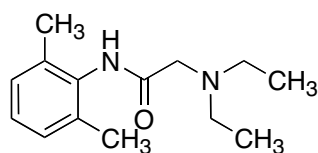


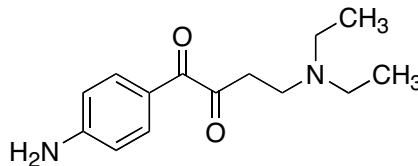
CHEMISTRY 338

THE SYNTHESIS OF LIDOCAINE

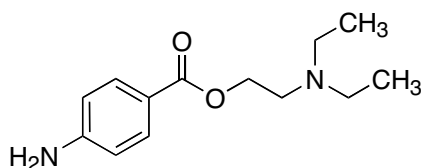
Lidocaine (**1**) is the common name of an important member of a category of drugs widely used as local anesthetics. Trade names for this substance include *Xylocaine*, *Isocaine*, and *Anestacon*, and its systematic chemical name is 2-(diethylamino)-N-(2',6'-dimethylphenyl)acetamide. Two other members of this same family are *procaine* (**2**), known more commonly by the trade name *Novocaine*, and *Isocaine* (**3**). Isocaine, in addition to having applications as a topical anesthetic, is commonly found in “sunscreens” that are applied to the skin to prevent sunburn because it absorbs the ultraviolet rays that are responsible for the burning of skin. Similarly, **1** and **2** are used in ways other than for anesthesia. Both are effective in the treatment of arrhythmia, a condition involving erratic beating of the heart, although **2** must be converted to the amide **4** in order to maximize its effectiveness in this application; this simple chemical transformation increases the drug's half-life under biological conditions and suppresses the rate at which it enters the central nervous system, an undesired property. Interestingly, the antiarrhythmic properties of these compounds were discovered accidentally by cardiologists during the course of surgical procedures for which their anesthetic applications were needed.



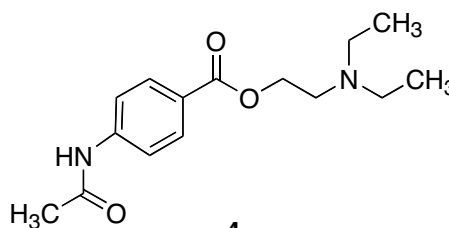
Lidocaine (**1**)



Procaine (**2**)

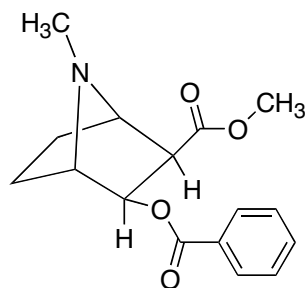


Isocaine (**3**)



4

It should not be too surprising to learn that many biologically active compounds that are available today as a result of the synthetic skills of chemists have molecular features that mimic those found in natural products. Compounds **1-4** can be considered to be structural mimics of cocaine **5**, a heterocyclic natural product found in the coca plant that is native to South America. Unfortunately, cocaine has addictive as well as anesthetic properties, so one of the more compelling reasons to develop synthetic analogs of it was to eliminate this undesired property of the natural product. The separation of desired and undesired effects due to a natural or unnatural substance destined for use as a drug is a major goal and challenge to the medicinal chemist and is often achieved by the preparation of a variety of compounds, each of which represents a structural modification of the parent substance of interest.



Cocaine (5)

The present synthesis of lidocaine from 2,6-dimethylnitrobenzene **6** is given in Figure 1. Some of the details of each step in the sequence are discussed in the following paragraphs.

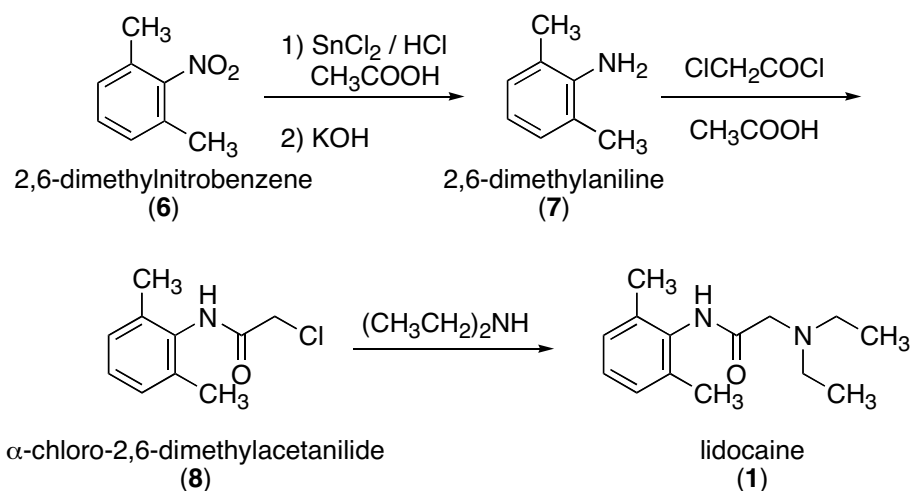
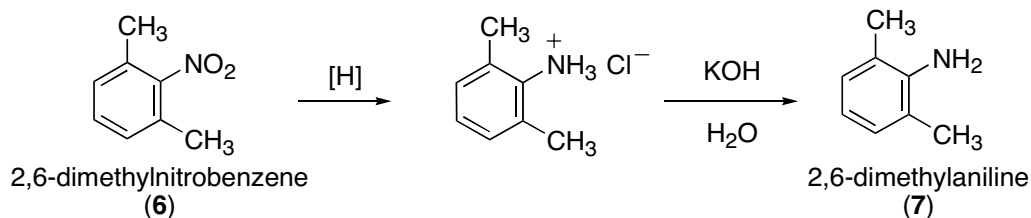


Figure 1. Synthesis of Lidocaine from 2,6-dimethylnitrobenzene.

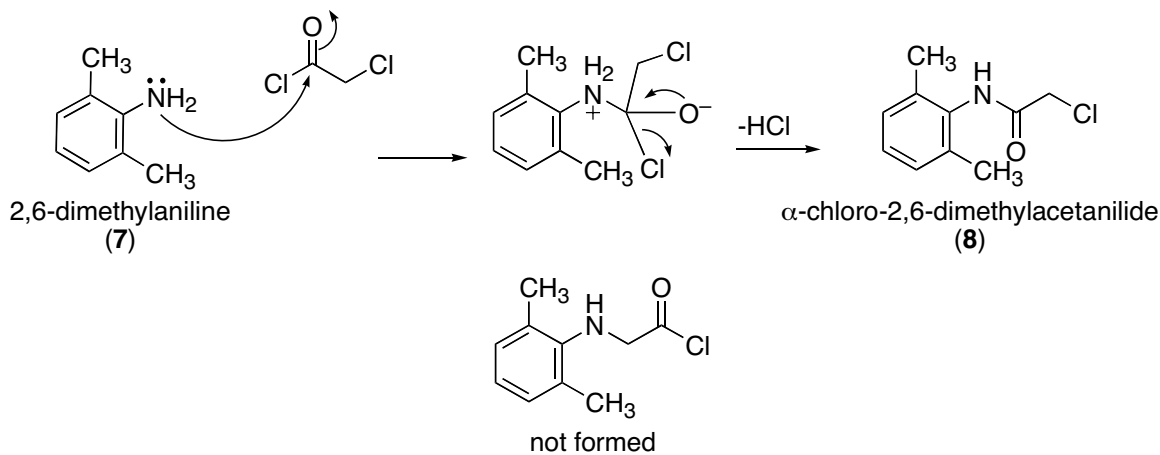
(a) 2,6-Dimethylaniline (7)

The preparation of lidocaine starts with the conversion of **6** to the dimethylaniline **7** by use of stannous chloride as a reducing agent. Purification of **7** is uncomplicated. The hydrochloric acid salt of **7** is formed upon reduction of the nitro group and precipitates from the reaction mixture. Isolation of the salt by filtration frees it from contaminants such as unchanged **6** and all by-products that are soluble in the reaction medium. Liberation of the salt by treatment with aqueous base gives the aniline **7** in a form sufficiently pure for use in the next step of the synthesis

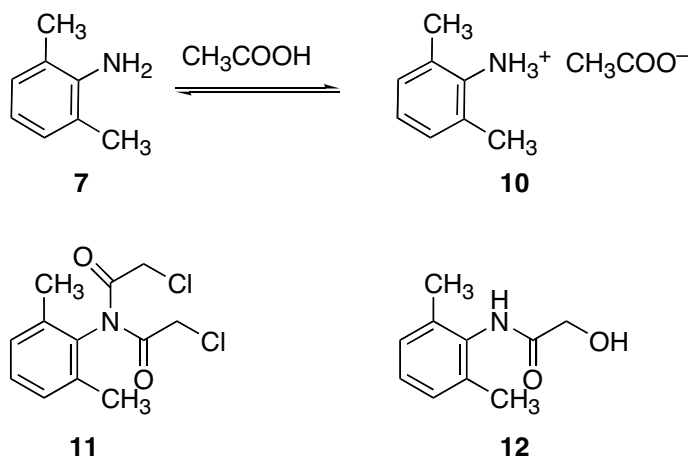


(b) a-Chloro-2,6-dimethylacetanilide (8)

The substituted aniline **7** is next converted to **8**, the immediate precursor of lidocaine, by treatment with the bifunctional reagent α -chloroacetyl chloride, ClCH_2COCl . Selective substitution at the acyl carbon atom in this step is a reflection of the substantially greater reactivity of nucleophiles with acid chlorides relative to alkyl chlorides because of the difference in electrophilicities and steric environments of the two possible sites for nucleophilic attack. Therefore, reaction at the α -carbon atom to give **9** is at best a minor competing reaction.



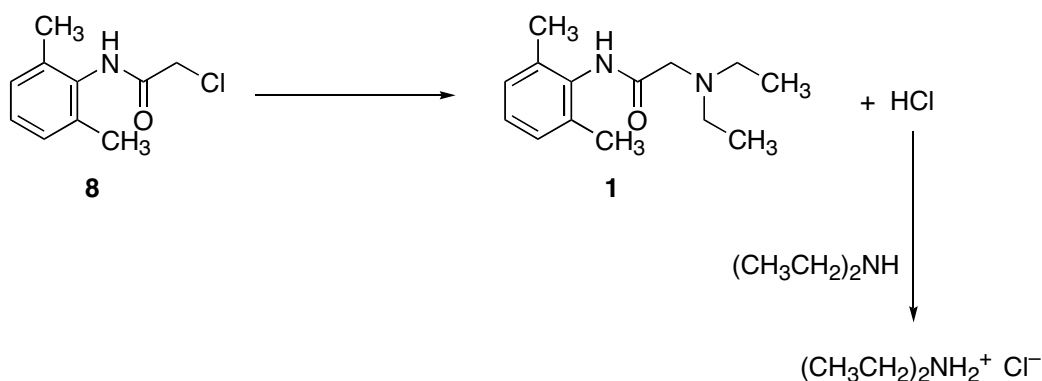
This reaction is performed in glacial acetic acid, which means that **7** is in equilibrium with the salt **10**. As the reaction proceeds, hydrochloric acid is liberated so that **7** is also partially converted to its salt with this acid. Should any of this salt remain at the end of the reaction period, it would contaminate the precipitated **8** because both the salt and **8** are insoluble in cold acetic acid. To avoid coprecipitation of **8** and the hydrochloric acid salt of **7**, aqueous sodium acetate is added to the warm reaction mixture to consume the hydrochloric acid. The acetate salt **10** is soluble in cold aqueous acetic acid, so that filtration allows isolation of crystalline **6**, with **7** and **10** appearing in the filtrate. Possible by-products like **11** and **12** (which arises by reaction of **9** with water) are also soluble in cold, aqueous acetic acid and therefore are removed from the crystalline **8** by filtration.



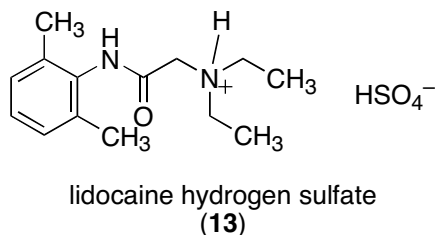
(c) Lidocaine (**1**)

The reaction of the chloride **8** with diethylamine completes the synthetic sequence and is another example of a selective reaction. In this case, nucleophilic attack at the carbonyl function of the amido group is disfavored relative to reaction at the carbon atom, a result that is anticipated in view of the disruption of amide resonance that would accompany attack the carbonyl group. The diethylamine serves the dual roles of acting as a nucleophile and as a base in this final step, not only displacing the chloride ion from **8** but also reacting with the hydrogen chloride formed in the reaction. The latter reaction makes the use of an excess of diethylamine a necessity if high yields of lidocaine **1** are to be obtained.

Isolation of **1** in pure form involves filtration of the reaction mixture to remove the hydrochloric acid salt of diethylamine, followed by extraction of the basic **1** into aqueous hydrochloric acid. All nonbasic contaminants, such as unchanged **8**, remain in the toluene solution. Liberation of lidocaine by treatment of its hydrochloric acid salt with base, extraction of it into petroleum ether, removal of solvent, and crystallization complete the synthesis.



The option of converting lidocaine to the salt **13** with sulfuric acid is also available in the Experimental Procedures. Many drugs are sold in the form of salts because the salts often are more stable and more compatible with the biological media--that is, the stomach, bloodstream, etc.--into which they are delivered. As is the case with **1** drugs containing a basic site are converted to their salts with hydrochloric or sulfuric acid, whereas those containing an acidic site--aspirin, for example--are commonly transformed to the corresponding sodium salts by reaction with sodium carbonate or sodium hydroxide.



DO IT SAFELY

1. Use care in handling and transferring concentrated hydrochloric and glacial acetic acids. Should these acids come in contact with the skin, flood the affected area with cold water and thoroughly rinse it with dilute aqueous sodium bicarbonate solution.
2. α -Chloroacetyl chloride is irritating to the mucous membranes and to the skin. Gloves should be worn when handling and transferring contains of this material, and such work should be done at the ventilation hood. Should this chemical come in contact with the skin, flood the affected area with cold water and thoroughly rinse it with dilute aqueous sodium bicarbonate solution.
3. Diethylamine is an unpleasant-smelling liquid. Measure it out in the ventilation hood. Should any of this chemical come in contact with the skin, flood the affected area with cold water.
4. Be certain that there are no open flames in the vicinity when you are working with diethyl and petroleum ethers.
5. Be certain that all ground-glass joints are well lubricated and tightly mated before heating solutions to reflux or performing distillations.

Procedure

A. 2,6-Dimethylaniline (7)

Dissolve 0.10 mol of $\text{SnCl}_2 \cdot \text{H}_2\text{O}$ in 40 mL of concentrated hydrochloric acid, using an appropriately sized Erlenmeyer flask; heating on a steam bath may be required for complete dissolution. Add this solution to a solution of 0.033 mol of 2,6-dimethylnitrobenzene in 50 mL of glacial acetic acid prepared in a 250-mL Erlenmeyer flask. Swirl the resulting mixture briefly and let the resulting warm solution stand for 15 min. Cool the reaction mixture and collect the precipitate that has formed by vacuum filtration. Place the damp product in another flask, add 25 mL of water, and make the resulting solution strongly basic by careful addition of 40-50 mL of 8 M aqueous KOH solution. Upon cooling of the warm basic solution to room temperature, extract the aqueous mixture first with a 25-mL portion and then with an additional 10-mL portion of diethyl ether. Combine the ether extracts, wash this solution twice with two 10-mL portions of water, and dry it over anhydrous K_2CO_3 . After gravity filtration, remove the ether by rotary evaporation, transfer the residue to a pre-weighed test tube, and determine the weight of the oily 2,6-dimethylaniline. Take IR and NMR spectra of this crude material as directed by your instructor.

B. α -Chloro-2,6-dimethylacetanilide (8)

Combine the dimethylaniline 7 from part A with 25 mL of glacial acetic acid and 0.033 mol of α -chloroacetyl chloride, in that order, in an appropriately sized Erlenmeyer flask. With the aid of a steam or hot-water bath, warm the solution to 40-50 °C, remove the flask from the bath, and add a solution of 5 g of sodium acetate trihydrate dissolved in 100 mL of water. Cool the resulting mixture in an ice-water bath and collect the product by vacuum filtration. Rinse the filter cake with water until the odor of acetic acid can no longer be detected, and dry it as completely as possible by pressing on it with a clean filter paper while the vacuum source is still attached. Transfer the solid to a fresh sheet of filter paper and allow it to air-dry for at least 24 hr. Determine the percent yield and melting point of the product (reported mp, 145-146°C). Save a small sample to turn in and take and ¹H-NMR spectrum of the dry solid.

C. Lidocaine (1)

Note: All reagents and equipment used in the first paragraph of the procedure must be dry. Place the α -chloro-2,6-dimethylacetanilide from Part B in an appropriately sized one-necked round-bottomed flask and add 45 mL of toluene, followed by three moles of diethylamine per mole of the acetanilide. Equip the flask with a reflux condenser and bring the reaction mixture to a vigorous reflux. After 90 min. at reflux, allow the mixture to cool, and isolate the crystalline solid that forms by vacuum filtration. Rinse the filter cake with a little cold hexane (30-60°C), and air-dry and weigh this product.

Transfer the filtrate to a separatory funnel and extract it with two 25-mL portions of 3 M HCl. Shake vigorously, with venting. Combine the acidic aqueous extracts in a 250-mL Erlenmeyer flask and add 50 mL of 8 M KOH solution to make the mixture strongly basic to pH paper. If the mixture is not strongly basic, add additional small portions of 8M KOH until it becomes so. You should anticipate seeing a thin, dark-yellow oil layer in the flask. Cool the alkaline mixture thoroughly by immersion into an ice-water bath; the use of an ice/salt/water bath may shorten this process. Once chilled, agitation by vigorous swirling or stirring should initiate crystallization of crude lidocaine; scratching with a stirring rod may also help. If no crystals form, consult the directions in the next paragraph. Collect the crude lidocaine by vacuum filtration, and wash the filter cake with a little cold water. Allow the crystals to dry. Save a small amount of the crude lidocaine for possible use later and seed crystals. Recrystallize lidocaine by dissolving the crude product in boiling hexane, using about 10 mL per g of solid. Allow the solution to cool, add decolorizing carbon, and reheat to boiling. Following hot gravity filtration, allow the solution to cool to room temperature and then chill in an ice-water bath. Beautiful long, white needles of lidocaine should form. Determine the yield and melting point (reported 68-69°C) of the product. Turn in a small sample of this compound and take IR and ¹H NMR spectra as directed.

If no crystals form with agitation of the chilled alkaline solution, transfer it to a separatory funnel and extract with two 50-mL portions of hexane (bp 30-60°C). The extractions should be carried out with vigorous shaking and frequent venting. Wash the combined petroleum ether extracts with 25 mL of water and dry them with anhydrous K₂CO₃. Add decolorizing carbon to the filtrate, heat the solution to boiling, and then filter using hot gravity filtration.

Concentrate the filtrate to a volume of about 40 mL by rotary evaporation and allow to cool to room temperature, followed by chilling in an ice-water bath. Crystalline white needles of lidocaine should form. Determine the yield and melting point (reported 68-69°C) of the product.

The crude, lidocaine is reconverted to the crystalline salt, lidocaine hydrogen sulfate, by first dissolving it in diethyl ether (10 mL of solvent per g of solute) and then adding a solution of 2 mL of 2.2 M sulfuric acid in ethanol per g of solute. Mix the solutions thoroughly and scratch at the air-liquid interface to induce crystallization. Dilute the mixture with an equal volume of reagent-grade acetone to facilitate filtration, and isolate the precipitated salt by vacuum filtration. Rinse the filter cake with a few milliliters of cold reagent-grade acetone and then air-dry and weigh the product. The salt may be recrystallized by dissolving it in an equal weight of hot water and adding 20 times this volume of reagent-grade acetone in one portion. Swirl to effect mixing, then allow the solution to stand until crystallization is complete. Isolate the lidocaine hydrogen sulfate and determine its melting point and percent yield (reported mp, 210-212°C). Turn in the final product to your TA.

EXERCISES

1. By reference to chemical catalogs, determine the costs of **6** and of the reagents and solvents necessary to convert it to **1**. Calculate the cost of the chemicals and solvents needed to produce one mole of **1**, given the yields that you obtained in the laboratory.
2. What is the precipitate that is originally collected in the reduction of 2,6-dimethylnitrobenzene **6** by stannous chloride?
3. Why would ethanol be a poor choice of a solvent for the reaction between 2,6-dimethylaniline and *a*-chloroacetyl chloride?
4. Why does sulfuric acid protonate the nitrogen atom of the diethylamine group preferentially to that of the amido group?