

The Preparation of the Local Anesthetic, Benzocaine, by an Esterification Reaction

Adapted by R. Minard (Penn State Univ.) from *Introduction to Organic Laboratory Techniques: A Microscale Approach*, Pavia, Lampman, Kriz & Engel, 1989. Revised 06/27/06

Introduction – Local Anesthetics

Local anesthetics, or "painkillers," are a well-studied class of compounds. Chemists have shown their ability to study the essential features of a naturally-occurring drug and to improve on them by substituting totally new, synthetic surrogates. Often such substitutes are superior in desired medical effects and also in lack of unwanted side effects or hazards.

The coca shrub (*Erythroxylon coca*) grows wild in Peru, specifically in the Andes Mountains, at elevations of 1500 to 6000 ft above sea level. The natives of South America have long chewed these leaves for their stimulant effects. Leaves of the coca shrub have even been found in pre-Inca Peruvian burial urns. The leaves bring about a definite sense of mental and physical well-being and have the power to increase endurance. For chewing, the natives smear the coca leaves with lime and roll them. The lime, $\text{Ca}(\text{OH})_2$, apparently releases the free alkaloid components; it is remarkable that the natives learned this subtlety long ago by some empirical means. The pure alkaloid responsible for the properties of the coca leaves is **cocaine**.

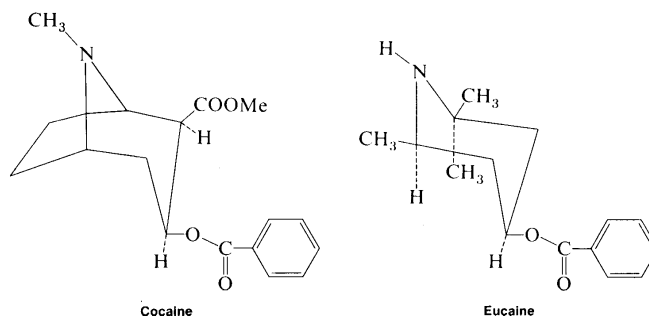


Figure 1. Cocaine and Eucaïne.

Moderate indulgence, as practiced by the coca-chewing natives, probably produces no more ill effects than moderate tobacco smoking does. The amounts of cocaine consumed in this way by the Indians are extremely small. Without such a crutch of central-nervous-system stimulation, the natives of the Andes would probably find it more difficult to perform the nearly Herculean tasks of their daily lives, such as carrying heavy loads over the rugged mountainous terrain. Unfortunately, overindulgence can lead to mental and physical deterioration and eventually an unpleasant death.

The pure alkaloid in large quantities is a common drug of addiction, which is psychological if not physical. Sigmund Freud first made a detailed study of cocaine in 1884. He was particularly impressed by the ability of the drug to stimulate the central nervous system, and he used it as a replacement drug to wean one of his addicted colleagues from morphine. This attempt was successful, but unhappily, the colleague became the world's first known cocaine addict.

An extract from coca leaves was one of the original ingredients in Coca-Cola. However, early in the present century, government officials, with much legal difficulty, forced the

manufacturer to omit coca from its beverage. The company has managed to this day to maintain the coca in its trademarked title even though "Coke" contains none!

Our interest in cocaine lies in its anesthetic properties. The pure alkaloid was isolated in 1862 by Niemann, who noted that it had a bitter taste and produced a queer numbing sensation on the tongue, rendering it almost devoid of sensation. (Oh, those brave, but foolish chemists of yore who used to taste everything!) In 1880, Von Anrep found that the skin was made numb and insensitive to the prick of a pin when cocaine was injected subcutaneously. Freud and his assistant, Karl Koller, having failed at attempts to rehabilitate morphine addicts, turned to a study of the anesthetizing properties of cocaine. Eye surgery is made difficult by involuntary reflex movements of the eye in response to even the slightest touch. Koller found that a few drops of a solution of cocaine would overcome this problem. Not only can cocaine serve as a local anesthetic, but it can also be used to produce mydriasis (dilation of the pupil). The ability of cocaine to block signal conduction in nerves (particularly of pain) led to its rapid medical use in spite of its dangers. It soon found use as a "local" in both dentistry (1884) and in surgery (1885). In this type of application, it was injected directly into the particular nerves it was intended to deaden.

Soon after the structure of cocaine was established, chemists began to search for a substitute. Cocaine has several drawbacks for wide medical use as an anesthetic. In eye surgery, it also produces mydriasis. It can also become a drug of addiction. Finally, it has a dangerous effect on the central nervous system.

The first totally synthetic substitute was eucaine (see Figure 1). This was synthesized by Harries in 1918 and retains many of the essential skeletal features of the cocaine molecule. The development of this new anesthetic partly confirmed the portion of the cocaine structure essential for local anesthetic action. The advantage of eucaine over cocaine is that it does not produce mydriasis and is not habit-forming. Unfortunately, it is highly toxic.

A further attempt at simplification led to piperocaine. The molecular portion common to cocaine and eucaine is outlined by dotted lines in the structure shown. Piperocaine is only a third as toxic as cocaine itself.

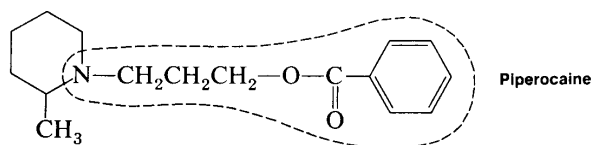
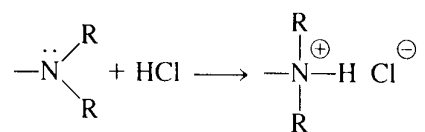


Figure 2. Piperocaine.

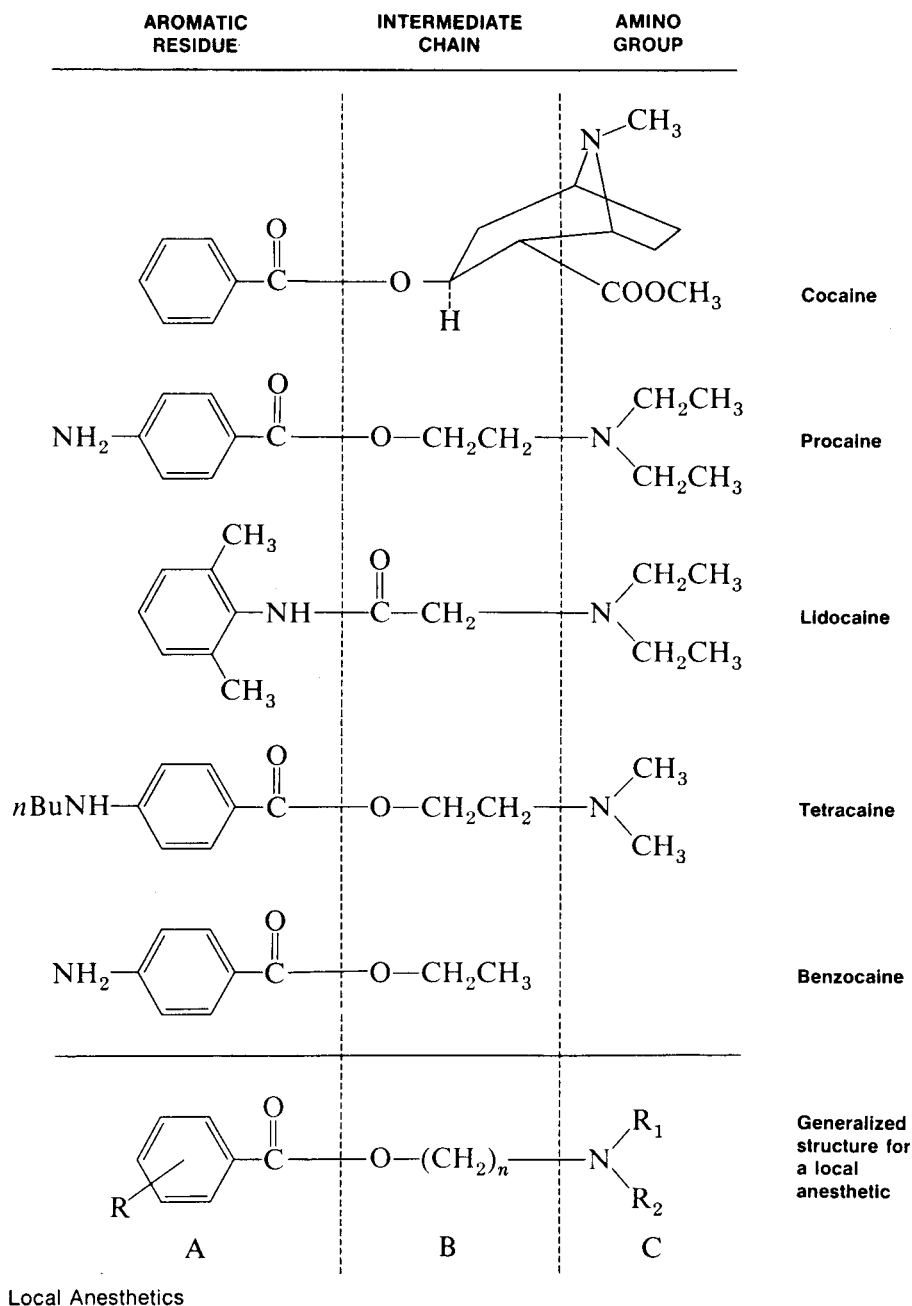
The most successful synthetic for many years was the drug procaine, also known more commonly by its trade name Novocain (see table). Novocain is only a fourth as toxic as cocaine, giving a better margin of safety in its use. The toxic dose is almost 10 times the effective amount, and it is not a habit-forming drug.

Over the years, hundreds of new local anesthetics have been synthesized and tested. For one reason or another, most have not come into general use. The search for the perfect local anesthetic is still under way. All the drugs found to be active have certain structural features in common. At one end of the molecule is an aromatic ring. At the other is a secondary or tertiary amine. These two essential features are separated by a central chain of atoms usually one to four units long. The aromatic part is usually an ester of an aromatic acid. The ester group is important to the bodily detoxification of these compounds. The first step in deactivating them is a hydrolysis of this ester linkage, a process that occurs in the bloodstream. Compounds that do not have the ester link are both longer lasting in their effect and generally more toxic. An exception is lidocaine, which is an amide. The tertiary amino group is apparently necessary to

enhance the solubility of the compounds in the injection solvent. Most of these compounds are used in their hydrochloride salt forms, which can be dissolved in water for injection. Benzocaine, in contrast, is active as a local anesthetic but is not used for injection. It does not suffuse well into tissue and is not water-soluble. It is used primarily in skin preparations, in which it can be included in an ointment or salve for direct application. It is an ingredient of many sunburn preparations.



How these drugs act to stop pain conduction is not well understood. Their main site of action is at the nerve membrane. They seem to compete with calcium at some receptor site, altering the permeability of the membrane and keeping the nerve slightly depolarized electrically.



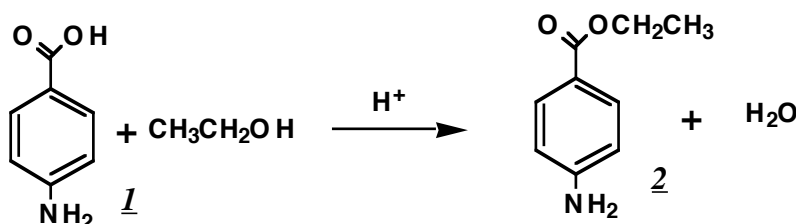
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R. F. Doerge.

Experiment

In this experiment, the synthesis of benzocaine (2) is carried out by the acid-catalyzed esterification of 4-aminobenzoic (1) acid with ethanol:



Prelaboratory Exercises

1. Refer to the structure of Procaine in the table in the above introduction, "Local Anesthetics." Using 4-aminobenzoic acid, give a reaction equation illustrating how Procaine could be prepared.
2. Which of the two possible amino functional groups in Procaine would be protonated first? Why?
3. Define reflux or refluxing in your own words.

Cautions

Sulfuric acid is very corrosive. Do not allow it to come in contact with your skin or clothes.

Synthesis

In a 5-mL round bottom flask, add 120 mg of 4-aminobenzoic acid (often called PABA for p-aminobenzoic acid), 1.5 mL of **absolute** ethanol (absolute ethanol is completely free of water and can be found on the hooded shelves), and 3 boiling chips. Heat this mixture on a sand bath until all the solid dissolves. Cool in ice and then add 0.25 mL of concentrated sulfuric acid dropwise. (One drop at a time.) A large amount of precipitate will form when the sulfuric acid is added, but this will dissolve during the reflux that follows. Attach an air condenser from the microscale kit, and reflux gently for 60-75 min. Check periodically to be sure that the mixture is refluxing gently, and that the ring of condensation of solvent lies somewhere along the inner surface of the air condenser; loss of solvent will cause overheating and significant decrease in yield.

Isolation and Purification

Detach the air condenser from the reaction tube and allow the reaction mixture to cool to room temperature. Take a TLC of the reaction mixture. TLC plates should have three spots (or lanes) on the origin: one for the main organic starting material that is being transformed (aminobenzoic acid), one for a cospot (starting material and the reaction mixture), and one for the reaction mixture. Find an appropriate mobile phase; start with 50% EtOAc in hexanes.

Using a Pasteur pipet, transfer the reaction solution to a 10-mL Erlenmeyer flask and add 3 mL of distilled water. Dropwise, add saturated sodium bicarbonate (about 3 mL, approximately 10% or 1 M) to neutralize the excess sulfuric acid and the ammonium sulfate salt form of the amino ester (making it neutral and insoluble in water). After each addition of the sodium bicarbonate, agitate the solution to mix thoroughly. Extensive CO₂ evolution (gas) and frothing will be observed until the mixture is nearly neutralized. As the pH increases, a white precipitate of benzocaine is produced. When gas no longer evolves as you add a drop of sodium bicarbonate, check the pH of the solution with "Alkacid" pH paper and, if it is less than 8, add further portions of saturated sodium bicarbonate solution.

Collect the benzocaine by vacuum filtration using a Hirsch funnel. Use three 1-mL portions of cold water to wash the product crystals from the flask onto the funnel. Make sure the product is rinsed thoroughly with cold water. After the product has dried thoroughly by leaving it in an open container until the next lab period, weigh it, calculate the % yield, and determine its melting point. The m.p. of pure benzocaine is 92°C.

Although the product should be fairly pure, it may be recrystallized by the mixed solvent method using methanol and water. Place the product in a preweighed reaction tube, and while stirring with a boiling stick and heating in a sand bath, add methanol dropwise until the solid just dissolves. Add 2 to 3 additional drops of MeOH and then add hot water dropwise until the mixture turns slightly cloudy or a white precipitate forms. Add methanol again while heating until the cloudiness or solid just disappears. Let cool slowly to room temperature and then complete the crystallization by cooling in an ice bath. Collect the solid by drawing the solvent off through a pipet using the pipet filtration technique. After the solid has dried in the open tube until the next lab period, reweigh the tube to determine the weight of recrystallized material and then take its melting point. Analyze the product as directed on your experimental assignment sheet. If you are doing an NMR analysis, you may have to use deuterio-DMSO as the NMR solvent as the product may have partial solubility in CDCl₃. Refer to Chap 11 of the Lab Guide for instructions on sample preparation.

Analysis

In addition to TLC analysis, you may be instructed to analyze your final product by IR, NMR or MS. Analyze your sample according to your assignment sheet and prepare it as per the instructions on Sample Preparation in the Lab Guide.

Cleaning Up

The filtrates from the first filtration, containing mainly ethanol and sodium sulfate, and the second filtration, containing mainly methanol and water, can both be flushed down the drain.

Final report

Annotate the spectrum, which you were assigned to collect. See Chapter 3 of the lab guide for examples on annotations of spectral data.

Postlab Questions

1. Give the full balanced equations for all three reactions that occur when the saturated sodium bicarbonate solution is added to the cooled reaction mixture.
2. If you analyzed the product by MS, how can you tell from the mass spectrum that the final product contains one nitrogen? If analyzed by NMR, define which of the aromatic region peaks are due to the Hs *ortho* to the carbonyl group.