water wash from the separatory funnel (Illustration 23). Try to avoid dispensing any of the cloudy, dark yellow toluene emulsion (Illustration 24).

Illustration 23: Dispense the water wash

Illustration 24: Stop dispensing when the emulsion reaches the stopcock

12. If a filter with more room is not available, weigh a coffee filter paper and write the weight, the date, the PVTA batch number and “Water washings” on it in pencil. Add 20 mL of 25% ammonia to the water wash (Illustration 25), mix until homogeneous (Illustration 26) and pour the suspension into the coffee filter dedicated to water wash precipitates (Illustration 27). Use this filter until it is full or the rate of filtration slows, rinse with 4 liters of water and set the paper on a towel in a warm breeze to dry and weigh. Once dried, these combined precipitates are recycled to recover the voacangine they contain by extracting them with the Voacanga bark.

Illustration 25: Add ammonia to the water wash

Illustration 26: Mix until homogeneous

Illustration 27: Pour the suspension into a filter

13. Add 30 mL of 32% hydrochloric acid (Illustration 28) and 3 liters of water (Illustration 29) to the toluene emulsion in the separatory funnel (Illustration 30), shake (Illustration 31) and wait one hour to allow the layers to separate (Illustration 32).

Illustration 28: Measure 30 mL of HCl

Illustration 29: Add the HCl to three liters of water

Illustration 30: Add the dilute HCl to the toluene emulsion

Illustration 31: Shake the funnel thoroughly

Illustration 32: Let the emulsion settle

14. Open the upturned stopcock of a second 5 liter separatory funnel which contains 100 mL of petroleum ether or reused emulsion containing an equivalent amount of petroleum ether to relieve any pressure (Illustration 33). Remove the stopper from the first separatory funnel (containing the toluene emulsion) and dispense the dark yellow or brown, clear lower acid layer into the one with the petroleum ether (Illustration 34) and shake (Illustration 35). Proceed to step 16 now but wait one hour to execute step 15.


Illustration 33: Vent the separatory funnel


Illustration 34: Dispense the acid layer


Illustration 35: Shake thoroughly

15. Once the layers have completely separated (Illustration 36), relieve any pressure that has built up from the petroleum ether in the separatory funnel by opening the stopcock momentarily while it is pointed upward (Illustration 37). Remove the stopper and drain the hydrochloric acid layer from beneath the petroleum ether layer (Illustration 38), stopping before petroleum comes out (Illustration 39). Add 60 mL of 25% ammonia (Illustration 40), mix until homogeneous (Illustration 41) and pour the suspension of PVTA into a labeled coffee filter dedicated to PVTA (Illustration 42). When filtering get slow, rinse the PVTA with 4 liters of water and then lay the filter paper on a towel to dry (Illustration 43) and weigh (Illustration 44).


Illustration 36: After an hour the layers should separate


Illustration 37: Vent pressure from the separatory funnel


Illustration 38: Unstopper and drain the lower layer

Illustration 39: Close the stopcock to keep the petroleum in the separatory funnel

Illustration 40: Add ammonia to the extract

Illustration 41: Mix until homogeneous

Illustration 42: Filter the PVTA

Illustration 43: Drying PVTA

Illustration 44: PVTA being weighed

16. If the vinegar extract of VTA set aside in step 8 has been extracted with toluene less than four times, return it to the separatory funnel containing the toluene emulsion (Illustration 45) along with 400 mg of sodium acetate (Illustration 46), shake (Illustration 47) and let settle for one hour. Return to step 9.


Illustration 45: Return VTA extract to separatory funnel


Illustration 46: Add 400 mg sodium acetate


Illustration 47: Shake thoroughly

17. Weigh a coffee filter paper and write the weight, the date, the PVTA batch number and "Recovered VTA" on it in pencil. Add 180 mL of 25% ammonia to the vinegar extract of VTA (Illustration 48), mix until homogeneous (Illustration 49) and pour the suspension into the coffee filter dedicated to recovered VTA (Illustration 50). The recovered VTA, which has been depleted of voacangine, may contain other alkaloids of value and should be combined in its own bucket and set aside. Rinse the recovered VTA with water (Illustration 51), let it dry (Illustration 52) and determine its weight.


Illustration 48: Add ammonia to the VTA extract


Illustration 49: Mix until homogeneous


Illustration 50: Filter the recovered VTA

Illustration 51: Rinse with water

Illustration 52: Dry the recovered VTA

18. Heat 4 liters of water containing 40 mL of concentrated hydrochloric acid to 60°C (Illustration 53). Put the filter paper bearing the vinegar-extracted VTA into a bucket (Illustration 54) and stir it with the hot, dilute hydrochloric acid (Illustration 55). Stir occasionally until the mixture has returned to room temperature.

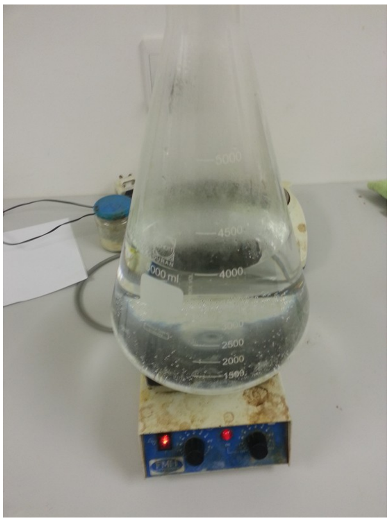

Illustration 53: Heat dilute HCl to 60°C

Illustration 54: Put the paper with the spent VTA in a bucket

Illustration 55: Stir the spent VTA with the hot dilute HCl

19. Pull the filter paper from the re-extracted spent VTA mixture (Illustration 56) and put it into a funnel lined with a plastic net (Illustration 57). The paper does not have to be completely clean (Illustration 58). Put the filter on a 25 liter bucket and pour the re-extracted VTA mixture into the filter (Illustration 59), washing any remaining solid in with water (Illustration 60). When the liquid has completely drained, which may take a few days, use a spray of water to rinse the spent VTA and wait for that to drain also. Dry and weigh the (doubly) spent VTA.

Illustration 56: Take the paper from the spent VTA for reuse

Illustration 57: Funnel lined with a plastic net

Illustration 58: Paper ready for reuse

Illustration 59: Pour the HCl extract of spent VTA into the filter

Illustration 60: Use water to wash in any remaining solid

20. Add 80 mL of 25% ammonia to the hydrochloric acid extract of the VTA (Illustration 61) and mix until homogeneous (Illustration 62). Weigh a filter paper (Illustration 63) and write the weight, the date, the PVTA batch number and “HCl washings of spent VTA” on the paper in pencil (Illustration 64). Put the paper into a funnel and fill it with the brown suspension (Illustration 65). After all the liquid has drained, rinse the solid with water, dry it and determine its weight. This precipitated HCl washing of VTA should be submitted for extraction with Voacanga bark to recover any voacangine it contains.


Illustration 61: Add ammonia to the HCl extract of VTA


Illustration 62: Mix until homogeneous


Illustration 63: Weigh a filter paper

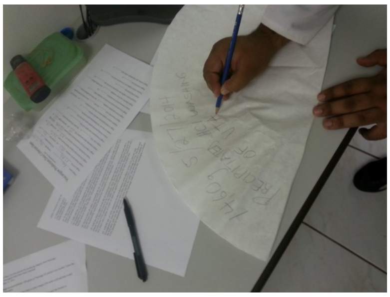
Illustration 64: Write the weight, date, PVTA batch number and product on the paper

Illustration 65: Filter the precipitated HCl washing of VTA

PVTA Production Data Collection Sheet

Last revised: May 31, 2014

Chemist name: ______________________________ Starting date: ________________________

1. Weight of VTA: ____________________________ Batch number of VTA: ________________
2. Volume of vinegar: ______________ mL Acidity of vinegar: ______ percent acetic acid
6. Volume of toluene added to top up the emulsion: _________________ mL
6. Volume of petroleum ether added to top up the emulsion: _________________ mL

8. Extraction cycle 1: Time VTA extract is shaken with toluene: ________________

10. Volume of water wash: ___________ mL Time shaken: _____________________
12. Volume of ammonia added to water wash: ________ mL
13. Volume of water _______________ and concentrated HCl __________________ in acid wash
13 and 16. Time shaken: _________________ Sodium acetate added: _______________ g
14. Time HCl layer was shaken with petroleum ether: ______________ Time separated: ________
15. Volume of ammonia added to acid wash: ________ mL

8. Extraction cycle 2: Time VTA extract is shaken with toluene: ________________

10. Volume of water wash: ___________ mL Time shaken: _____________________
12. Volume of ammonia added to water wash: ________ mL
13. Volume of water _______________ and concentrated HCl __________________ in acid wash
13 and 16. Time shaken: _________________ Sodium acetate added: _______________ g
14. Time HCl layer was shaken with petroleum ether: ______________ Time separated: ________
15. Volume of ammonia added to acid wash: ________ mL

8. Extraction cycle 3: Time VTA extract is shaken with toluene: ________________

10. Volume of water wash: ___________ mL Time shaken: _____________________
12. Volume of ammonia added to water wash: ________ mL
13. Volume of water _______________ and concentrated HCl __________________ in acid wash
13 and 16. Time shaken: _________________ Sodium acetate added: _______________ g
14. Time HCl layer was shaken with petroleum ether: ______________ Time separated: ________
15. Volume of ammonia added to acid wash: ________ mL

8. Extraction cycle 4: Time VTA extract is shaken with toluene: ________________

10. Volume of water wash: ___________ mL Time shaken: _____________________
12. Volume of ammonia added to water wash: ________ mL
13. Volume of water _______________ and concentrated HCl __________________ in acid wash
13 and 16. Time shaken: _________________
14. Time HCl layer was shaken with petroleum ether: ______________ Time separated: ________
15. Volume of ammonia added to acid wash: ________ mL

17. Volume of ammonia used to precipitate recovered VTA: ______________ mL
Weight of dried recovered VTA: ______________ g Weight of water washings of toluene: ___________ g
18. Volume of water _____________ and concentrated HCl _______________ used to rinse the spent VTA
19. Weight of spent VTA:________________ g
20. Volume of ammonia used to precipitate HCl rinse: _______ Weight of HCl washings of VTA: _______ g
Weight of PVTA: ____________ g Batch number for PVTA: ___________________