EXPERIMENT 8

Local Anesthetics: Synthesis of Benzocaine

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Introduction – Local Anesthetics

- Local anesthetics, or "painkillers," are a well-studied class of compounds.
- Chemists studied the essential features of a naturally-occurring drug and tried to substitute it totally by new, synthetic surrogates.
- Substitutes are superior in desired medical effects and also in lack of unwanted side effects or hazards.
- One important naturally-occurring drug is cocaine present in Coca.
- The coca shrub *(Erythroxylon coca)* grows wild in Peru, specifically in the Andes Mountains.
- 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.
- For chewing, the natives smear the coca leaves with lime and roll them.
- The lime, $Ca(OH)_2$, apparently releases the free alkaloid components.

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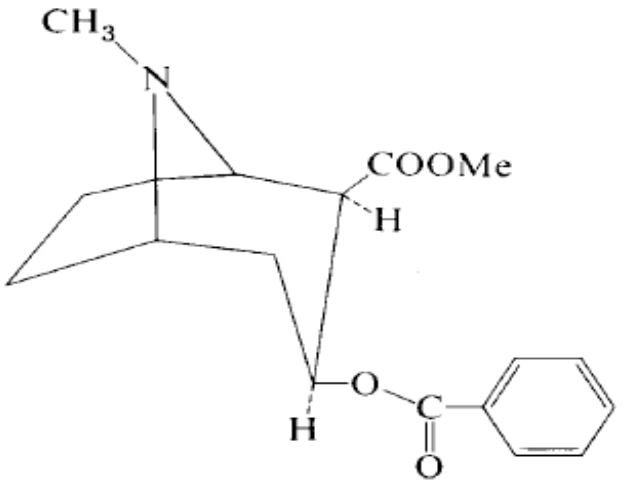
Introduction – Local Anesthetics

- The pure alkaloid responsible for the properties of the coca leaves is **cocaine.**



Cocaine

- It was noticed that the coca-chewing, probably produces no more ill effects than moderate tobacco smoking does.
- 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. Cocaine can serve as a local anesthetic, and can also be used to produce dilation of the pupil.

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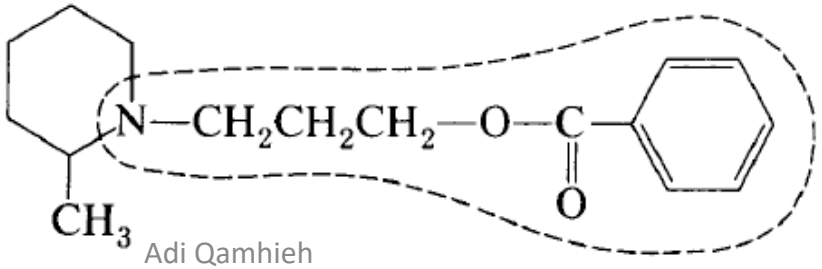
Introduction – Local Anesthetics

- 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.
- 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.
- It can become a drug of addiction and it has a dangerous effect on the central nervous system.
- The molecular portion common to cocaine is outlined by dotted lines in the structure shown. Piperocaine is only a third as toxic as cocaine itself.



Piperocaine

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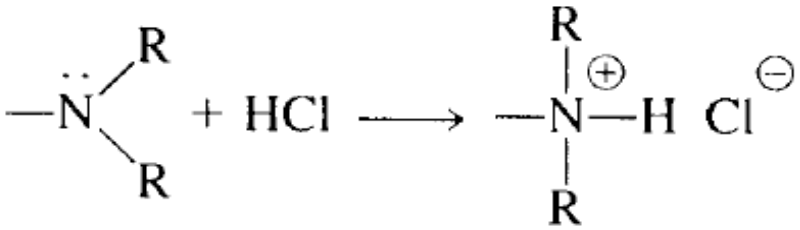
Introduction – Local Anesthetics

- The most successful synthetic for many years was the drug procaine, also known more commonly by its trade name Novocain(see table).
- 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.

Local Anesthetics: Synthesis of Benzocaine

Introduction – Local Anesthetics

Benzocaine :

- Is active as a local anesthetic.
- It lacks the tertiary amine component, it is less active as an injectable drug.
- 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 of salve for direct application.
- It is an ingredient of many sunburn preparations.
- Their main site of action is at the nerve membrane.
- Nonirritating and no allergic.
- Have a low toxicity

Local Anesthetics: Synthesis of Benzocaine

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.

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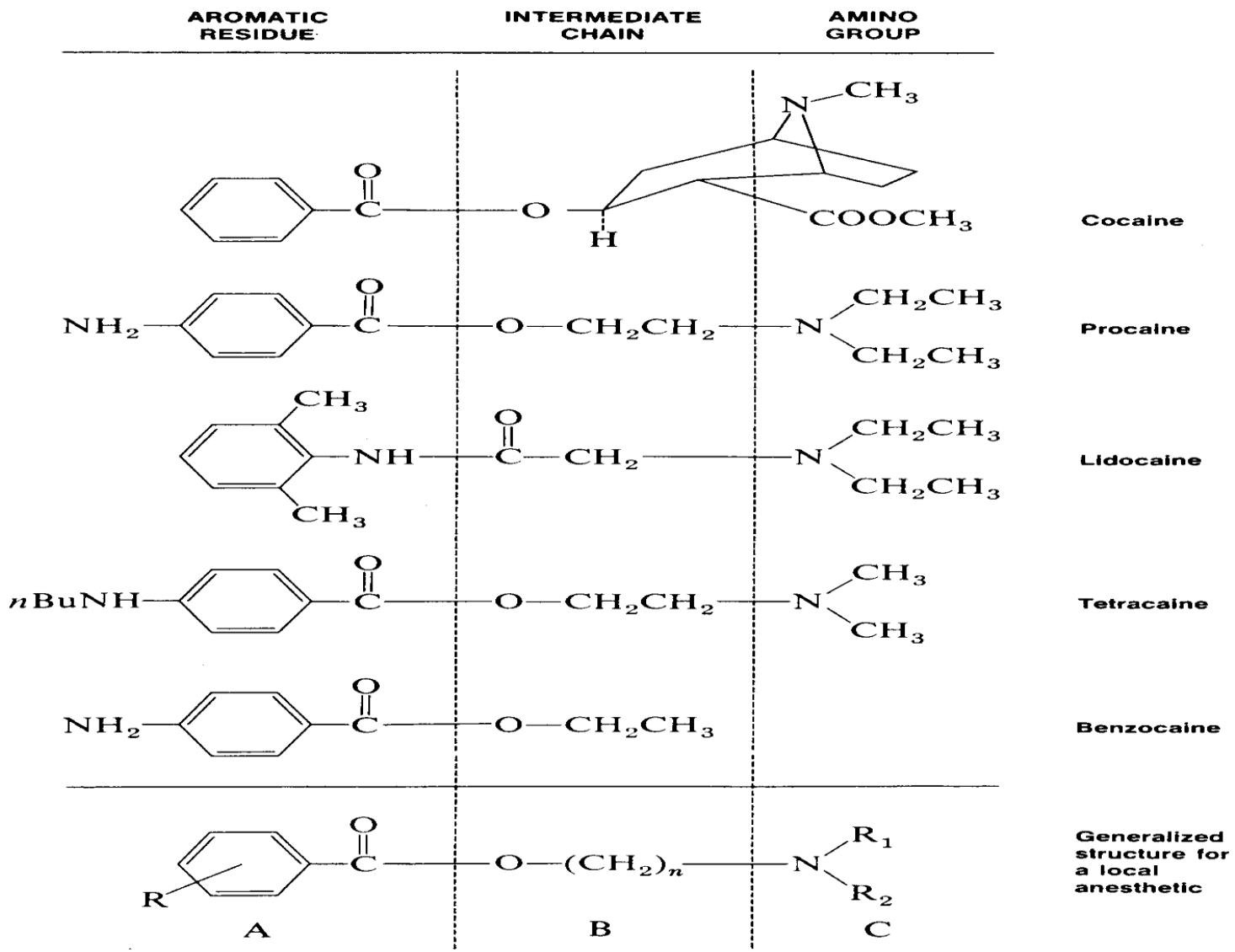
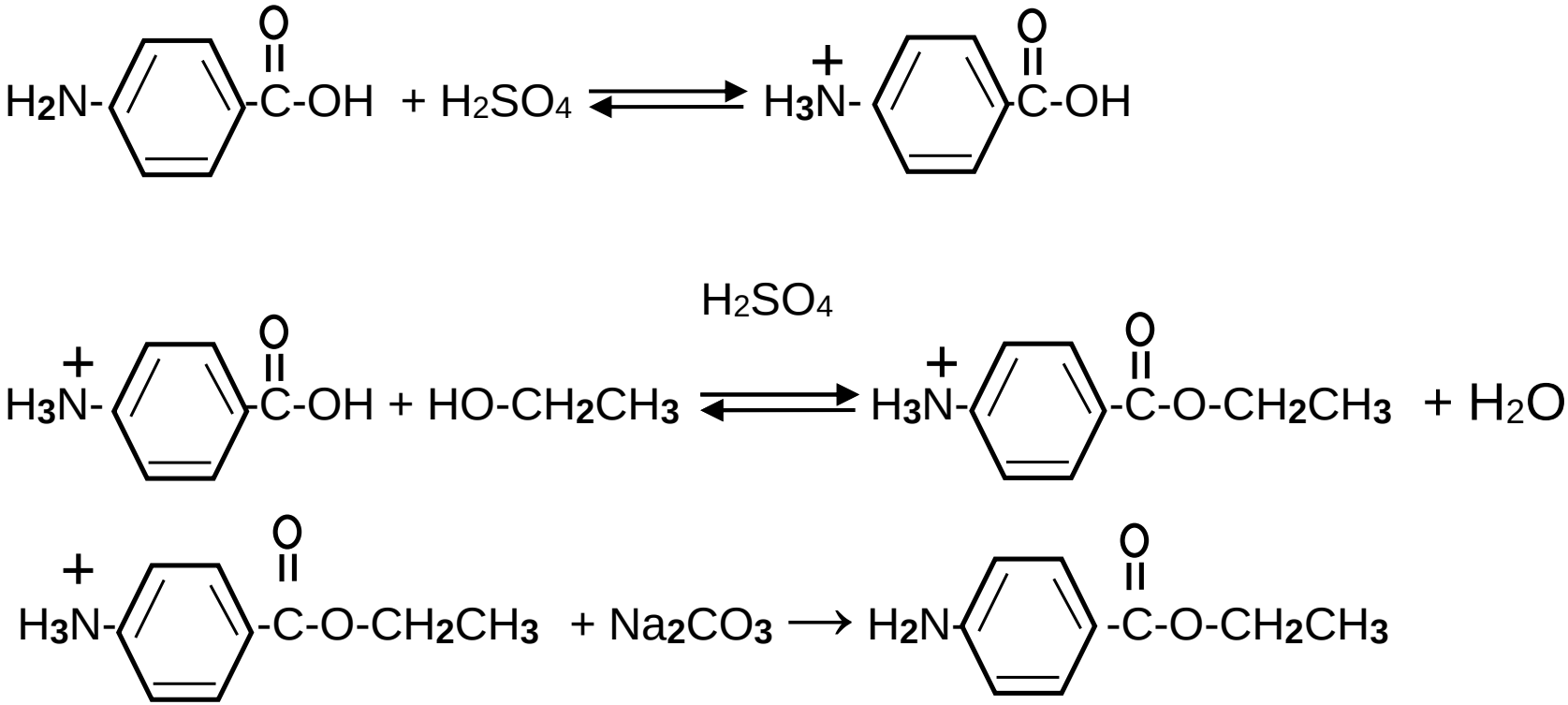


Local Anesthetics: Synthesis of Benzocaine

Synthesis of Benzocaine: acid-catalyzed esterification of 4-aminobenzoic acid with ethanol:

Equations:



Local Anesthetics: Synthesis of Benzocaine

Experimental procedure:

1. In a 100-mL round bottom flask, add 2.5 g (0.018 mole) of 4-aminobenzoic acid (often called PABA for p-aminobenzoic acid), 25 mL of ***absolute*** ethanol (0.425 mole).
2. Using a small graduated cylinder add 3 mL concentrated sulfuric acid gradually, with cooling if necessary and 3 boiling chips.
3. Construct the apparatus by attaching a water cooled reflux condenser to the flask.
4. Heat this mixture using a Bunsen burner 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;

Note: Loss of solvent will cause overheating and significant decrease in yield.

5. Allow the reaction mixture to cool, detach the reflux condenser from the reaction flask.
6. pour the contents of the flask into a 100 mL. ice cooled water in a 250mL. beaker.

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Experimental procedure:

7. Add solid sodium carbonate with stirring until the solution is alkaline to litmus paper and further addition of sodium carbonate produces no further effervescence.

8. Cool the beaker in an ice bath and collect the product by suction filtration.

9. Recrystallize the precipitate from water and 95% ethanol using mixed solvent technique.

10. Allow your sample to dry, weigh your sample.

11. Measure its melting point and calculate your experimental yield.

Notes:

- ***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.***

- ***The m.p. of pure benzocaine is 92°C.***

Local Anesthetics: Synthesis of Benzocaine

Recrystallization

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 or hot plate) until the cloudiness just disappears.
- Cool to room temperature, then in an ice bath.
- Collect the re-crystallized product by suction filtration.