Exp't 14

The Preparation of a Heterocyclic Compound:
3-Carbethoxycoumarin


Introduction:
Cyclic organic compounds can be classified as either "carbocyclic", in which the ring systems contain all carbons, or "heterocyclic", in which the ring systems contain other ("hetero") atoms such as nitrogen, oxygen, sulfur, etc. in addition to carbon atoms. Many heterocycles have important pharmaceutical properties. The structures of two biologically important heterocycles are shown below.

![Penicillin G: an antibiotic](image)

![sodium pentothal: an anesthetic barbiturate](image)

A subclass of heterocyclic compounds are fused-ring heterocycles. These compounds contain a benzene ring fused to a heterocyclic ring. Some examples are shown below.

![N,N-dimethyltryptamine: a hallucinogen](image)

![Luminol: a chemiluminescent substance](image)

![Saccharin: an artificial sweetener](image)

In this experiment, you will be synthesizing a fused-ring heterocycle, 3-carbethoxycoumarin, which is an example of a class of heterocyclic compounds called coumarins.

![Coumarin, the parent heterocycle: a flavoring](image)

![3-Carbethoxycoumarin: your synthetic goal](image)

![Warfarin: a rat poison](image)

A very important coumarin compound is Warfarin, a powerful anticoagulant. In low doses, it is used as a blood thinner in humans with high blood pressure. It is applied at higher concentrations to corn or other grains and sold as a rodenticide. When eaten by rats or mice, the higher concentrations of Warfarin cause them to bleed internally. To replace body fluid losses, the rodents move out of grain storage areas into the outdoors in search of water. Thus, they are less likely to die within the grain elevator, which is obviously a much less disgusting situation. The "Warf" in Warfarin stands for Wisconsin Alumni Research Fund, which makes a bundle from the patent it holds on this compound.
The synthesis of the 3-carbethoxycoumarin heterocycle involves an aldol condensation reaction between salicylaldehyde and diethyl malonate. The aldol condensation is described in "Organic Chemistry" by McMurry or any large organic textbook.

Prelab Exercises:
1.) Draw the step-by-step mechanism (use arrow pushing) for the synthesis of 3-carbethoxycoumarin from salicylaldehyde and diethyl malonate. (Hint: the mechanism involves both an aldol condensation and a transesterification step; start with transesterification.)
2.) Why are the hydrogens on the carbon of diethyl malonate acidic enough to be removed by the base piperidine? Draw all pertinent resonance structures.
3) What advantage(s) could there be for using piperidine rather than hydroxide as a base?

Cautions:
Piperidine is toxic, salicylaldehyde is a toxic irritant, and glacial acetic acid is a corrosive agent. Be careful when handling these chemicals.

TLC
You are required to run a TLC to monitor the progress of the reaction. Plates should have three spots (or lanes) on the origin: one for the main organic starting material that is being transformed, one for a cospot (starting material and the reaction mixture), and one for the reaction mixture.

Synthesis:
Place 1.1 mL salicylaldehyde and 1.7 mL diethyl malonate into a 25-mL round-bottom flask with a 1/2-inch magnetic stir bar. Add 4 mL ethanol, 20 drops piperidine, and 4 drops of glacial acetic acid. Connect the flask to a water condenser. Fill a plastic drying tube with Drierite (Common Shelf), using a glass wool plug at each end to hold the pellets in. Connect this drying tube at the top of the condenser using the glass/red rubber thermometer adapter from your kit. Reflux the solution for 2 hours using a heating mantle (no sand) and continuous stirring.

Isolation and Purification:
Let the solution cool slowly to room temperature, then cool in an ice bath. Stir the solution for 5 minutes in the ice bath after crystals first appear. Vacuum filter off the solid using a Buchner funnel with the two pieces of filter paper in it. Rinse out residual crystal from the flask with cold ethanol and add to solid in the funnel. Allow the crystals to dry until the next laboratory period.

Weigh the dry crystals on the filter paper and determine the percent yield and the melting point. If the melting point is low, recrystallize from 95% ethanol.

Analysis
In addition to TLC analysis, you may be instructed to analyze your final product by IR or NMR. Analyze your sample according to your Assignment sheet and the instructions on Sample Preparation in Lab Guide.

Cleaning Up
Dispose of all filtrates down the drain with lots of water.

Final Report
Include the spectrum from the analysis method assigned with the structure and interpretation written directly on it. Answer these questions at the end of the report:
1. What is the purpose of using the water condenser and drying tube?
2. Why is the hydrogen on carbon 4 of the product so far downfield in the proton NMR?
3. A solution of 3-carbethoxycoumarin was refluxed in a solution of NaOH and water. What product(s) would you expect to form from the reaction?