Party like a Rockstar: The Occurance, Bioactivity, Biosynthesis, and Synthesis of Benzoylmethyl Ecgonine (Cocaine)

\textit{Anthony Hsiao, Fall 2008}

\section*{Introduction}

Benzoylmethyl Ecgonine, more commonly known as cocaine, is a crystalline tropane alkaloid\textsuperscript{1}. Its cultivation, distribution, and use is strictly prohibited in the United States. Despite that, cocaine is still widely used as a recreational drug in underground venues. The cocaine alkaloid is traditionally isolated from the leaves of the coca plant\textsuperscript{2}, though it can also be created synthetically today as well. Cocaine has been used since ancient times; the indigenous people of many South and Central American countries have been chewing the leaves of the coca plant for thousands of years, both for its pleasurable numbness and feelings of euphoria. Benzoylmethyl Ecgonine has also been used medicinally, generally as a local anesthetic\textsuperscript{3}.

There are several acute and unique human responses to the consumption of cocaine, many of which are adverse and destructive. The biological activity of cocaine on the human body will be the focus of this paper. The occurrence, synthesis, and biosynthesis of Benzoylmethyl Ecgonine will be discussed as well.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{benzoylmethyl_ecgonine.png}
\caption{The chemical structure for Benzoylmethyl Ecgonine (Cocaine).}
\end{figure}

\section*{I. Occurrence}

Benzoylmethyl Ecgonine has traditionally been extracted from the leaves of \textit{Erythroxylon Coca}, the coca plant. The plants are generally found and cultivated in the lower altitude areas of South America and Central America, especially in Peru and Bolivia which account for over 90% of the world's \textit{Erythroxylon Coca} production\textsuperscript{4}. \textit{Erythroxylon Coca} plants are generally cultivated until they reach a height of one to two meters, when they are then pruned. Their leaves are harvested by hand, roughly four times per calendar year. The collected leaves are sun-dried immediately after harvest, losing up to 75% of its mass due to water evaporation.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{coca_leaves.png}
\caption{Erythroxylon coca leaves, immediately after being harvested.}
\end{figure}

The Benzoylmethyl Ecgonine alkaloid is then isolated and extracted from the dried \textit{Erythroxylon Coca} plants. Typically, 0.8% of the dried leaf mass can be isolated into Benzoylmethyl Ecgonine, or 8mg of cocaine per 1g of dried coca plant leaf\textsuperscript{5}. The isolated alkaloid is then generally treated with hydrochloric acid to form cocaine hydrochloride, the "refined" and ready for use version of cocaine.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{cocaine_hydrochloride.png}
\caption{Cocaine Hydrochloride, refined and ready for recreational use.}
\end{figure}

\section*{II. Biological Activity}

Cocaine is notoriously known for being one of the most addictive and destructive recreational drugs currently in use. It can be introduced to the human body via smoking, snorting, ingesting, or injection. Upon entering the human body, cocaine acts on the mesoaccumbens dopamine pathway\textsuperscript{6}, an area of the brain responsible for conveying messages of euphoria and joy.

Once introduced into dopamine rich regions of the human brain, cocaine binds to and blocks dopamine reuptake transporters, which are responsible for the reuptake of dopamine after sufficient feelings of euphoria have been achieved. Consequently, with the dopamine reuptake...
transporters blocked, dopamine molecules are unable to be shuttled back, leading to a build up of dopamine levels in the synapse. This creates a heightened, artificial feeling of euphoria since the "euphoria" neurons are constantly being stimulated. Thus, the primary effect of cocaine is a heightened and unnatural sense of euphoria.

Figure 4. Cocaine (teal) shown blocking transporters from their reuptake of dopamine molecules (orange). http://www.nida.nih.gov/pubs/teaching/largegifs/slide-13.gif

The positive reinforcement one experiences from the constant feeling of euphoria due to cocaine slowly alters the brain to believe the uptake of cocaine is mandatory, much like food or water. This is why cocaine is known as a highly addictive drug; it alters one's brain chemistry to "believe" it needs to cocain to survive. Subjects that are denied cocaine once a addiction is manifested undergo withdrawal, meaning the subject may feel anxiety, irritability, agitation, and in extreme cases paranoia and depression.

Besides disrupting the dopamine reuptake transporters and causing unhealthy levels of dopamine build-up, cocaine has other adverse effects on the human body. Inhaling, or snorting of cocaine can result in damage to the mucous membrane, causing nosebleeds and an eventual loss of smell. Injections of cocaine greatly increase the risk of HIV and other blood borne illnesses. High dosage levels of cocaine may also lead to full blown paranoid psychosis in some subjects.

Prolonged and continued use of cocaine will ultimately lead to death. Cocaine related deaths are often caused by cardiac arrest or seizure. There is no known toxic level of cocaine consumption in humans, and for ethical reasons it would be impossible to determine via a study. Nevertheless, the average lethal dosage via inhalation of cocaine has been determined to be 750 mg. There is significant variation in this figure however, as deaths have occurred with as little as 25 mg of cocaine being inhaled. Cocaine remains one of the most lethal drugs available for mass consumption.

III. Biosynthesis

Cocaine is an alkaloid derived from L-ornithine. The biosynthesis of cocaine is summarized in Figure 4. L-Ornithine, an amino acid, is decarboxylated to form the intermediate depicted at 2. Methylation by SAM brings us to 3, followed by dehydration that leads us to 4. An aldol reaction then takes place, adding an acetyl CoA unit as depicted in 5. This intermediate undergoes a claisen condensation, resulting in 6. Next, the product is oxidized, then dehydrated again, leading to the 8. Finally, another aldol reaction brings us to the intermediate at 9, which ultimately evolves into Benzoylethyl Ecgonine (Cocaine).

Figure 5. Biosynthesis of Benzoylethyl Ecgonine

IV. Synthesis

The total synthesis of cocaine starts with 3-benzyloxypropionaldehyde being treated with tributylstannylithium and phthalimide to produce α-stannyl phthalimide (11) in a 98% yield. This intermediate was then deprotected by hydrazinolysis to produce α-amino stannane (12) in a 96% yield. Condensation of 3-benzyloxypropionaldehyde and α-amino stannane resulted in a 95% yield of (2-azaalyl)stannane (13). This intermediate was then treated with n-butyllithium and phenyl vinyl sulfide, resulting in a 3+2 cycloaddition and the formation of cis-pyrrolidine (14) in a 97% yield. Next, Boc was used to protect the secondary amine, leading to the product at 15, which was then oxidized with TPAP/NMO to produce the dialdehyde depicted at 16 at a 62% yield. Subsequently, the dialdehyde (16) underwent a proline-catalyzed aldol reaction, yielding 87% aldol products as depicted in 17. These unstable aldol products immediately underwent oxidation and esterification to produce the β-hydroxy esters at 18 in a 76% yield. Next, the β-hydroxy esters underwent benzoylation using benzoic acid and DMAPP, providing a 60% yield of the tropane compounds depicted at 19. Finally, the Boc carbonates were removed using trifluoroacetic acid followed by reductive amination, resulting in cocaine (20) being produced in a 74% yield.
Figure 6. Synthesis of Benzylocarbonyl Egonine.}

**Conclusion**

Cocaine is a molecule that has the potential to singlehandedly take over a person's entire psyche, a fact that many addicts can attest to. One can easily become addicted to cocaine, both physiologically and psychologically, after just one use. By disrupting the human brain's natural "reward system", cocaine can quickly convince a subject that he/she needs it to survive. There have even been reported cases of instantaneous death upon first time cocaine users. Despite all this, cocaine remains one of the most popular recreational drugs, most notably for the intense feelings of euphoria it provides. It does have some potential medicinal purposes as an anaesthetic or intermediary in dopamine regulation/manipulation, but the side effects are so adverse that it is highly unlikely that cocaine will ever be recommended for use under any circumstances. In fact, further research into cocaine will likely be geared towards helping addicts and preventing abuse, rather than the potential beneficial usage of cocaine.

**References**


