



A Concise Synthesis of 1,3-Disubstituted Beta-Carbolines



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Introduction

It has been known for some time that the condensation of tryptophan and ninhydrin produces a novel pentacyclic heterocycle, which is referred to as a yohimbanone. The yohimbanone is interesting in its own right given the bioactivity of compounds such as yohimbine and reserpine, which have similar skeletons. Additional biological relevance stems from the ability to convert yohimbanones into beta-carbolines via oxidative ring cleavage. Current work in our laboratories focuses on exploiting this concise synthetic sequence for the preparation of novel beta-carbolines. The target molecules are potential ligands for the benzodiazepine (GABA_A) receptor (Figure 1).

Beta-carbolines can be extremely useful molecular tools to further our understanding of the GABA_A receptor, which is also known as the benzodiazepine receptor. Benzodiazepines, such as Valium and Librium, bind to the GABA_A receptor. The conformational change that results enhances the affinity of the gamma-aminobutyric acid (GABA) receptor for its ligand. When GABA binds chloride channels are opened, which ultimately alleviates anxiety.

Beta-carbolines also bind to the GABA_A receptor, but unlike benzodiazepines, beta-carbolines may serve as agonists, antagonists, or inverse agonists. This greater spectrum of bioactivity provides a unique opportunity to enhance our understanding of the GABA_A receptor through a study of the structure-activity relationship (SAR). Also, beta-carbolines have demonstrated anti-HIV activity, so novel syntheses are of interest (Pauwels et al.).

The objective of the study was to prepare novel beta-carbolines that can be later used for biological screening to help develop the SAR.

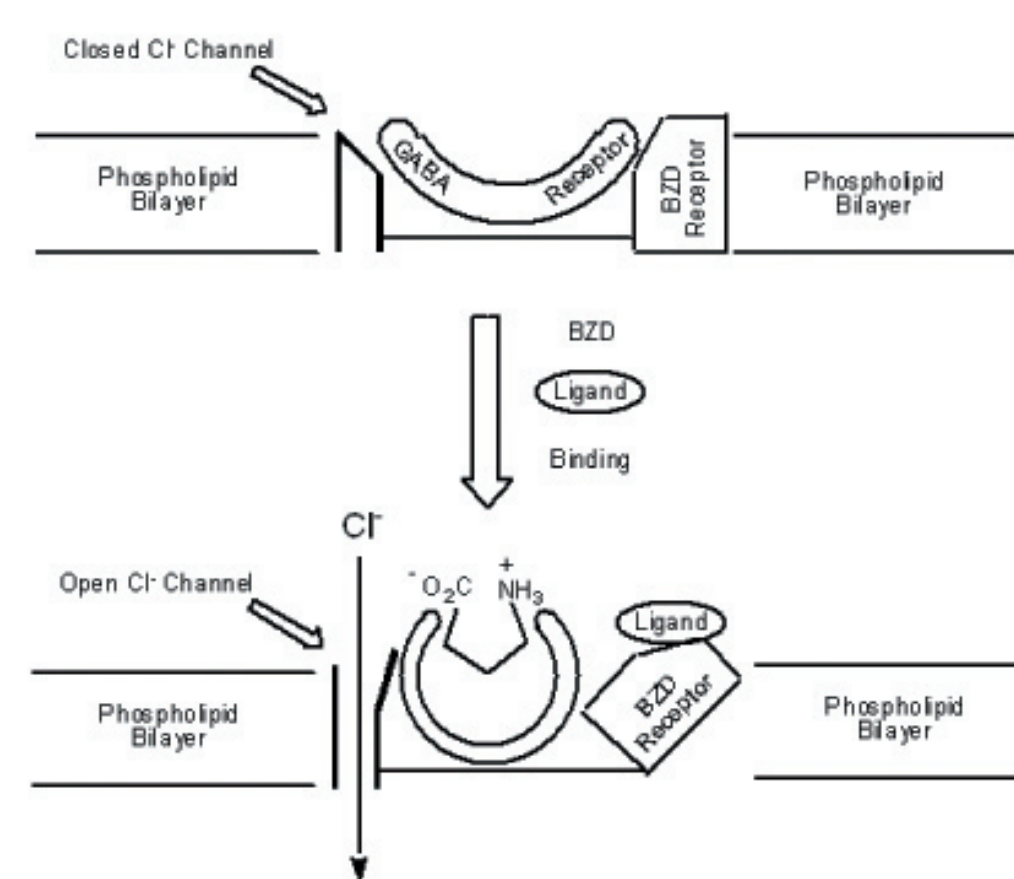


Figure 1. Diagram of the Benzodiazepine (GABA_A) receptor. (Cannon et al.)

Ninhydrin is a potent chemical used to detect ammonia or primary amines. When ninhydrin reacts with these free amines, a deep blue-purple color is evolved (Ruhemann's Purple) (Figure 2). In 1970, Heising and coworkers found that tryptophan (1) behaved differently than all other amino acids and proposed that a Pictet-Spengler reaction produced product (2). In 1989, Neuzil et al. repeated Heising's work, this time using X-ray crystallographic analysis to identify the end product of the reaction as the yohimbanone (3, Figure 3). These results were conflicting until recent research resolved the mechanism (Leonard et al.). There is in fact a Pictet-Spengler reaction, the product of which is isolable when using the methyl ester of tryptophan. However, upon heating with a Lewis or protic acid, the Pictet-Spengler product (4) will rearrange to form the yohimbanone, via the intramolecular attack of the nitrogen on the carbonyl of ninhydrin (Figure 4).

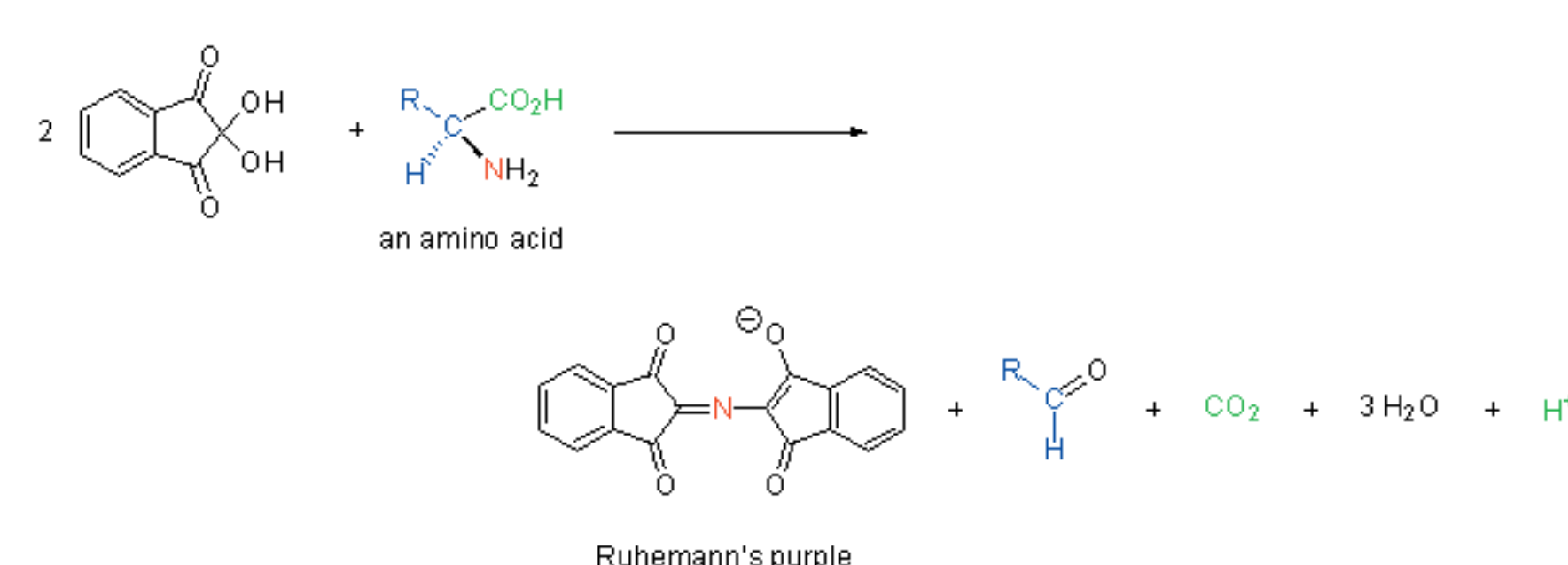


Figure 2. Reaction of ninhydrin with an amino acid produces a purple dye.

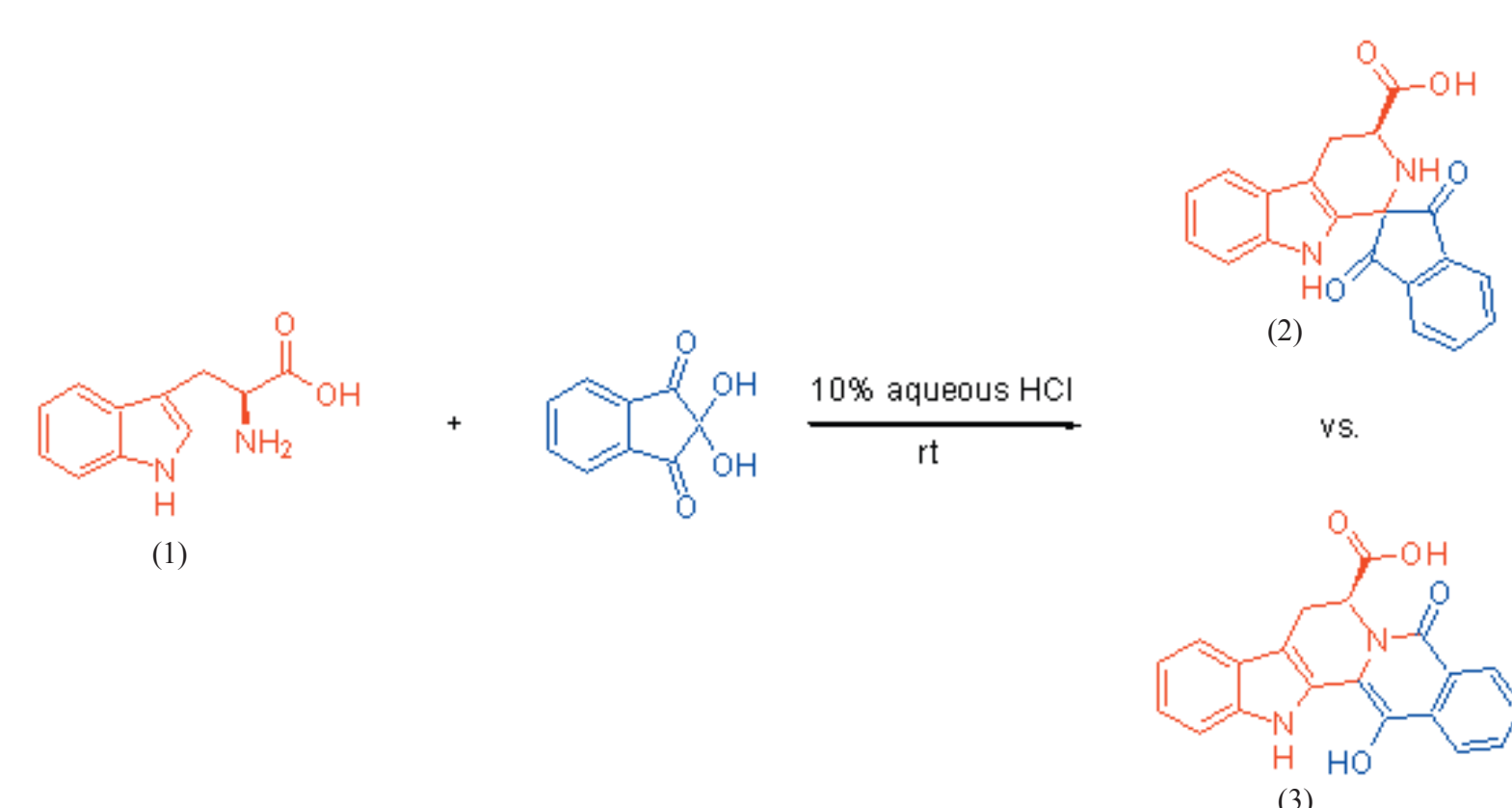


Figure 3. Two products were proposed in the literature for the condensation of tryptophan and ninhydrin: Pictet-Spengler product (2) and yohimbanone (3).

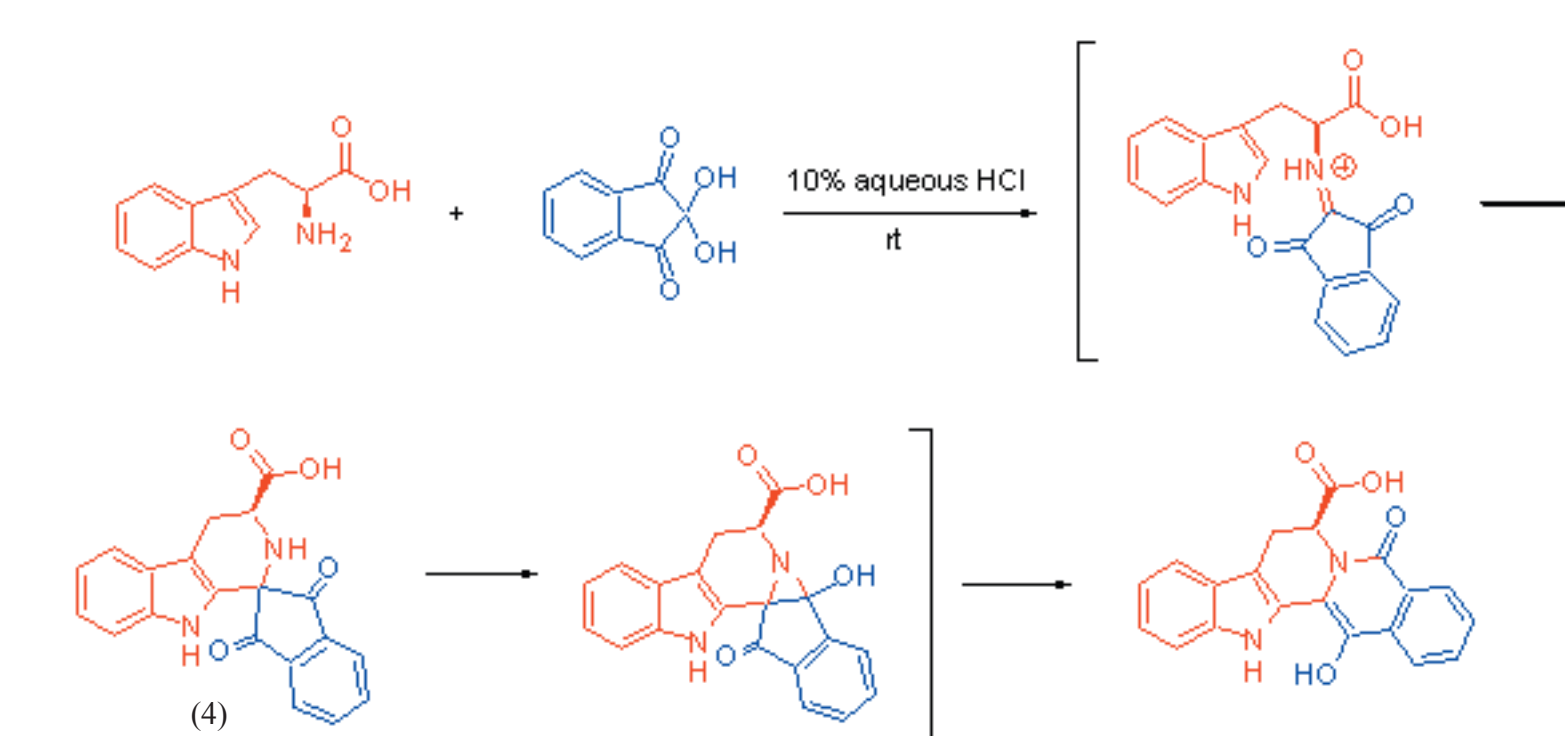


Figure 4. The yohimbanone is produced by rearrangement of the Pictet-Spengler product. When using the methyl ester of tryptophan, the Pictet-Spengler product is isolable.

Formation of a beta-carboline product using L-tryptamide hydrochloride salt

The objective of this study is to prepare a beta-carboline bearing an amide at the 3 position. This compound will have a hydrogen bond donor/acceptor at the 3 position; whereas, the parent compound has only a hydrogen bond acceptor at the 3 position. This structural difference may elicit a different biological response.

Initially, a Pictet-Spengler product (6) was prepared by combining L-tryptamide hydrochloride salt (5) with ninhydrin in 10% aqueous HCl (Figure 5). The product structure was verified by ¹H NMR, ¹³C NMR, and IR spectroscopy.

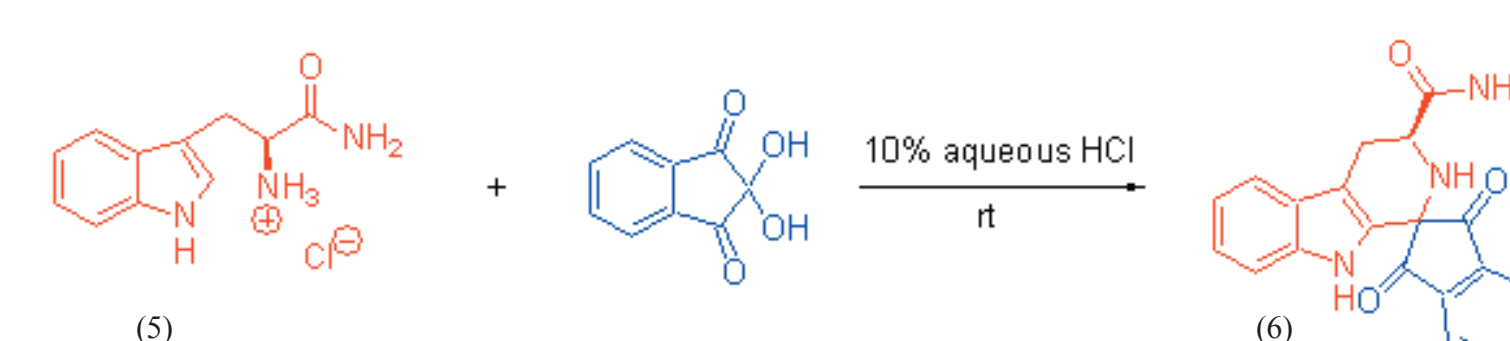


Figure 5. Pictet-Spengler reaction of tryptamide hydrochloride and ninhydrin produces a spirocyclic heterocycle.

The next step in the synthetic sequence, involved the formation of a yohimbanone by combining the Pictet-Spengler product (6) with SnCl₂•2H₂O and heating at reflux in methanol (Figure 6). NMR spectroscopy revealed that the yohimbanone (7) product was successfully produced. Notable differences include: the presence of two alicyclic carbons in 7 and three in 6; fewer carbonyls in 7; and a greater distinction between the aromatic protons of the ninhydrin residue in 7.

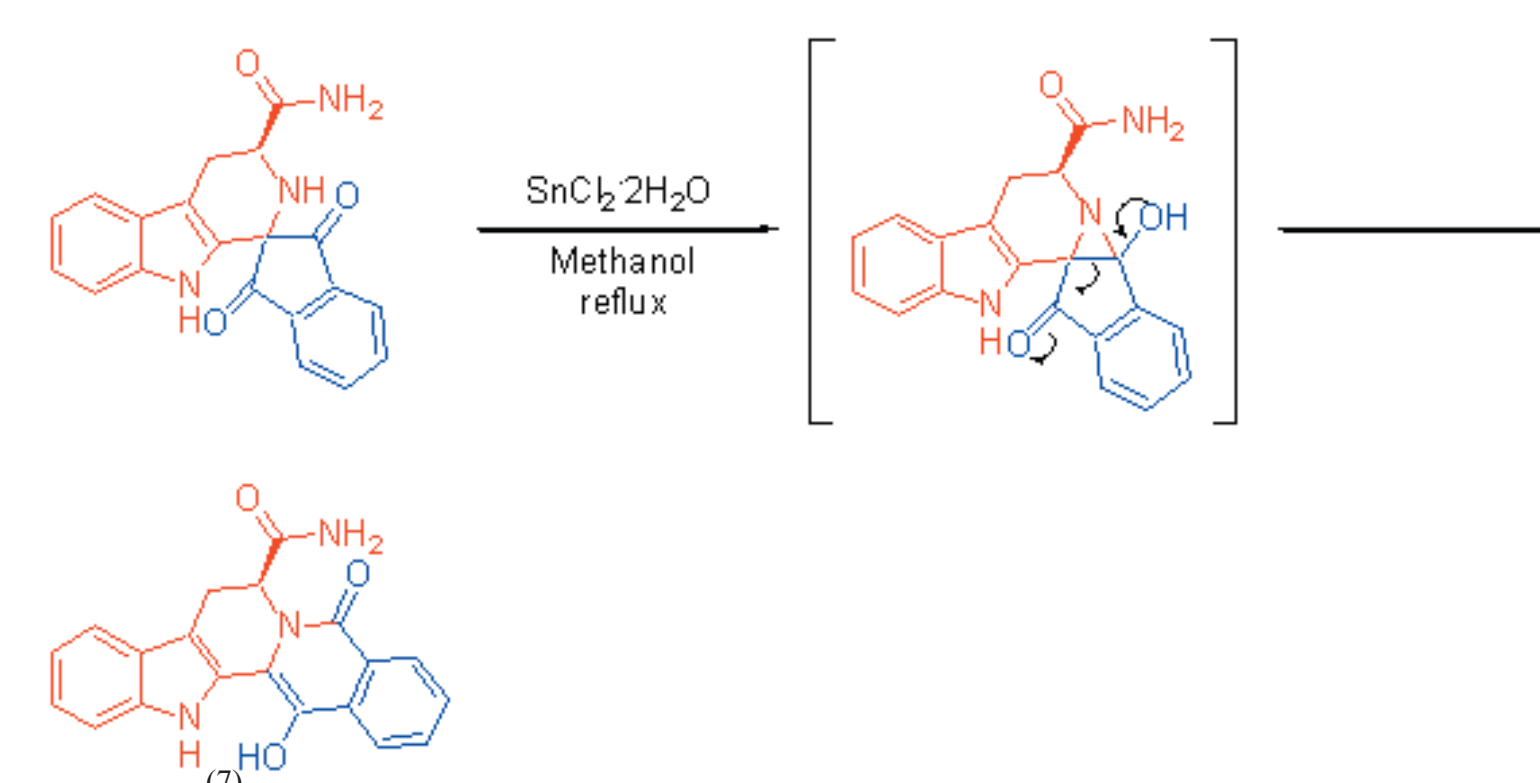


Figure 6. Lewis-acid rearrangement of Pictet-Spengler product yields a yohimbanone.

The third step in the sequence was the oxidative ring cleavage of the yohimbanone to produce the 1,3-disubstituted beta-carboline (8, Figure 7). This was achieved by combining the yohimbanone product (7) with cupric acetate monohydrate in methanol. The resultant mixture was stirred at room temperature for 24 hours. The product structure was verified by ¹H NMR, ¹³C NMR, and IR spectroscopy.

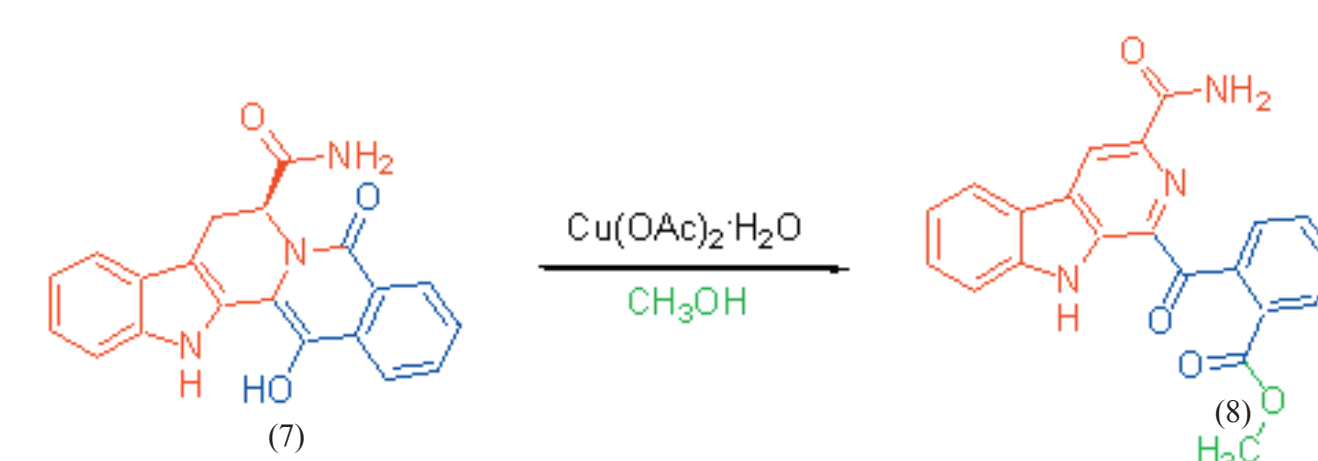


Figure 7. Oxidative ring cleavage of the yohimbanone produces a 1,3-disubstituted beta-carboline.

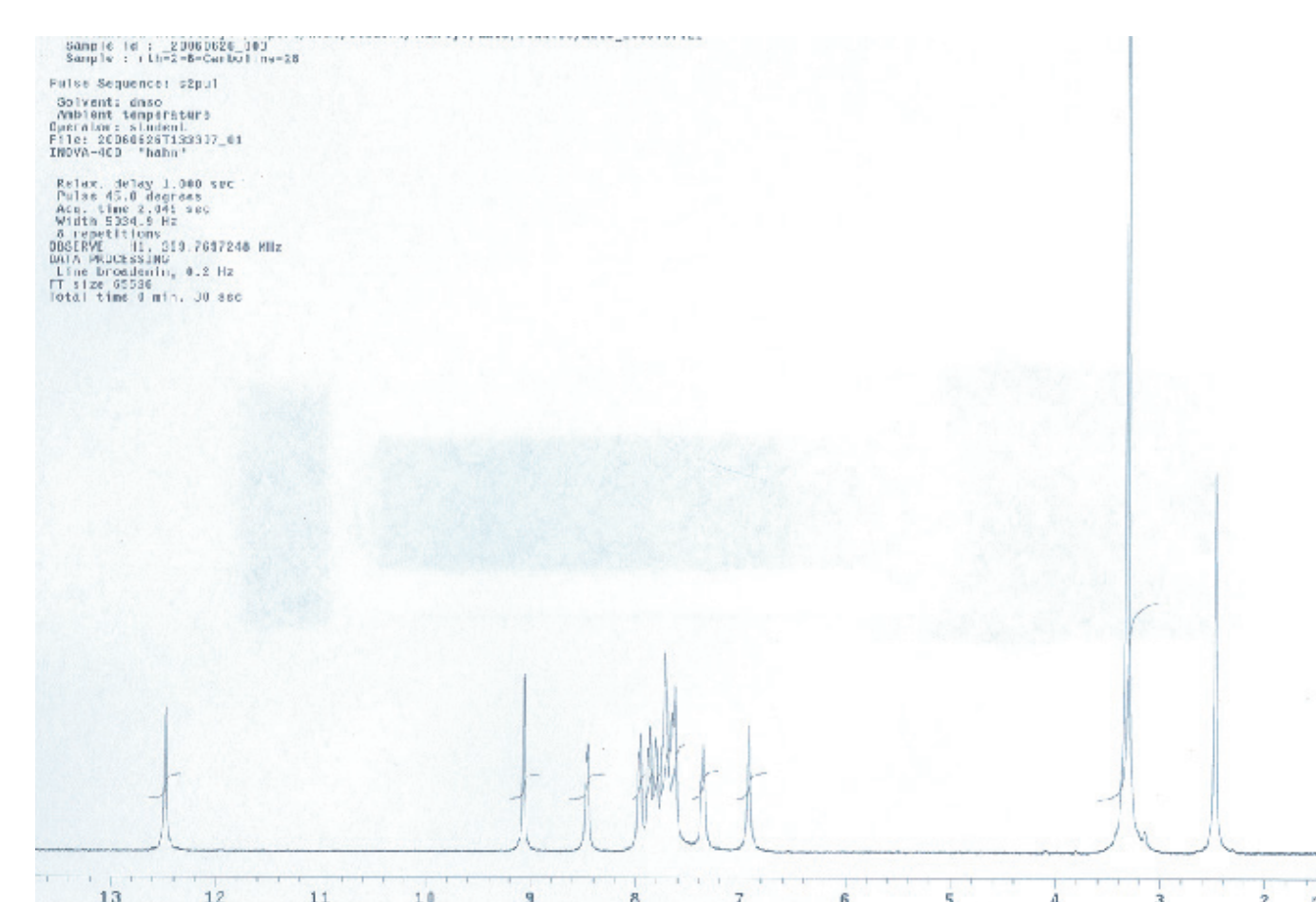


Figure 8. ¹H NMR of beta-carboline (8) provides evidence that the correct structure was produced.

Adding Conformational Constraint to 1,3-Disubstituted Beta-Carbolines

The objective of this project is to form a lactone, thereby introducing an additional ring to a disubstituted beta-carboline in order to make the structure more rigid. The reduction in degrees of rotational freedom may affect how the beta-carboline binds to the GABA_A receptor. Thus, conformation constraint could be a factor in whether a beta-carboline has anxiolytic or anxiogenic properties.

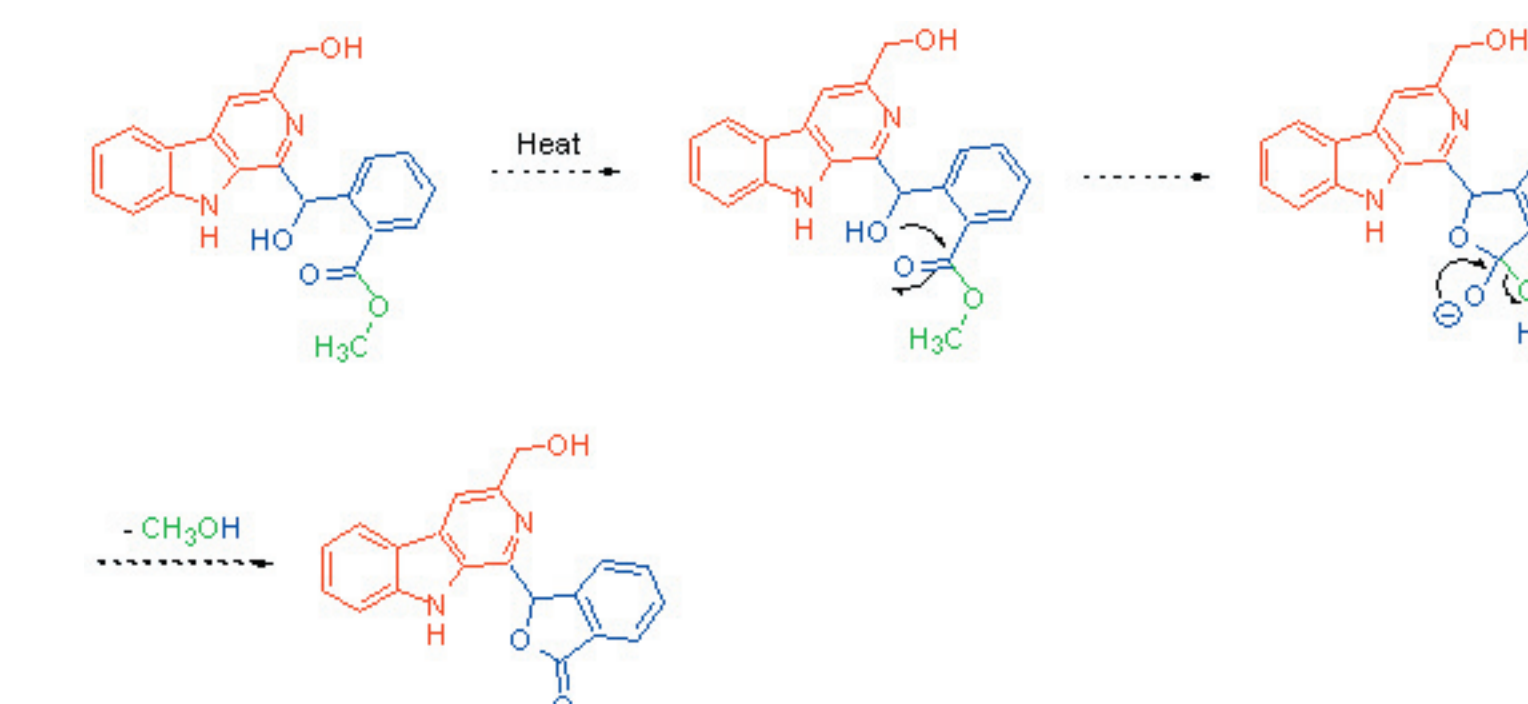


Figure 9. Cyclization that may occur upon heating to introduce a lactone into the structure.

This project utilized the beta-carboline produced in the original series (Leonard et al.). The method to produce the beta-carboline was analogous to method described in previous section. Once the beta-carboline (9) was produced, the product was combined with NaBH₄ and methanol. The solution was stirred and gently heated. Unfortunately, a few problems arose with the resulting compound (10). ¹H and ¹³C NMR data show that the nucleophile attacked the desired ketone, but also reduced one methyl ester to an alcohol (Figure 10). Also, the compound had several impurities and decomposed when attempting to purify using a column. Currently, we are trying other methods of purification that will not decompose the desired compound. We anticipate that 10 can be manipulated to provide the lactone ring.

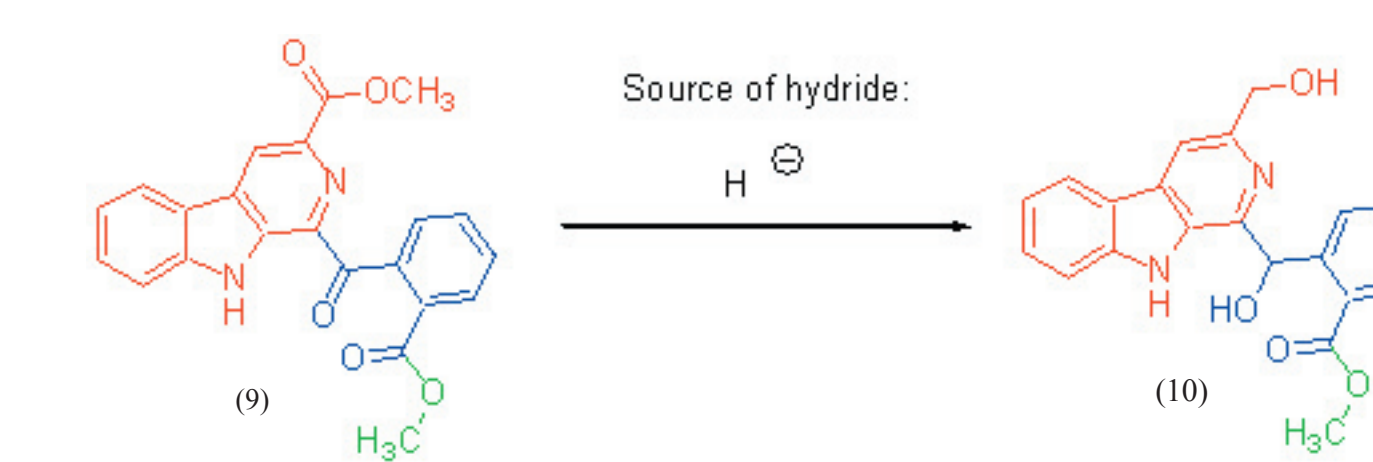


Figure 10. Reduction of the ketone was accompanied by unexpected reduction of one ester.

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Acknowledgements

R. Troy Hull was a participant in the ACS Project SEED program, which was made possible by the Project SEED Endowment and by generous donations from Ferro Corporation, Westinghouse, Bayer MaterialScience LLC, PPG Industries, Eastman Chemical Company, and LabChem, Inc. Tabitha Riggio (Bayer MaterialScience LLC) is gratefully acknowledged for her tireless fundraising efforts. Cecilia Hernandez and Raihanah Rasheed of the American Chemical Society provided valuable assistance with the SEED program. The authors also wish to thank the Washington & Jefferson College Department of Chemistry for providing the reagents used in this research.