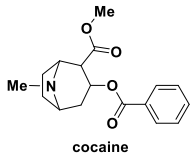
Experiment 8
Local Anesthetics:Synthesis of Benzocaine:

Local Anesthetics:Synthesis of Benzocaine:

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.



cocaine

One important naturally-occurring drug is cocaine present in Coca. The natives of South America have long chewed the leaves of the coca shrub for their stimulant effects. The leaves bring about a definite sense of mental and physical well-being and have the power to increase endurance. The pure alkaloid responsible for the properties of the coca leaves is **cocaine.**

Local Anesthetics:Synthesis of Benzocaine:

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!

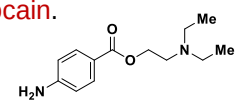
3

Anesthetic Properties of Cocaine

Our interest in cocaine lies in its anesthetic properties. Cocaine can serve as a local anesthetic, and can also be used to produce 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 and in surgery. In this type of application, it was injected directly into the particular nerves it was intended to deaden.

Cocaine has several drawbacks for wide medical use as an anesthetic.
It can become a drug of addiction and it has a dangerous effect on the central nervous system.

Soon after the structure of cocaine was established, chemists began to search for a substitute.
The most successful synthetic for many years was the drug procaine, also known more commonly by its trade name Novocain.



4

Essential Features of Local Anestetics:

1-Produce an action that is reversible

2-Nonirritating and nonallergic

3-Have a low toxicity

4-Have a rapid onset and a sufficient duration

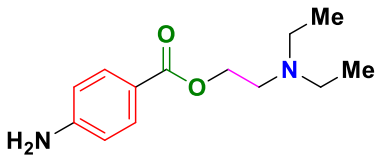
5-Have good penetrating properties

6-Have a potency sufficient to give complete anesthetization without using harmful concentrated solutions

7-Have stability in solution, but readily biotransformed or hydrolyzed in the body

5

Structural Features:



6

Structural Features:

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.

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.

7

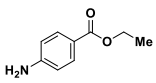
Benzocaine:

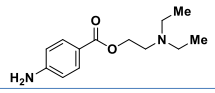
Benzocaine is a simpler analogue of procaine (Novocain). It is the ethyl ester of *para*-aminobenzoic acid (see the Figures below).

It lacks the tertiary amine component, so not surprisingly, it is less active as an injectable drug.

Benzocaine does not suffuse well into tissue and is not water-soluble. Nevertheless, it retains anesthetic properties, and is used extensively as a topical pain reliever, for example in medications for treating sunburn and in skin preparations.

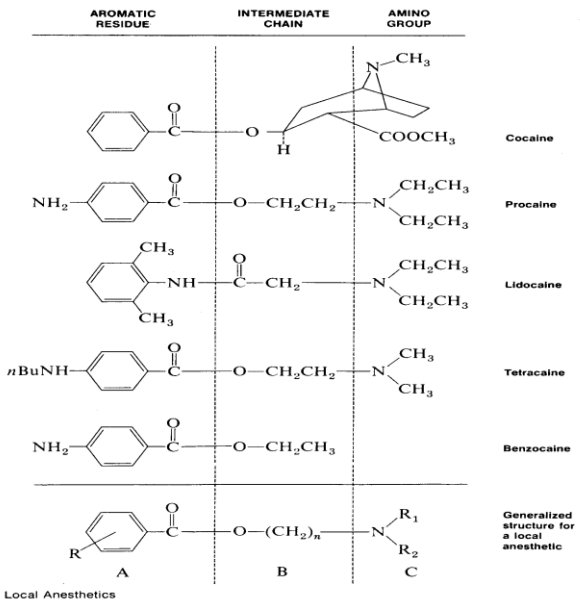
How these drugs act to stop pain conduction is not well understood. Their main site of action is at the nerve membrane. They seem to compete with calcium at some receptor site, altering the permeability of the membrane and keeping the nerve slightly depolarized electrically.

Benzocaine 

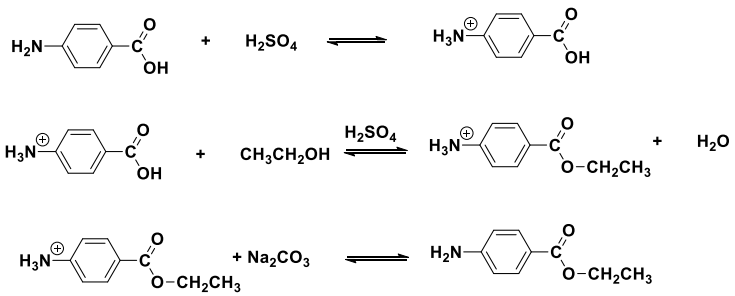


Procaine (Novacaine)

8



Synthesis of Benzocaine: reactions



Procedure:

Add 2.50g (0.018 mole) of p-aminobenzoic acid, and 25mL of absolute ethanol to a round bottom flask. Swirl the mixture until the solid is completely dissolved.

Add 2mL of concentrated sulfuric acid **dropwise** with a Pasteur pipette to the ethanol-aminobenzoic acid solution. A solid will precipitate out of the solution.

Please Note: sulfuric acid is very corrosive and can cause serious chemical burns if allowed to come into contact with your skin. Use extreme caution when handling this chemical.

Attach a reflux condenser to the round bottom flask containing the ethanol solution, and heat under reflux for ~ 75 minutes.

If any solid precipitate remains after heating, cool the solution at room temperature for 2-3 minutes then add 3mL of absolute ethanol and 0.5mL of sulfuric acid (dropwise) to the round bottom flask containing the solution and precipitate.

11

Procedure (cont'd):

Resume heating under gentle reflux until all of the solid has dissolved. It is very important for this experiment to succeed that ALL of the solids dissolve during this period.

Once the solid is completely dissolved, continue heating the solution under gentle reflux for another 30 minutes.

Remove the condenser and pour the hot solution into a beaker containing 100ml of cold water.

Immediately basify the reaction mixture and water solution by adding solid sodium carbonate in small quantities with stirring until the solution is alkaline to litmus and additional sodium carbonate produces no further evolution of CO_2 gas.

Crude benzocaine should precipitate. Cool if necessary and collect the product by suction filtration. Re-crystallize the product from water and 95% ethanol using mixed solvent technique. Allow the crystals to dry and determine the weight and the melting point.

12

Mixed Solvent Technique :

Place the crude solid into a small Erlenmeyer flask, add hot ethanol slowly while shaking until the solid just dissolves.

Add 2-3 drops of ethanol, then add hot water dropwise until the mixture turns slightly cloudy.
Add few drops of ethanol while heating (water bath) until the cloudiness just disappears.
(If solid sodium carbonate is present, make hot filtration)
Cool to room temperature, then in an ice bath.

Collect the re-crystallized product by suction filtration.

13

Mechanism???

14