The Isolation of Tabersonine and the Synthesis of Vincamine

by Rodney A. Gagne

A new procedure for isolating tabersonine:

After repeating Dr. Feng's procedure for isolating tabersonine from ground beans from *Voacanga africana,* I decided to alter the procedure to increase the yield and shorten the amount of time needed to obtain pure tabersonine.

One hundred grams of beans were ground and placed in a 1 / erlenmeyer flask to which 1 / of 1 % aqueous sulfuric acid was added. This mixture was allowed to stir overnight. The stirring was ceased in order for the plant material to settle to the bottom. The acid extract was then siphoned off using a hose attached to a 1 / filter flask and another hose attached to a vacuum outlet. More water was added to efficiently remove the acid extract (separating it from the plant material). The acid extract was then placed into a 4 / erlenmeyer flask and 100 g of sodium chloride was added. This new solution was allowed to sit overnight.

The following day, 750 ml of chloroform was added and the solution was stirred between three and four hours. The stirring was then stopped to allow the layers to separate. After a few minutes, the solution had separated into an upper aqueous layer (which was later discarded because only a very small of tabersonine was present in it) and a lower emulsion layer. The upper aqueous layer was siphoned off and the bottom layer was filtered through celite in a Buchner funnel. After passing through celite, the bottom layer completely separated into two distinct layers. These

layers were poured into a separatory funnel and separated. The chloroform layer was dried with magnesium sulfate and placed on a rotary evaporator. After all the chloroform was removed, 2.2 g of crude tabersonine hydrochloride was recovered. After recrystallization with acetone, 1.7 g of pure tabersonine hydrochloride was recovered. The spectral data for this compound is identical with the literature data (see data sheet).

Conversion of tabersonine hydrochloride to the free base:

The isolated tabersonine hydrochloride was placed into a round-bottomed flask and about 10 ml of chloroform was added. After stirring for a short time to let the solute dissolve, 10 ml of ammonia solution was added. This new solution was allowed to stir for 10 minutes whereupon 10 ml of water and 10 ml of chloroform was added. The layers were separated and the organic layer was shaken with 10 % sodium carbonate. The organic layer was then dried with magnesium sulfate and the chloroform was removed with a rotary evaporator. A thick, yellow oil resulted. To solidify the product, 5 ml of chloroform was added and then removed totally under reduced pressure. This procedure was done four times whereupon the product solidified. The spectral data was then obtained.

Conversion of tabersonine to vincadifformine:

Five hundred milligrams of tabersonine was added to a 500 ml hydrogenation bottle along with 50 ml of ethyl acetate and 100 mg of 5% palladium of charcoal. This was placed into the Parr shaker and flushed three times with hydrogen gas. After flushing, a static 50 pounds per

square inch of hydrogen was applied. The bottle was shaken for three hours. It was determined using thin layer chromatography that the reaction was complete. The charcoal was then filtered off using gravity filtration through filter paper. The filter paper was immediately discarded because palladium causes small fires on filter paper if allowed to sit. The solution was then placed on the rotary evaporator to remove the ethyl acetate. After doing so, a white solid (compound 2) remained. This was dried under reduced pressure.

Oxidation of vincadifformine (2 --> 3):

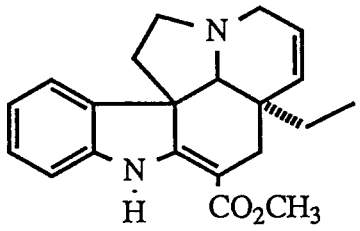
Three hundred milligrams of vincadifformine was added to a 100 ml round bottomed flask along with 20 ml of benzene (or chloroform). After letting the solute dissolve, 325 mg of metachloroperbenzoic acid was added. This solution was stirred for sixteen hours. Thin layer chromatography showed that the reaction was complete after the specified time. The solvent was then removed under reduced pressure. Dilute (10%) acetic acid was added to dissolve most of the residue. Diethyl ether was then added and the layers were allowed to separate. The acetic acid layer was basified with 10% sodium carbonate. This new solution was then extracted with dichloromethane. The organic layer was dried with magnesium sulfate and the solvent was removed. One hundred and seventy milligrams of compound 3 was obtained. The yield of the reaction was only fifty per cent (lit. 75%). More work is needed on this step, if required.

Removal of the N-oxide (3 --> 4):

One hundred milligrams of compound 3 was placed in a 50 ml round bottomed flask and 3 ml of acetone was added along with 20 mg of 5% palladium on charcoal. A balloon filled with hydrogen gas was placed on the flask and the solution was allowed to stir overnight. Thin layer chromatography of the solution the next day showed that the reaction did not proceed. Therefore, the summer's work ended at this stage.

The final step in the reaction scheme (on next page) could not be tried and therefore, if one wants to fully convert tabersonine into vincamine, more work needs to be done on the final three steps in the reaction scheme.

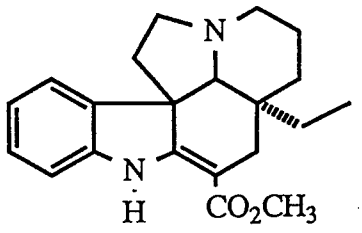
Reaction Scheme



1

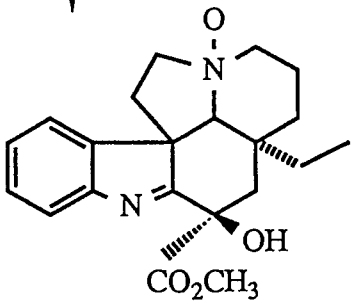
H_2, Pd/C

50 psi, EtOAc



2

2 eq. mCPBA
benzene or chloroform
16 h

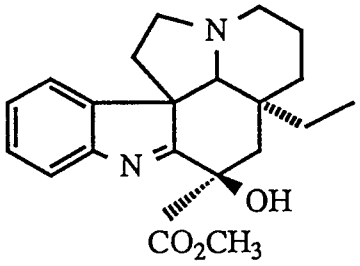


3

To here

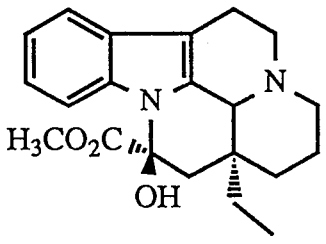
H_2, Pd/C

17 psi, acetone



4

40:60
AcOH:H_2O



5

Vincamine