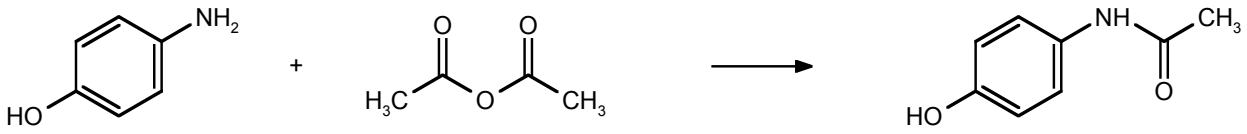
Synthesis of Acetaminophen and Analysis of Some Common Analgesics

Background

In this experiment, *p*-acetamidophenol (acetaminophen) will be prepared from *p*-aminophenol by reaction with acetic anhydride. Note that *p*-aminophenol is a bifunctional compound, containing both a phenol and an amine, and that both of these groups can participate to form either an ester or an amide. Under these conditions, however, only the amide is isolated. Once prepared, the synthetic *p*-aminophenol will be analyzed qualitatively by TLC. The product will be compared with commercial acetaminophen and a series of other analgesics, and this information will be used to determine the active component(s) of several unknowns.



p-Aminophenol Acetaminophen

Procedure

A. Synthesis of Acetaminophen

Place 2.1 g *p*-aminophenol (Caution: avoid contact, it's a sensitizer) and 35 mL water in a 125-mL Erlenmeyer flask. Add concentrated hydrochloric acid dropwise with frequent swirling until the p-aminophenol dissolves completely. (**Caution**: Do not add too much conc. HCl. Why?) Add a spatula tip-ful of decolorizing charcoal to the solution, swirl the solution in a hot water bath for a few minutes, and remove the charcoal by gravity filtration. Use a *FLUTED filter paper* (Zubrick p. 136).

Prepare a solution for use as a buffer by dissolving 2.5 g sodium acetate in 7.5 mL of water and clarify the solution by gravity filtration. Use a *FLUTED filter paper* (Zubrick p. 136).

Transfer the filtered *p*-aminophenol hydrochloride solution to a 125-mL Erlenmeyer flask and warm in a hot water bath for a few minutes. Add the sodium acetate solution in one portion. Immediately add 2 mL of acetic anhydride while swirling the solution on the hot water bath. Stir with a magnetic stir bar in the hot water bath for 10 minutes to ensure reaction.

Cool the reaction mixture by immersing the flask in an ice-water bath, and stir the mixture with the magnetic stir bar (on a cool stir plate) until crude acetaminophen crystallizes. Allow the flask to sit in the ice bath for about 20 minutes. Once crystallization is complete, collect the crude product by vacuum filtration using a Hirsch or a Büchner funnel. Using 1 mL or less ice cold water, wash the remaining solids out of the flask. After filtration is complete, dry your

crystals by continuing to apply a vacuum and gently scraping them with a spatula. Record the weight of your crude product, and its melting point.

B. Recrystallization of Acetaminophen

Add about 0.5 g of your crude product to a large test tube. Be sure you have enough left over (at least 5-10 crystals) for use later in TLC analysis. Add boiling water drop wise to your product while heating it in the hot water bath. Swirl the tube often to help dissolve the solid. Too much solvent will markedly reduce your recovery of acetaminophen.

Once your solid has dissolved, allow the solution to cool slowly to room temperature. Do not shake or stir the test tube while crystals are forming. Do not touch it to a cool surface (like the lab bench). When crystallization is complete at room temperature, cool the mixture further in an ice bath. Collect the product by vacuum filtration using your Buchner funnel, and wash the collected crystals over vacuum with ~0.5 mL ice cold water. Record the weight of your recrystallized product, and obtain a melting point and an IR (use mineral oil; be sure you have a mineral oil standard). Save a few crystals of recrystallized product for TLC, and prepare an NMR sample.

C. TLC Analysis of Analgesic Drugs

1. TLC Analysis of Active Ingredients

In separate test tubes, dissolve approximately 10 mg (exact weights are unimportant) of the following compounds in 1 mL dichloromethane: your crude acetaminophen, your recrystallized acetaminophen, *p*-aminophenol, aspirin, and caffeine. Run a TLC of the crude acetaminophen, recrystallized acetaminophen, and *p*-aminophenol using ethyl acetate (EtOAc) to develop the plate. Allow sufficient time for the solvent to evaporate, then visualize the plate first using UV light, then in an I_2 chamber (note the order). Circle the spots with a pencil, using a solid line for the UV visualization and a dashed line for the I_2. Record this information in your notebook. Identify the spots observed, and calculate their R_f values.

Run a TLC of your recrystallized acetaminophen, aspirin, caffeine, and a reference sample (available in the lab) containing all three of these compounds. Elute with EtOAc, then repeat using CH_2Cl_2 as the eluting solvent. Visualize the plates as before, being sure to record your observations. Note the effect of eluant polarity on R_f, as well as any variation in the shapes of the spots (i.e., tailing, elongation, etc.).

2. Evaluation of Commercial Analgesics and Unknowns

Obtain two of the commercial analgesics available in the laboratory. Transfer the powders into separate small test tube and dissolve it in about 2 mL of CH_3OH. You may need to heat the tube slightly in warm water. Since these tablets usually contain inert ingredients such as starch binders and inorganic buffering agents, not all of your tablet will dissolve. Allow the sample to cool and settle before running your TLC. Run a TLC of your reference solution (from

part 1), the commercial analgesics, and of Unknowns A and B. Elute with EtOAc. Visualize the TLC plate as above, and record all R_f values. Determine and report the composition of the active ingredients of the analgesic drug you chose, as well as of the unknowns. Identify the unknowns.

Results and Discussion

Discuss both proof of structure and proof of purity of your recrystallized product. Consider all the information you have at your disposal (e.g., IR, NMR, MP). Don't forget to include literature values where appropriate. Calculate the percent yield of the acetaminophen you prepared. Include the IR spectrum in Appendix B of your report.

Staple the completed data sheet (below) to your report. You will need to incorporate the data presented here within the body of your report.

References

Pavia, D.L.; Lampman, G.M.; Kriz, G.S. "Introduction to Organic Laboratory Techniques", 3nd ed. Saunders Publishing: Philadelphia, PA, 1988, pp 29-46.

Zubrick, J.W "The Organic Chem Lab Survival Manual: A Student's Guide to Techniques", 4th ed. John Wiley and Sons: New York, 1997, pp 121-136.

Harwood, L.M.; Moody, C.J. "Experimental Organic Chemistry: Principles and Practice"; Blackwell Scientific Publications: Oxford, England, 1989, pp 127-132.

Name: _____ Section: _____

ID #: _____ Date: _____

Acetaminophen:

1) Crude Acetaminophen (g): _____ 4) Amount Recovered (g): _____

2) % Yield (crude):_____ 5) Percent Recovery: _____

3) Amount Recrystallized (g): _____6) Purified Percent Yield: _____

TLC of Analgesics:

	R_f value(s)	TLC plate drawing:
p-aminophenol	_____	
crude acetaminophen	_____	
recrystallized acetaminophen	_____	

R_f value(s)	EtOAc	CH_2Cl_2
aspirin	_____	_____
acetaminophen	_____	_____
caffeine	_____	_____
reference sample	_____	_____

	R_f value(s)	Active Ingredient(s)	Identity
Tylenol:	_____	_____	n/a
Excedrin:	_____	_____	n/a
Unknown A:	_____	_____	_____
Unknown B:	_____	_____	_____