Lidocaine Synthesis - Remote Activity

Purpose: In this virtual experiment, you will be preparing your notebook for a two-part synthesis. Rather than executing the experiment in person, you will be watching videos of each procedure and recording observations. You will be analyzing IR and NMR spectra of the reactants and products.

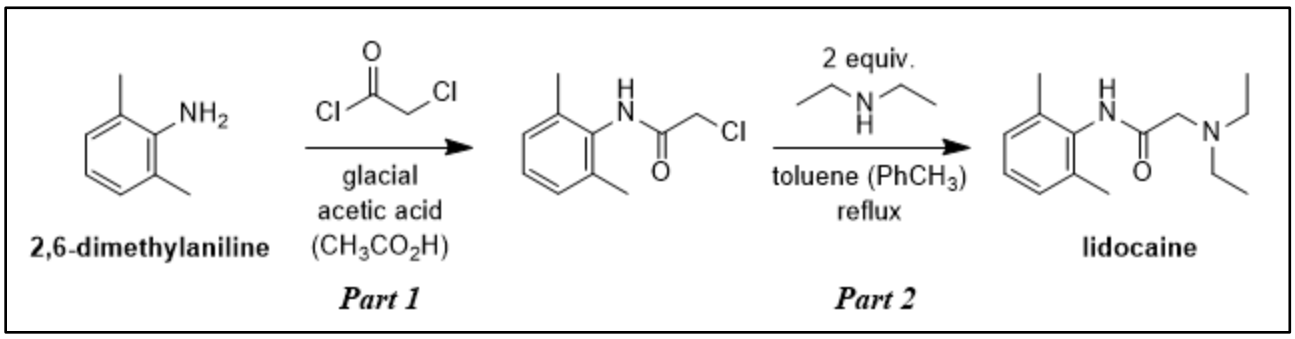


Figure 1. Two-part synthesis of lidocaine from 2,6-dimethylaniline

Part 1: Amide Formation

- Prepare your notebook (introduction, reagent table, procedure) according the format required by your instructor. The procedure to follow is provided on the following pages. For the reagent table, don't forget to look up the relevant SDS to identify any hazards associated with the materials and solvents being used. Also, you should calculate the theoretical yield of the chloroamide product.
- Watch a video of the experimental procedure being conducted, and record observations into your notebook. You may disregard the amounts being used, because the video demonstration is run on a slightly different scale than the written procedure, but it's a good idea to pay attention to the comments being made about what is being done! https://youtu.be/A2bouOZAZ6s
- Your instructor may provide the final weight and melting point of the purified product for analysis.
- IR and ^{1}H NMR data for the starting material and product are provided at the end of the document.

Part 2: Preparation of Lidocaine

- As done for Part 1, prepare your notebook (introduction, reagent table, hazards, TY, procedure) according the format required by your instructor. The procedure is provided on the following pages.
- Watch a tutorial on acid-base extraction techniques. https://youtu.be/Pq1TySRBreM
- Watch a video of the experimental procedure being conducted, and record observations into your notebook. You may disregard the amounts being used, because the video demonstration is run on a slightly different scale than the written procedure, but it's a good idea to pay attention to the comments being made about what is being done! https://youtu.be/r3T1M7Yr7ik
- Your instructor may provide the final weight for analysis.
- A ^{1}H NMR spectrum of lidocaine is provided for analysis at the end of this document.
- Use data from the NIST government site https://webbook.nist.gov to find an IR spectrum of lidocaine.

Lab Report

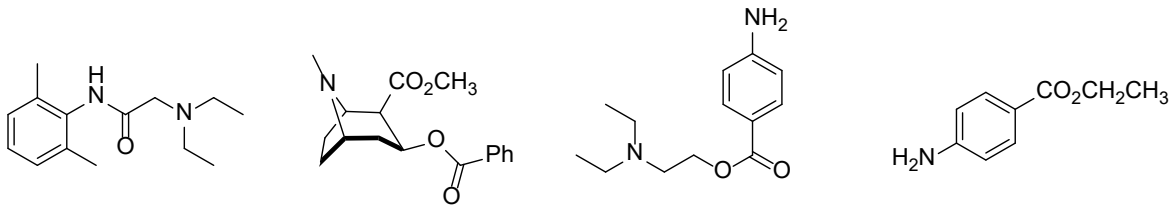
Submit your notebook pages, IR spectrum of lidocaine (with peaks labeled), and answers to questions 1-9.

The 2-Step Synthesis of Lidocaine

Review – You should review SN2 reactions. You also need to do some on your own reading of section 20-15 in Wade and become familiar with macroscale recrystallization and macroscale separation using a separatory funnel.

Introduction: Lidocaine is a member of the Caine Family of pharmaceutical local anesthetics. Figure 1 below shows the chemical structure of Lidocaine as well as three other members of this important family of numbing agents.

Figure 1. Well-known compounds in the Caine family of local anesthetics.



Lidocaine Cocaine Novocaine Benzocaine

When used correctly, these compounds are very effective at providing local anesthesia, or the numbing feeling you get when you go to the dentist for a filling, for example. These compounds are administered topically, orally or injected, depending on the situation. Topical creams and ointments that are available over the counter (OTC) generally contain Lidocaine and sometimes Benzocaine. Of the four compounds in figure 1, Cocaine is not available OTC (hopefully this is obvious) and is uncommon among the medical community due to its extremely addictive nature.

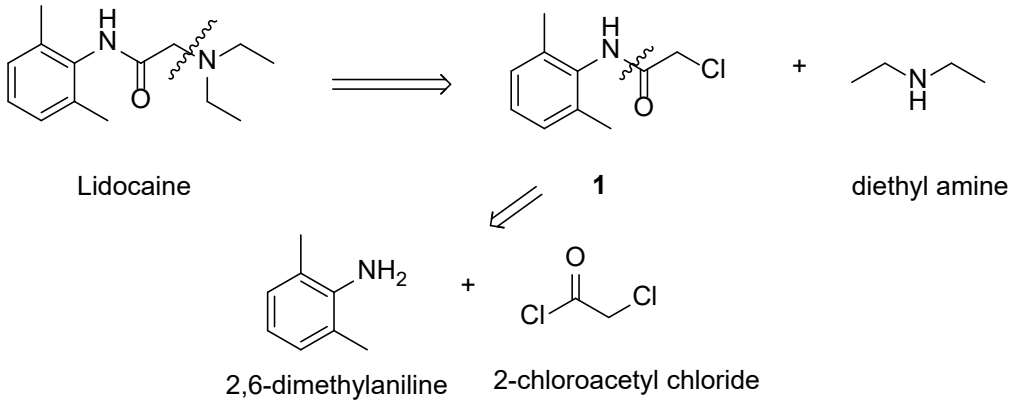
Local anesthetics prevent us from experiencing pain in a small portion of the body, i.e., wherever it is applied. When a local anesthetic is injected directly into the spinal fluid, our entire lower body goes numb. An example of the latter is an epidural given to a woman in labor and is most commonly Bupivacaine (structure not shown). A common example of a local anesthetic is the use of Benzocaine in teething gel (Orajel®) in infants. The gel is applied to the affected area and numbs the gums temporarily.

These compounds are classified together because they show the same, or similar, mechanisms of action. Most members of the Caine family inhibit the sensation of pain by blocking the transfusion of sodium ions across the cell membrane. We experience pain when our nerve endings are stimulated. When this stimulation occurs, the nerve cell (neuron) is depolarized by the influx of sodium ions. This causes a drastic change in the electric action potential (AP) and is then transferred down the nerve, directly to the central nervous system (CNS). The CNS construes this AP as pain. In short, the blocking of the "sodium gate" prevents this depolarization and pain is not experienced.

Retrosynthetic Analysis: Recall that retrosynthesis is working backwards from the desired compound and putting it together, piecewise, with known reactions. The synthesis of Lidocaine may be envisioned as outlined in the retrosynthesis in figure 2 below. The indicated carbon-nitrogen bond (a wavy line through the bond) in Lidocaine can be formed via the Sn2 reaction between commercially available diethyl amine and synthetic intermediate α-chloro amide **1**. Intermediate **1** is obtained via the commercially available compounds 2-chloroacetyl chloride and 2,6-dimethylaniline. There are other reagents involved in the synthesis of Lidocaine, however, they are generally omitted in a retrosynthetic

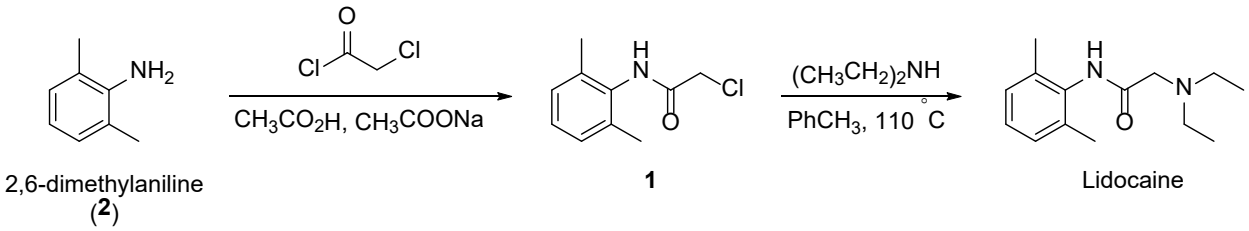
analysis. Only the key bond formations are discussed. They detail is outlined in the explanation of each forward step.

Figure 2. Retrosynthesis of Lidocaine.



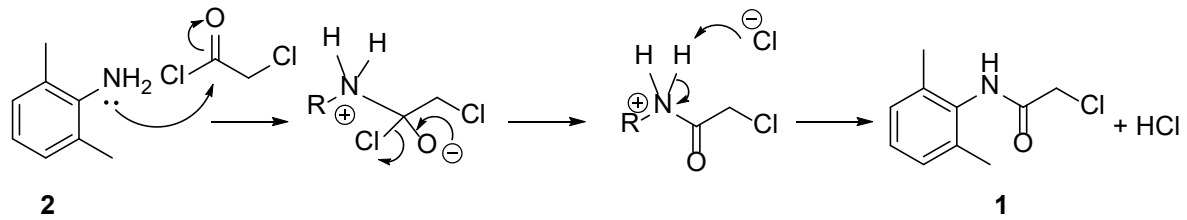
The Reaction, the mechanism and Background - The forward synthesis of Lidocaine is outlined in figure 3.

Figure 3. The synthesis of Lidocaine.



In step 1 of the reaction, 2,6-dimethylaniline is treated with α-chloroacetyl chloride in acetic acid in the presence of sodium acetate. Selective substitution at the acyl carbon (C=O) atom in this step is a reflection of the substantially greater reactivity of nucleophiles with acid chlorides (electrophile) relative to alkyl chlorides because of their electronic differences. Of the acid chloride, the chlorine and oxygen both pull electron density away from the carbon atom, which enhances its electrophilicity 10-fold. The mechanism is outlined in figure 4 and is classified as an addition-elimination, very similar to the trimyristin saponification mechanism.

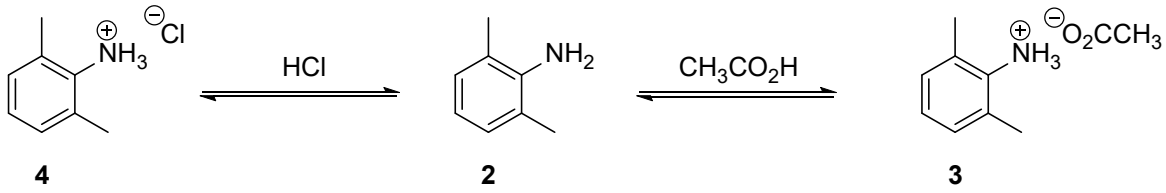
Figure 4. Mechanism of the formation of 1 from 2.



Acetic acid (AA) is the solvent for this first step, the sodium salt of its conjugate base (sodium acetate) is also used, and their roles together are very important. Because acetic acid is chosen, an equilibrium is setup between itself and 2,6-dimethylaniline (*figure 5*) to yield the ammonium acetate salt **3**. The

conversion of **2** to **1** (*figure 4*) also liberates hydrochloric acid, and upon its generation, equilibrium is setup between itself and unreacted compound **2** to yield the ammonium chloride salt **4** (*figure 5*). These two salts may appear to be the same, and they are with respect to the cationic portion. The difference is their ionic strengths! The desired α-chloroamide **1**, and the chloride salt **4**, are both **insoluble** in AA, but acetate salt **3** is **soluble** in AA. *In short, desired compound **1** would co-precipitate with the undesired salt **4**.* This would prohibit isolation of α-chloroamide **1** by filtration. To combat this, the system is flooded with sodium acetate.

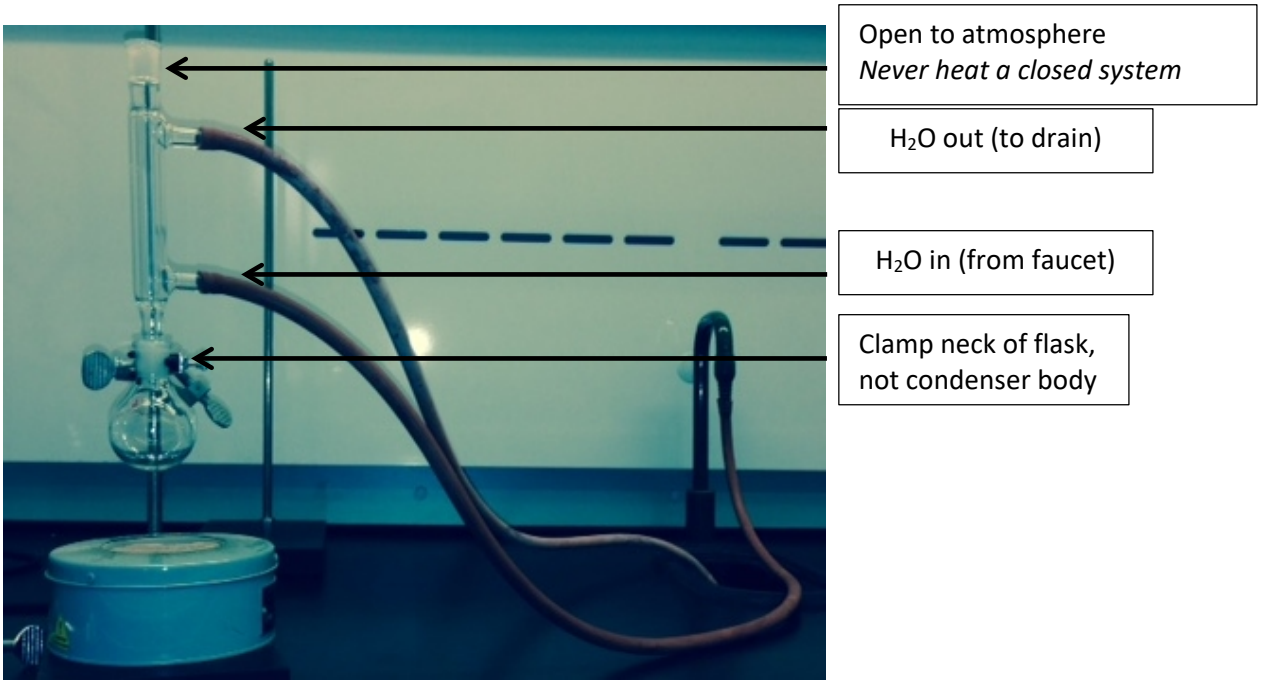
Figure 5. The different salts that compound 2 can form in the reaction mixture.



4 **2** **3**

The acetate destroys any formed HCl so the only salt possible is the acetate version **3**. Now, desired compound **1** can be isolated via suction filtration without other solid contaminants. All contaminants are left in the filtrate, which will be discarded. The second step is an Sn2 reaction, of which you should know the inner workings from organic lecture (CHEM-255).

Special Notes: Some of the glassware used in this experiment is not in your drawer. This will be pointed out in the procedure and by your TA. For the first time you will be using a water-cooled reflux condenser. Water goes in the bottom port and out the top. Think about why . . .



Pre-lab Assignment: You need to research all physical aspects of the chemicals used in this experiment. Your table of reagents (TOR) should be quite extensive and should also note the hazards associated with

each. It should also show masses, volumes and mmol of reagents. Your TA will want to see ALL physical aspects of everything used in this experiment.

1. What is the limiting reagent in step 1? What is the theoretical yield of amide 1 in figure 3?
2. What is the theoretical yield of Lidocaine? Base calculations on 2,6-dimethylaniline.
3. How many molar equivalents of diethyl amine are used in step 2?

Safety: 2,6-dimethylaniline is toxic and readily absorbed through the skin. You must wear gloves when handling this and any chemical during this experiment. 2-chloroacetyl chloride is toxic, corrosive and is a lachrymator (makes you cry); again wear gloves. **Diethyl amine is toxic and is very foul smelling.** The diethyl amine is to be dispensed by your TA. Follow the procedure exactly. Pardon the cliché, but it must be followed "to a T."

Experimental Procedure – Preparation of *N*-(2,6-Dimethylphenyl)chloroacetamide 1. First, get ~ 100 mL of water cooling in an ice-bath. You will use it soon. Wearing gloves, measure out 3.0 mL of 2,6-dimethylaniline into a 10-mL graduated cylinder and set aside in your hood. Using a larger graduated cylinder that your TA will have for you on the common bench, measure out 15-mL of glacial (concentrated) acetic acid (be very careful as it is corrosive) and add it to a 125 mL Erlenmeyer flask. Immediately r*inse the graduated cylinder that held the acetic acid with acetone a few times and allow to air dry. You will use it again soon*. Add the amine, via a Pasteur pipet, to the acetic acid in the Erlenmeyer flask. Rinse out your 10-mL graduated cylinder with acetone a few times and dry with the air jet. In this cylinder, measure out 2 mL of 2-chloroacetyl chloride and transfer to the Erlenmeyer flask containing acetic acid and 2,6-dimethylaniline. Add your thermometer to the Erlenmeyer. Using the larger graduated cylinder that you cleaned out a moment ago measure out 25 mL of 0.333 M aqueous sodium acetate. Add this directly to the Erlenmeyer. *Note any observations and temperature changes*! Next, remove the thermometer and rinse it into the flask with the cold water you previously prepared and add 60 mL directly to the flask (reserve the remaining cold water for use soon), stir thoroughly for 10 minutes using your glass stir rod. Isolate the product via vacuum filtration using a Buchner funnel on the common bench. Rinse with a few portions of the remaining cold water. Press as dry as possible with another piece of filter paper.

Preparation of Lidocaine, AKA: 2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide – To a ***pre-weighed*** 50-mL round bottomed flask, add the pressed-dry amide **1** and re-weigh the flask to get an exact amount of amide **1** used (record this mass). Sequentially add 7.5 mL diethylamine, 25 mL toluene and a few boiling stones. **Special Note: The TA will add your diethyl amine for you from the reagent bottle to minimize the stench in the lab.** Attach a water-cooled reflux condenser to the round bottomed flask (see section above for the proper hook-up of a water-cooled condenser). ***Turn water on very slowly***. ***Your water going to the drain should just trickle out***, not flow like white-water rapids! Lower assembly close to the hot plate and reflux for 90 minutes (note any and all observations). Cool to room temperature, unaided. Transfer to a separatory funnel and wash the organic layer with 3x50 mL portions of water. Extract the organic layer with 3M HCl (2x20 mL). Remove aqueous layer into a new Erlenmeyer and wash organic layer in sep funnel with water (1x20 mL). Drain aqueous layer into the acidic extract just performed. Cool this flask in an ice-bath and add a thermometer to the solution. When it has reached 10 °C, add a small portion of 3M NaOH. Continue to add 3M NaOH, in portions, while keeping the temperature below 20 °C until the solution is strongly basic (green by pH paper). Note observations upon additions of base. Isolate via vacuum filtration on a Buchner funnel and let air pass through as long as possible.

Lidocaine Synthesis - Questions

Part 1

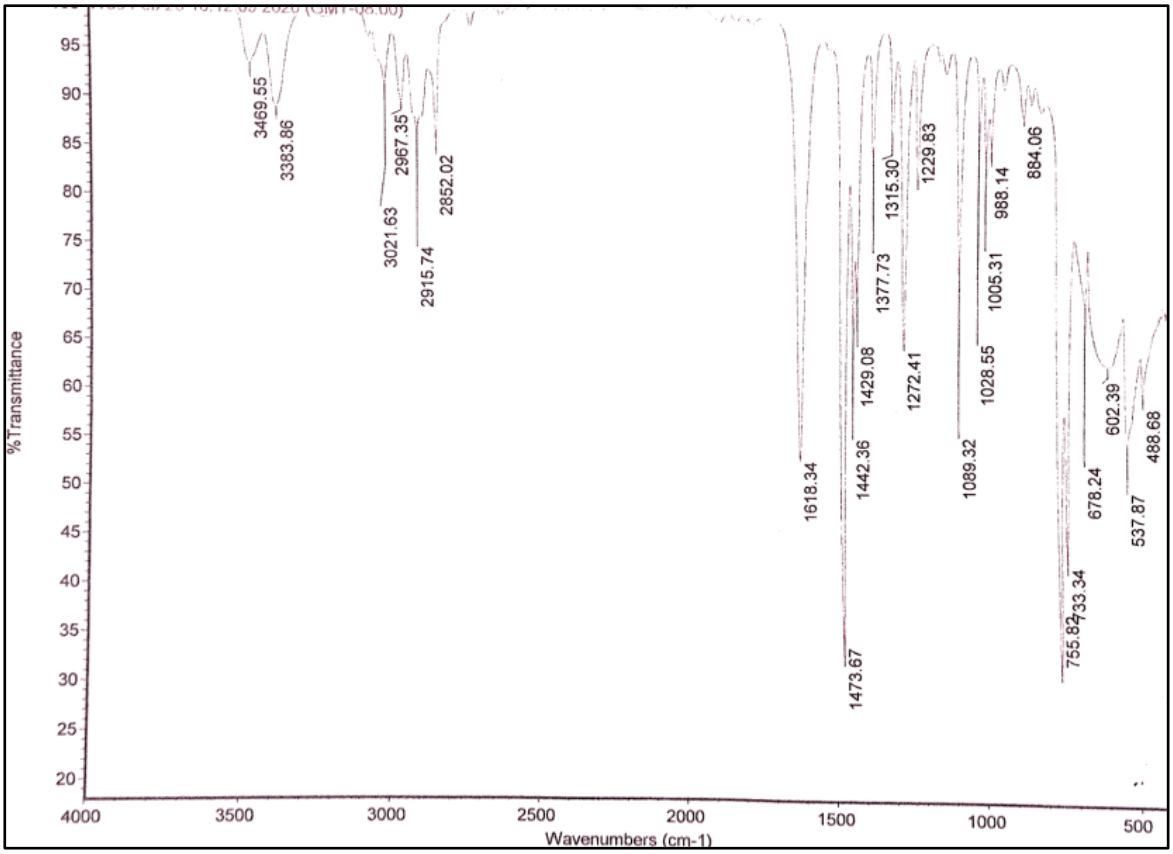
Name:_____

1. **NMR Analysis of Starting Material.** In the table below, draw the structure of 2,6-dimethylaniline, with every H atom drawn out explicitly. The peaks in the NMR spectrum are labeled a-d. Complete the table below to describe each peak, and label each proton on your drawing (a-d) to match the corresponding peak in the NMR.

^{1}H NMR	Peak	Chemical Shift (δ)	Multiplicity†	H‡
	a			
	b			
	c			
	d			
2,6-Dimethylaniline (draw structure & label protons)				

† Specify the splitting pattern as a singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).
‡ Specify the number of protons associated with each peak (peak integration, such as 1H, 2H, 3H).

2. **IR Analysis of Starting Material.** Label the significant absorbances in the IR spectrum of the starting material, 2,6-dimethylaniline.



3. Calculate the theoretical yield of the Part 1 product. Show calculation with units for full credit.

4. **NMR Analysis of Part 1 Product.** In the table below, draw the structure of the chloroamide product, with every H atom drawn out explicitly. The peaks in the NMR spectrum are labeled a-d (note that the sample was wet, so the broad signal at 1.6 ppm can be ignored). Complete the table below to describe each peak, and label each proton on your drawing (a-d) to match the corresponding peak in the NMR.

^{1}H NMR	**Peak**	**Chemical Shift (δ)**	**Multiplicity†**	**H‡**
	a			
	b			
	c			
	d			
Part 1 Product (draw structure & label protons)				

† Specify the splitting pattern as a singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).
‡ Specify the number of protons associated with each peak (peak integration, such as 1H, 2H, 3H).

Part 2

5. Calculate the theoretical yield of lidocaine in Part 2. Show calculation with units for full credit.

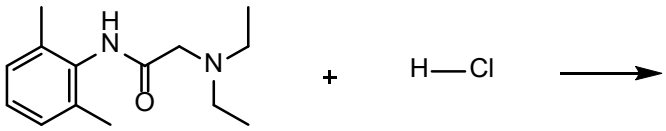
6. Why was an excess of the amine required in Part 2? Explain, using drawings to support your answer.

7. **NMR Analysis of Part 2 Product (Lidocaine).** In the table below, draw the structure of lidocaine, with every H atom drawn out explicitly. The peaks in the NMR spectrum are labeled a-e (the splitting patterns are provided because they are hard to read on the spectrum). Complete the table below to describe each peak, and label each proton on your drawing (a-e) to match the corresponding peak in the NMR.

^{1}H NMR	**Peak**	**Chemical Shift (δ)**	**Multiplicity†**	**H‡**
	a		broad singlet	
	b		multiplet	
	c		singlet	
	d		quartet	
Lidocaine (draw structure & label protons)	e		singlet	
	f		triplet	

† Specify the splitting pattern as a singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).
‡ Specify the number of protons associated with each peak (peak integration, such as 1H, 2H, 3H).

8. **Lidocaine isolation.** The final product is removed from the organic layer by extraction with hydrochloric acid solution. Draw the curved arrows for the proton transfer reaction that takes place, and draw the resulting product. Explain how this reaction enables the removal of the lidocaine from the organic layer.

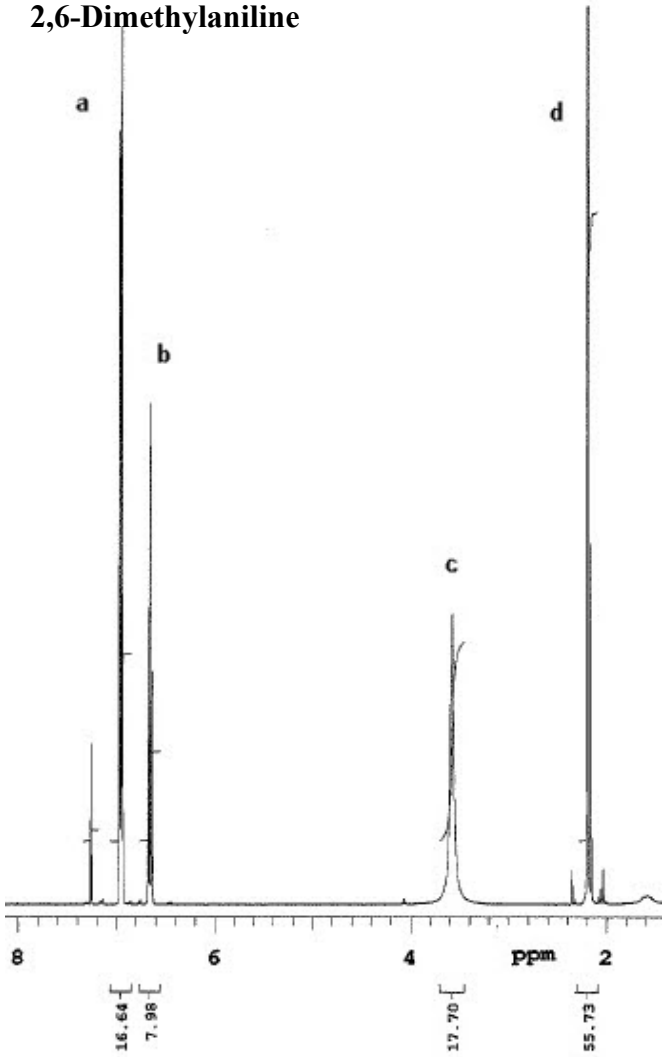


9. **Lidocaine isolation.** Upon addition of base to the aq. HCl layer described above, the lidocaine product precipitates out and can be collected by vacuum filtration. Why did the solubility of lidocaine change in this step? Use drawings to support your answer.

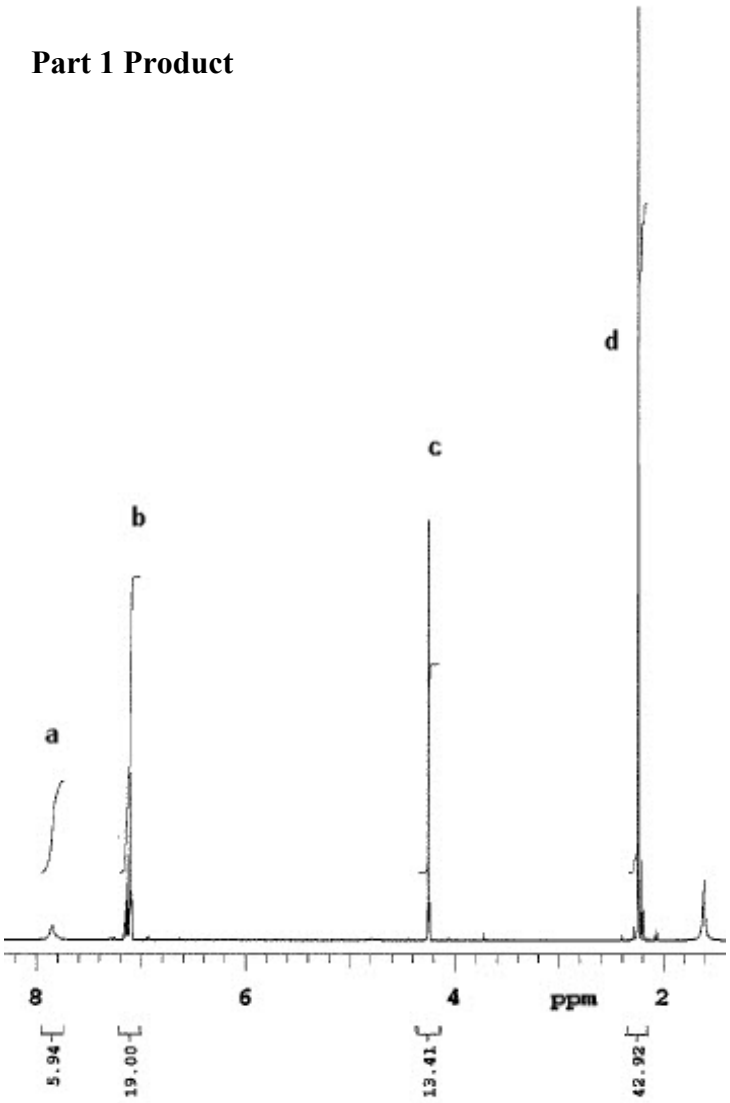
Handout prepared by Laurie Starkey (Cal Poly Pomona), with thanks for generous contributions to Chris McDaniel (UMass) for the procedure and to Allison Dick (Wheaton College) for the videos.

^{1}H NMR Spectra

2,6-Dimethylaniline



Part 1 Product



Part 2 Product (Lidocaine)