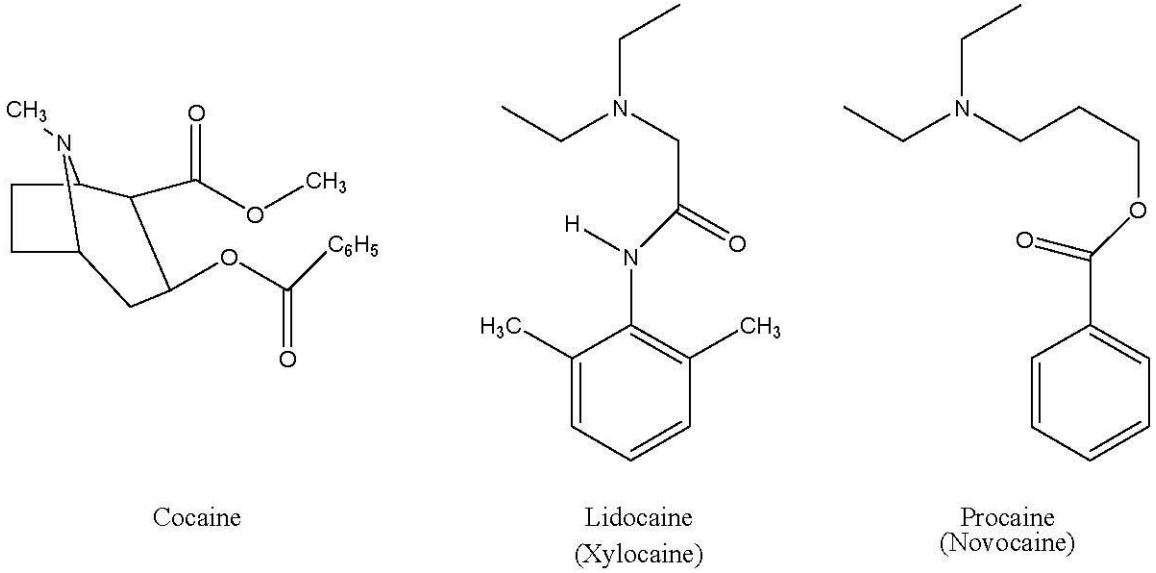
Synthesis of Lidocaine

INTRODUCTION:

Local anesthetics (pain killers) are an important and well-studied class of synthetic drugs. Some common local anesthetics are shown below. Of these, only cocaine is a naturally occurring compound, and the synthetic drugs are used to avoid the narcotic effects of the former.



Cocaine | Lidocaine (Xylocaine) | Procaine (Novocaine)

Figure 1: Some samples of local anesthetics, cocaine, lidocaine and procaine.

In most of the hundreds of local anesthetics that have been synthesized, two features are prominent: The compounds are benzoate esters or anilides and contain a dialkylamino group separated by one or four atoms from the carbonyl center, as indicated in the structure of cocaine. The dialkylamino group is a characteristic unit in the structures of many diverse medicinal agents such as antihistamines, antimalarial compounds, and tranquilizers.

In this experiment the local anesthetic lidocaine will be synthesized and isolated in the form of its bisulfate salt. (The hydrochloride is the salt generally used in medicine, but it is considerably more difficult to purify.) Lidocaine (the generic name) is sold under various trade names, the most common of which is Xylocaine. It is noted for its relatively high anesthetic activity when applied to the skin or injected into nerves, it also has a low toxicity and incidence of side effects. Another important use of lidocaine is treatment of arrhythmia.

The synthetic sequence shown below illustrates several important reactions. The reduction of an aromatic nitro compound is most commonly accomplished with metals such as iron, zinc, or tin. Stannous chloride is more rapid and convenient because the reaction is homogeneous; however it is a rather expensive reagent. It is possible to begin the sequence with 2,6-dimethylaniline, since this compound is commercially available and actually costs less per gram than the nitro compound. The second and third steps in the synthesis are

acylation of the aniline by the highly reactive chloroacetyl chloride and alkylation of dimethylamine by the chloroamide. This last step is an SN2 displacement, which is facilitated by the adjacent carbonyl group.

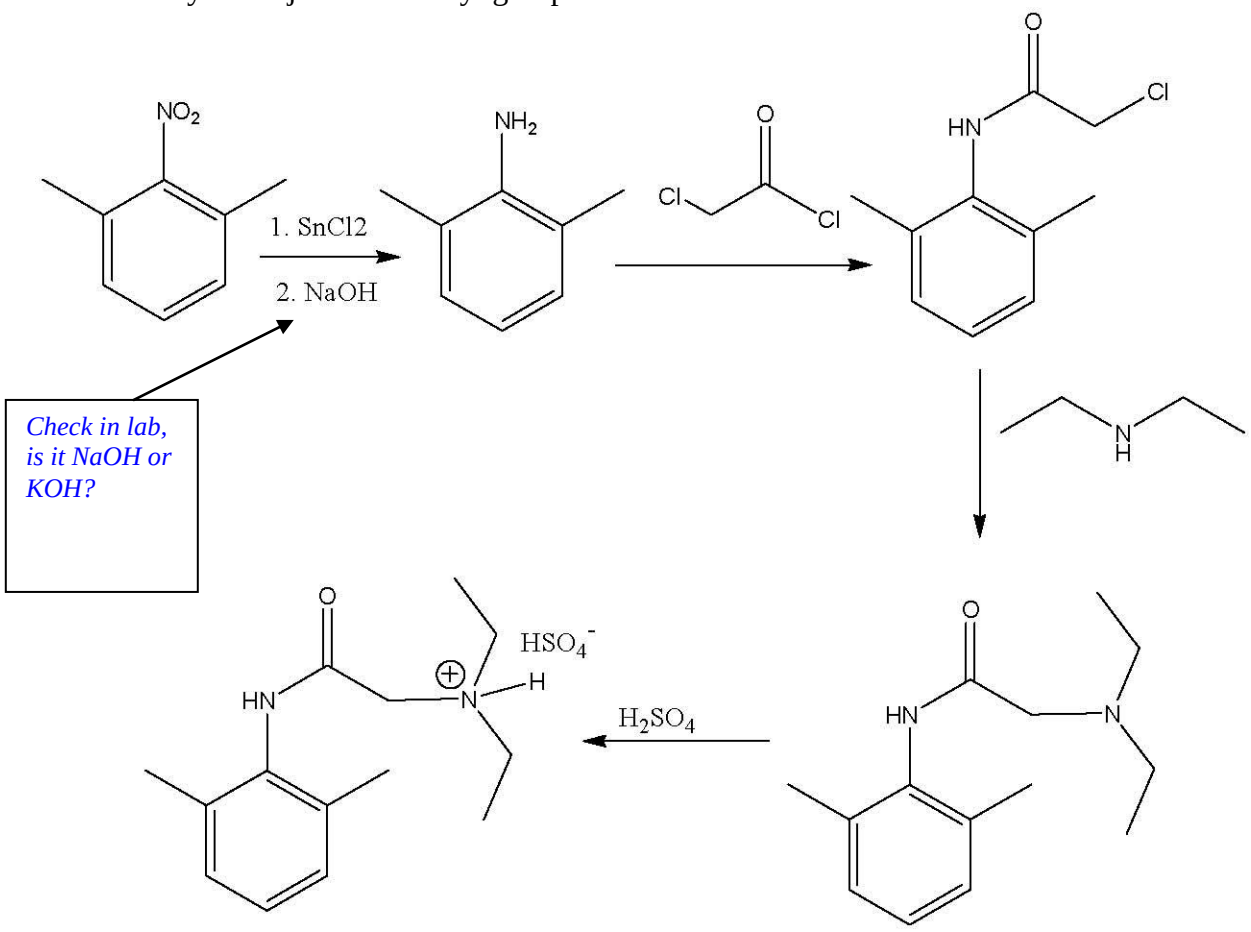


Figure 2: The synthetic sequence for the conversion of of 2,6-Dimethylnitrobenzene to the bisulfate salt of lidocaine.

Procedure:

(1st week)

A: Synthesis of 2,6-Dimethylaniline via Reduction of 2,6-Dimethylnitrobenzene

1. Dissolve1.0 g of 2,6-dimethylnitrobenzene in 10 mL of glacial acetic acid in a 50 mL Erlenmeyer flask.
2. In a 25 mL flask, dissolve 4.6 grams of $SnCl_2 \cdot 2H_2O$ in 8 mL of concentrated HCl, inside the fume hood.
3. Add the $SnCl_2$ solution in one portion to the nitroxylene solution, magnetically swirl and mix, and let the mixture stand for 15 minutes.
4. Cool the mixture and collect the crystalline salt (dimethylaniline in the salt form: $C_6H_5NH_3^+Cl^-$) in a Buchner funnel.
5. Transfer the moist crystals to an Erlenmeyer flask, add 5-10 mL of water, and make the solution strongly basic (to remove the acid and change $C_6H_5NH_3^+Cl^-$ back into

$C_6H_5NH_2$) by adding 30% KOH solution (12 to 17 mL required).

6. After cooling extract with three 10 mL portions of ether, rinse the ether extracts twice with 10 mL of water, and dry over K_2CO_3.
7. Evaporate the dried and filtered solution to an oil, transfer and rinse into a 50 mL Erlenmeyer flask, complete evaporation, weigh, and calculate the %yield of 2,6-dimethylaniline.

B: Synthesis of α-Chloro-2,6-dimethylacetanilide *(prepare for a steam bath ahead of time)*

1. For every 7 grams *(from this step on, you need to calculate proportionally how much you need to add according to the actual weight that you got)* of dimethylaniline from the previous step, add 50 mL of glacial acetic acid, and 7.2 g (or 5.2 mL) of chloroacetyl chloride, in that order.
2. Warm the solution on a steam bath to (40–50)ºC, remove, and add a solution of 1 gram of sodium acetate in 100 mL of water.
3. Cool the mixture and collect the product in a Buchner funnel.
4. Transfer the product to a disk of medium–sized filter paper, finely divide it with a spatula, and let air dry until the next laboratory period.
5. Upon drying, measure the mass and the melting point. Also, calculate the % yield.

(2nd week)

C: Synthesis of α-diethylamino-2,6-dimethylacetanilide

1. In a 50 mL round-bottom flask, place the chloroacetoxylidide obtained from the preceding step and 25mL of toluene; then add three moles of diethylamine per mole of xylidide.
2. Save out a few milligrams of the starting material for later TLC analysis. In order to observe the progress of the reaction and make a quick and direct comparison, you should, for every 15-30 minutes, run your starting material right next to (on the same TLC plate) your reaction mixture collected in the following steps.
3. Fit the flask with a reflux condenser, add a boiling stone, and reflux vigorously.
4. The progress of the reaction can be measured conveniently at 15 to 30-minute intervals by TLC. (TLC solvent: Chloroform)
5. After the starting materials are consumed (based on the TLC results), or after 90 minutes of refluxing, whichever comes first, cool the mixture to room temperature, and then in ice bath, and filter out the crystals.
6. Rinse the crystals with small amount of pentane, let air dry, and weigh. At the same time, proceed to step 7 with the filtrate.
7. Transfer the filtrate to a separatory funnel and extract with two 10 mL portions of 3 M HCl solution.
8. Cool the acidic aqueous layer in an Erlenmeyer flask and add 30% KOH solution until the mixture is strongly basic.
9. Extract with two 10 mL portions of pentane.
10. Rinse the pentane layer with six 10 mL portions of water to remove unreacted diethylamine, dry over sodium carbonate (Na_2CO_3) and concentrate in a tared flask.
11. Measure the mass of the product.

D. Synthesis of the bisulfate salt of lidocaine

1. Dissolve the lidocaine in ether (10 mL per gram of lidocaine) and add 2 mL of 2.2 M sulfuric acid in ethanol per gram of lidocaine.
2. Stir and scratch with a glass rod to mix and induce crystallization.
3. Dilute the mixture with an equal volume of acetone to aid filtration and collect the salt in a small Buchner funnel.
4. Rinse the solid on the funnel with a few milliliters of acetone and air dry and weigh the product.
5. Calculate the % yield of this step.

*** **Overall % Yield**

The overall % Yield for a multistep process is the product of all the individual yield percentages.

For your report report all melting points taken and discuss. Calculate your percent yield for each step and discuss each step. Calculate your overall percent yield and discuss this value.