Chemistry 373F Lab Manual

2007

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Chem 373 Laboratory Schedule for Fall 2007

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<th>Activity</th>
<th>Report Due</th>
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<tr>
<td>September 17</td>
<td>Check-In and begin benzoin condensation</td>
<td>-</td>
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<tr>
<td>September 24</td>
<td>Dilantin and related compounds</td>
<td>-</td>
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<tr>
<td>October 1</td>
<td>continue dilantin lab</td>
<td>benzoin</td>
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<tr>
<td>October 15</td>
<td>pseudopelletierine, finish dilantin lab</td>
<td>-</td>
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<tr>
<td>October 22</td>
<td>finish pseudopelletierine</td>
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<td>October 29</td>
<td>5,5-dimethyl-1,3-eyclhexanone</td>
<td>dilantin and others</td>
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<td>November 5</td>
<td>Diels-Alder Reactions</td>
<td>pseudopelletierine</td>
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<tr>
<td>November 12</td>
<td>Fischer Indole Synthesis, lab checkout</td>
<td>dimedone</td>
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<td>November 19</td>
<td>Possibly a Written Laboratory Final Exam,</td>
<td>Diels-Alder</td>
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<tr>
<td></td>
<td>other activity, review session, or nothing at</td>
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<tr>
<td></td>
<td>all</td>
<td></td>
</tr>
<tr>
<td>November 26</td>
<td>-</td>
<td>Fisher Indole (submitted in lecture).</td>
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</table>

Generally, before you will be allowed to begin the lab, you must have in your notebook a drawing showing each separate reaction to be performed and then below the reaction in columns list the chemicals and reagents to be used, molecular weight, equivalents, mmol, wt, density (where applicable), mL (where applicable), bp (where applicable), mp (where applicable). There should also be a row for the product.

Your lab report should be quite brief. It should consist of a copy of your lab notebook, copies of your spectra along with interpretive comments, and a detailed reaction mechanism. The notebook should show the calculation of the percent yield, mp, etc, and the procedure. Neatness counts. The procedure does not need to be in complete sentences. Each spectra will have a neatly computer made structure using a program such as chemdraw or one of the free alternatives (see the course website under links), your name and your lab section. In this lab you will turn in the products you make, and quality and quantity (as determined visually and by NMR) count. The initial plan is to have the demonstrators prepare the $^1$H NMR samples from the bulk material that you submit to them. The $^1$H NMR spectra will be provided to you the following week. The reports will be due one week after that.
The Benzoin Condensation of Benzaldehyde

Aromatic aldehydes, in the presence of catalytic cyanide ion, dimerize to form the corresponding α-hydroxyketone (acyloin). This reaction, which is reversible, is known as the benzoin condensation. This “condensation” is a bit of a misnomer since it is not actually a condensation reaction since no water or alcohol is produced but two species do come together. Cyanide acts as a catalyst and has three different roles in this process as shown in the mechanism below.

Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation:

A strong base is now able to deprotonate at the former carbonyl C-atom:

A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction:

Then
The cyanide ion catalysis works only for aromatic aldehydes presumably because the carbanion is stabilized not only by the cyano group but also by delocalization into the aromatic ring. Of course one of the drawbacks with using cyanide as a catalyst is the toxicity of cyanide or HCN. Care must be taken not only with the handling of the cyanide but also with its disposal. If it is inadvertently poured down a sink in which acid might be present then volatile and poisonous HCN is produced. Not a good thing!

Thiamine (vitamin B1) is a small molecule coenzyme responsible for many biological processes. A quick Google search will convince you of that. Thiamine and related thiazolium salts are more general catalysts for the acyloin condensation because they catalyze the reaction with aliphatic and aromatic aldehydes.

The C-2 proton has a pKa of 12.7, which is quite low, because the carbanion formed when the proton is removed is stabilized by the adjacent positively charged nitrogen, yielding the highly stabilized ylide. This ylide can react with an aldehyde to produce an enamine:

The enamine which we will produce, using benzaldehyde, can react with a second benzaldehyde molecule to produce the desired product, following the acyloin condensation pathway described for cyanide.

**Experimental Procedure:** Add 1.30 g of thiamine hydrochloride to a dry 50-mL R.B. flask, and add a stir bar. Dissolve the solid in 4.0 mL of water by stirring. Add 15 mL of 95% ethanol and cool the solution for a few minutes in an ice bath. Slowly, add 2.5 mL of cold 3 M NaOH dropwise, making certain that the temperature of the solution never rises above 20 °C. To the yellow solution, add 7.5 mL of pure benzaldehyde. Equip the flask with a reflux condenser. A small piece of Teflon tape should be used between the condenser and flask to prevent freezing the joint. Attach a blue keck clip to hold the flask and condenser together. Using a 250 mL beaker as a water bath heat the mixture at 60 °C for about 1.5 hours. (*Do not heat the reaction to reflux. If you see it boiling, it’s too hot.*)

Cool the reaction mixture in an ice bath. If crystallization does not occur immediately, withdraw a drop of the solution on a stirring rod and let it dry to produce a solid; then, rub it against the
inside surface of the flask to induce crystallization. Collect the product by vacuum filtration and wash it free of any yellow mother liquor with a cold 1:1 mixture of 95% ethanol and water. The product should be colorless and of sufficient purity (mp 134-135°C) to use in subsequent reactions. Usual yield is about 5 - 6 g. It is in your best interest to recrystallize the moist product from 95% ethanol (~8 mL of ethanol per gram of product).

Characterization of the Product:

Your lab report should be quite brief. It should consist of a copy of your lab notebook, copies of your spectra along with interpretive comments, and a detailed reaction mechanism using thiamine, not cyanide. The notebook should show the calculation of the percent yield, mp, etc, and the procedure. Neatness counts. The procedure does not need to be in complete sentences.

Each spectra will have a tag with a neatly computer made structure that you will make yourself using a program such as chemdraw or one of the free alternatives (the course website under links), your name and your lab section. Print out the tag, stick it to the spectra, and submit a photocopy.

Provide your demonstrator a 15 mg sample of your benzoin product labeled with your name and lab section. A \(^1\)H NMR of the sample will be provided to you the next week.

Save your benzoin for next week’s lab.
Synthesis of Dilantin and Related Compounds (two weeks)

Benzoin, a keto-alcohol, is readily oxidized to the yellow diketone, benzil, and both can be reduced to the diol, hydrobenzoin. Base-catalyzed condensation of benzil with urea produces a heterocyclic derivative, dilantin, which is useful in medicine because of its anticonvulsant properties. (Unlike phenobarbital, which was widely employed to control epileptic seizures prior to the discovery of dilantin’s medicinal properties, dilantin has no sedative side-effects.) Base-catalyzed condensation of benzil with dibenzyl ketone gives the cyclic ketone, tetracyclone, an unusual deep purple compound. The reduction of benzil with sodium borohydride gives a mixture of diastereomers, racemic- and meso-hydrobenzoin. The meso diastereomer predominates and can be isolated by crystallization from water, in which it is much less soluble than the racemic diastereomer.

It is important to organize your approach to this lab since several operations must be completed in one lab period. The dilantin preparation should be started immediately after benzil has been prepared by the oxidation of benzoin. During the 1 hour reflux period required for the dilantin preparation, a second portion of the benzil will be reduced and a third portion purified by recrystallization. The aldol condensation of the fourth portion of benzil with dibenzyl ketone should be started early in the third hour.

**Before you will be allowed to begin the lab**, you must have in your notebook a drawing showing the reaction to be performed and then below the reaction in columns list the chemicals and reagents to be used, molecular weight, equivalents, mmol, wt, density (where applicable), mL (where applicable), bp (where applicable), mp (where applicable). Each reaction should be
entered on a separate page in your notebook.

**Procedure for the oxidation of benzoin**

This experiment is for 4 grams of benzoin. If you have more than 4 g of benzoin you may scale up your reaction or share with a friend. If you don’t have 4 grams, you can get some from the demonstrators.

Add 14 mL of concentrated nitric acid to 4 g of benzoin in a 125 mL Erlenmeyer flask, and stopper it with a cork to transport the flask to your work area. Remove the cork and heat the mixture gently on a hotplate for 12 minutes. (This must be done in a hood to carry off the noxious nitrogen oxides which are formed.) Add 75 mL of water to the mixture, and cool it to room temperature before neutralizing the mixture by the *dropwise* addition of 30% aqueous sodium hydroxide. Swirl the flask for a few minutes before collecting the yellow solid product on a Büchner funnel. It is essential to press out as much water as possible while the solid is on the filter.

Weigh the dry solid product, and determine the crude yield. Then divide the product into four portions: 0.4 g for the dilantin preparation, 0.5 g for the reduction, 2.1 g for the tetracycline preparation and the remainder (weigh it) for purification and testing.

Dissolve 80% of the remaining product in a *minimum amount* of hot 95% ethanol. Add water dropwise to the cloud point and set the mixture aside to crystallize. Collect the crystalline material, allow it to dry, and determine its melting point.

The remaining crude product and the recrystallized benzil can each be tested for the presence of unreacted benzoin as follows. Dissolve a small crystal in 0.5 mL of ethanol or methanol and add one drop of 10% sodium hydroxide solution. The development of a dark reddish color indicates the presence of benzoin since it complexes with benzil under these conditions. If no color is seen after a few minutes, add a little benzoin to observe the color.

**Procedure for the preparation of dilantin**

Place the 0.4 g sample of crude benzil in a 25 mL round-bottomed flask with 0.2 g of urea, 6 mL of absolute ethanol and 1.2 mL of 30% aqueous sodium hydroxide. Add a boiling chip, attach a condenser after wrapping the ground glass joint with Teflon tape, and heat the mixture on a sand bath under reflux for 1 hour. Cool the reaction mixture before adding 10 mL of water. (If the solution is not clear, remove the suspended solids by filtration.) Then, *cautiously* acidify the clear solution with concentrated hydrochloric acid. Collect the product by vacuum filtration and wash thoroughly with water. Recrystallize the product from ethanol, weigh it dry and calculate the yield.

**Procedure for the reduction of benzil**

Place 0.5 g of crude benzil in a small Erlenmeyer flask and add 5 mL of 95% ethanol. Cool the mixture while swirling the flask to obtain a fine suspension of the solid before adding 0.1 g of sodium borohydride. After 10 min, add 5 mL of water and heat to boiling. If the solution is not clear, do a hot filtration through fluted filter paper before dilution with water to the saturation (cloud) point; this should require approximately 10 mL of water. Allow the product to crystallize;
meso-hydrobenzoin should separate in thin lustrous plates. Determine the melting point and yield of dry crystalline product.

**Procedure for the preparation of tetracyclone**

To a 100 mL RB flask, add 2.1 g of crude benzil, 2 mL (2.2 g) of 1,3-diphenylacetone and 15 mL of absolute ethanol. Attach a reflux condenser and heat the flask gently on a sand-bath until the solids dissolve. Increase the temperature of the benzil/ketone solution to just below the boiling point and slowly add the 3 mL of 10% KOH in ethanol solution through the top of the condenser. Heat the reaction mixture under reflux for 15 min, during which time the flask should be shaken several times. Cool the reaction mixture to less than 5 °C in an ice-bath before collecting the purple crystals by vacuum filtration. Wash the crystals with three 5 mL portions of cold 95% ethanol. Weigh the dry product and calculate the yield.

**Characterization and Reports**

Obtain a mp and 1H NMR from your products (use no more than 15 mg for analysis), and submit the remainder of the materials to your demonstrator, except for the tetracyclone. **Save your tetracyclone for the Diels-Alder experiment.**
Synthesis of an Alkaloid: Pseudopelletierine (two weeks)

One of the most amazing syntheses ever reported was the synthesis of the alkaloid tropinone in 1917 by Robert Robinson at the University of Liverpool. For this and many other accomplishments in organic chemistry, he was awarded the Nobel Prize in 1974. His synthesis of tropinone was notable not only because of its efficient (one step, high yield) formation of the bicyclic heterocyclic ring system, but also because it mimicked the process believed to be at work in the biosynthesis of the alkaloid in nature. Seven years later, in 1924, he and his coworker, R. C. Menzies, reported an analogous synthesis of the pomegranate alkaloid, pseudopelletierine. In this lab we will use Robinson’s method to synthesize pseudopelletierine in one step from glutaraldehyde, methylamine and acetonedicarboxylic acid. The glutaraldehyde will be generated \textit{in situ} by hydrolysis of a heterocyclic precursor, 3,4-dihydro-2-ethoxy-2\textit{H}-pyran.

All synthetic chemists are familiar with preparations from \textit{Organic Syntheses}, which provides specialized highly detailed experimental procedures on important molecules of current interest. What separates these procedures from those in regular peer reviewed journals is the level of
detail and that the procedures are checked in someone else’s lab before being published. For this lab you will check out *Organic Syntheses* by going on-line to www.orgsyn.org (it is also set of books in the library), and finding the pseudopelletierine procedure. You will reproduce the original *Organic Syntheses* procedure at 1/100th scale.

**Before you will be allowed to begin the lab**, you must have in your notebook a drawing showing the reaction to be performed and then below the reaction in columns list the chemicals and reagents to be used, molecular weight, equivalents, mmol, wt, density (where applicable), mL (where applicable), bp (where applicable), mp (where applicable).

1. You will be provided with the dilute HCl solution made with “deoxygenated” water described in the first line of the procedure.
2. Where the procedure says to let the product sit for 24 hours, you will leave yours for the next week. However, be sure to degas it with nitrogen and then cover the flask with parafilm.

Obtain a mp of your (use no more than 15 mg for analysis) and submit the remainder of the product to your demonstrator.
Synthesis of 5,5-dimethyl-1,3-cyclhexanone

In this experiment diethylmalonate will undergo 1,4-addition (Michael) to 4-methyl-3-pentene-2-one, and the intermediate $A$ will undergo a Claisen type condensation reaction to give $B$. Treatment with aqueous KOH followed by acid results in a decarboxylation to give 5,5-dimethyl-1,3-cyclhexanone (dimedone). Dimedone is a cyclic 1,3-diketone, and it exists in both enol and keto tautomers that can be observed spectroscopically.

\[
\begin{align*}
\text{diethyl malonate} & \quad + \quad \text{4-methyl-3-pentene-2-one} \quad \xrightarrow{\text{NaOEt}} \quad A \\
\text{B - not isolated} & \quad \xrightarrow{\text{KOH (aq) then HCl (aq)}} \quad \text{dimedone}
\end{align*}
\]

The dimedone can be condensed with an aldehyde, and this is illustrated in a separate step by reaction with formaldehyde.

\[
\begin{align*}
\text{dimedone} & \quad \xrightarrow{\text{H}_2\text{CO}} \quad \text{(condensed)}
\end{align*}
\]

Your task is to prepare dimedone on a 5 mmol scale, based on 4-methyl-3-pentene-2-one.

A 2.5 M solution of NaOEt in EtOH will be provided for you.

Routine details are lacking from this procedure, and part of the exercise is your ability to figure these things out. **Before you will be allowed to begin the lab**, you must have in your notebook a drawing showing the reaction to be performed (this will be two separate reaction schemes on two separate pages) and then below the reaction in columns list the chemicals and reagents to be used, molecular weight, equivalents, mmol, wt, density (where applicable), mL (where applicable), bp (where applicable), mp (where applicable). Give some thought to the size and nature of the flasks that your will employ.
The general procedure.
Obtain a 25mL round bottom flask (rbf) and a water condenser from the oven. Add a stir bar and 1.05 equivalents (1.9g) of NaOEt as a 2.44M solution in EtOH (provided for you) to the rbf. Apply a small piece of Teflon tape to the condenser to prevent the round bottom flask from seizing to it. Attach the rbf to the water cooled condenser and a blue clamp over the joint and the rbf. Set the apparatus up so that the hot plate / stirrer with a sand bath on it can be raised and lowered to and from the rbf using a labjack. With rapid stirring, slowly add 1.1 equivalents (0.9g) of diethylmalonate to the flask from the top of the condenser. Place a drying tube on top of the condenser and heat the reaction mixture in a sand bath for 5 minutes at reflux (~ 90-95°C), with continued rapid stirring. After heating, lower the stirrer with the heated sand and allow the rbf to air cool for 5 minutes. Slowly add 1.0 equivalent’s (0.5g) of Mesityl Oxide, from the top of the condenser, replace the drying tube, and re-heat the mixture with rapid stirring for an additional 35 minutes to reflux (90-95°C). Solids will form and care should be taken to ensure reflux occurs but the solids are not heated excessively.

Next, lower the sand bath once more with continued stirring, to allow the mixture to cool for 5 minutes. Remove the rbf, stopper it, and take the mixture to the Roto-vap to remove the liquid (mostly EtOH). Add 2 equivalents (3mL or 3.5g) of a 3.5 M solution of KOH in water, reinstall the condenser and drying tube and heat to reflux (~90-95°C) for 45 min. Remove the heater and cool to room temperature, remove the stir bar, and slowly adjust the pH to 1 using conc. HCl (~1 mL) and heat again at reflux for 15 minutes. Cool the flask on ice for 10-15 minutes with the occasional gentle swirl. Collect the crystals on a Hirsch filter. Wash the crystals with ~ 5 mL H₂O and then 2 portions (~ 3 mL. each) of Petroleum Ether (30-60). Allow the crystals to dry on vacuum and collect your sample for NMR and melting point.

Notes:

Most of the reagents for this experiment are measured gravimetrically.

1. Use a 100mL beaker to hold the round bottom flask when weighing in the Sodium Ethoxide.

2. Use disposable test tubes and corks to obtain:
   Diethyl Malonate-0.9g
   Mesityl Oxide-0.5g
   HCl~1mL
Diels-Alder Syntheses of Polycyclic Compounds

In 1921, Otto Diels and Kurt Alder discovered that alkenes add to conjugated dienes to give cyclohexenes:

Similarly, alkynes add to conjugated dienes to give 1,4-cyclohexadienes:

The Diels-Alder reaction also provides a route to aromatic compounds through cycloadditions with “benzyne” as the dienophile. This is a highly unstable and reactive fleeting intermediate which is generated in situ by elimination (of ortho substituents from a suitable benzene derivative) and immediately trapped by Diels-Alder cycloaddition to a diene. In this lab benzyne will be generated by heating a relatively complex reagent, diphenyliodonium-2-carboxylate, at 200 °C. (This internal carboxylate salt is prepared from 2-iodobenzoic acid by oxidation with potassium persulfate to give an iodonium sulfate, followed by electrophilic aromatic substitution with benzene.) The tetracyclone that you made previously will be the diene used to trap the benzyne as it forms. At the temperatures used for the reaction, the resulting Diels-Alder adduct is unstable and quickly loses carbon monoxide to give 1,2,3,4-tetraphenylnaphthalene.

Procedure for the preparation of diphenyliodonium-2-carboxylate

Place 8 mL of concentrated sulfuric acid in a 25 mL Erlenmeyer flask and cool the flask in an ice-bath. Mix 2.0 g of 2-iodobenzoic acid and 2.6 g of potassium persulfate in a mortar, crush these into small particles, and place the mixture in a 125 mL Erlenmeyer flask. Swirl the flask
containing the sulfuric acid in the ice-bath for a few minutes, and then wipe it dry. Place the 125 mL flask in the ice-bath, and pour the cold acid down the wall of the larger flask to wash the solid to the bottom of the flask. Swirl the larger flask in the ice-bath for 5 min to disperse the particles in the liquid as uniformly as possible. Remove the flask from the ice-bath, note the time, and then let it stand for 20 min.

Swirl the flask again in the ice-bath for 5 min before cautiously adding 2 mL of benzene. Continue to swirl the flask until the benzene freezes. Remove the flask from the bath, wipe it dry, and note the time at which the benzene melts. Warm the flask with your hands, and swirl it several times at room temperature over a 20 minute interval. Swirling is essential to obtain complete reaction in the two-phase system. During this interval, chill three 50 mL Erlenmeyer flasks in the ice-bath: one with 19 mL of distilled water, the second containing 23 mL of 27% ammonium hydroxide and the third with 40 mL of methylene chloride.

After the 20 min interval, thoroughly chill the reaction mixture in the ice-bath, and mount a small separatory funnel over the flask containing the reaction mixture. Put the 19 mL of cold water in the funnel. While swirling the reaction flask, add the cold water slowly; a solid will separate. Place the chilled ammonia solution in the funnel, and pour the cold methylene chloride into the reaction flask. Again, swirl the reaction flask in ice while trickling the ammonia solution very slowly into it from the funnel; this addition should take about 10 min. Make sure that the resulting mixture is alkaline with pH > 9; if not add more ammonia solution.

Pour the reaction mixture into the separatory funnel, and rinse the flask with a little more methylene chloride. Let the layers separate, and then draw off the lower, organic layer through a filter paper cone containing some anhydrous sodium sulfate into a tared 250 mL round bottom flask. Extract the aqueous layer twice with 10 mL portions of methylene chloride, running the extracts through the drying agent into the tared flask. Use a roto-vap to remove the solvent. Weigh the crude iodonium carboxylate inner salt. (The product should weigh ~2.5 g.)

Transfer the solid to a 50 mL Erlenmeyer flask. Add 14 mL of distilled water to the 250 mL flask, swirl the flask, and add its contents to the 50 mL flask before again adding 14 mL of water to the smaller flask. Heat the contents of this flask to boiling, then add a little charcoal for decolorizing, swirl, and filter at the boiling point through moistened filter paper in a stemless funnel which has been preheated on a steam-bath. The benzyne precursor, diphenyliodonium-2-carboxylate, should crystallize in colorless, rectangular prisms. Weigh the dry crystalline material, and calculate the yield.

**Procedure for the preparation of 1,2,3,4-tetraphenylnapthalene**

Place half of the diphenyliodonium-2-carboxylate and half of that weight of tetracyclone (that you prepared previously in the dilantin laboratory) in a 25 X 150 mm test tube. Rinse the solids down the sides of the tube as you add 6 mL of triglyme. Clamp the test tube vertically, insert a thermometer, and heat the tube with a butane torch (ask your demonstrator for assistance with this.). No open flames allowed outside of the hood, and when in use no flammable solvents are allowed in or near the hood. When the temperature reaches 200 °C, remove the flame, note the time, and, with intermittent heating, maintain the temperature near 205 °C until the purple color disappears and bubbling ceases. If the color persists for more than 3 min, add a little more of the benzyne precursor,
and heat until the solids are dissolved and the purple color is completely discharged. Allow the yellow solution to cool to 90 °C, and heat 6 mL of 95% ethanol to boiling in a separate small flask. Pour the yellow solution into a 25 mL Erlenmeyer flask, and use small portions of the hot ethanol to rinse the test tube. Add the rest of the ethanol to the yellow solution, and heat to boiling. Add water dropwise until crystals begin to separate. Let it stand to cool to room temperature before chilling to ice temperature. Collect the product, weigh it dry, and determine its melting point and the yield.
The Fischer Indole Synthesis: Preparation of 2-Phenylindole

Indoles are among the most important of all biologically active organic compounds. The indole ring system is found in diverse naturally occurring molecules including tryptophan (an essential amino acid), 3-indoleacetic acid (the main plant growth hormone of higher plants), and serotonin (a bioregulator that plays an essential role in our mental health). Skatole (3-methylindole), arising from the digestion of proteins, is responsible for the repulsive odor of feces, but in more dilute form it has a pleasant floral fragrance and is a common ingredient in perfumes!

As expected, indoles are also represented among medicinal drugs, including indomethacin (like aspirin, used as an anti-inflammatory, an antipyretic and an analgesic) and indoxole, an anti-inflammatory antipyretic. Many of these drugs are synthesized using the Fischer indole synthesis. (In this lab we will use this reaction to synthesize a compound closely related to indoxole, 2-phenylindole.) Psilocybin and psilocin are the major and minor active ingredients, respectively, in the hallucinogenic sacred mushroom of the Aztecs, teonanacatl (“flesh of the gods”), still used today in religious ceremonies by native peoples in the southwestern United States and in Mexico.
In this experiment, 2-phenylindole will be prepared by acid catalyzed rearrangement of acetophenone phenylhydrazone, with elimination of ammonia. While the formation of the phenylhydrazone from acetophenone and phenylhydrazine is catalyzed by mild acid (acetic acid), the Fischer indole synthesis of 2-phenylindole from the phenylhydrazone requires a very strong acid. For this purpose we will use “polyphosphoric acid” (PPA), made by heating a mixture of phosphoric acid and phosphorus pentoxide. It consists of about 55% triphosphoric acid and 45% other polyphosphoric acids.

Procedure for the preparation of acetophenone phenylhydrazone

Dissolve 1.2 g (10 mmol) of acetophenone in 5 mL of 95% ethanol in a test tube. Carefully stir in 1.0 g (10 mmol) of phenylhydrazine [Toxic liquid and vapor! A station to weight out these reagents will be set up in the dispensing hood. Work or in hood! Wear gloves!] and then 2 drops of glacial acetic acid. Return to your work area add a boiling chip, and heat the mixture gently on a sand bath for 15 min, adding more ethanol if it boils away. Cool the mixture in an ice bath, allow the product to crystallize (scratching may be necessary), and collect the phenylhydrazone by filtration on a Büchner funnel. Wash the crystals with a few mL of 1 M aqueous hydrochloric acid, followed by a few mL of ice cold 95% ethanol, and allow it to air dry on the filter. Blot the crystals
as dry as possible by pressing between two large pieces of filter paper [*Wear gloves!*].

**Procedure for the preparation of 2-phenylindole**

Using a poly squeeze bottle, weigh 20 g of the syrupy polyphosphoric acid into a *dry* 50 mL beaker. Place the beaker on a steam bath, and clamp a thermometer so that it measures the temperature of the liquid near the wall of the beaker. Warm the acid to 50 °C, and slowly stir in the acetophenone phenylhydrazone, taking care not to hit the thermometer bulb with the stirring rod. (Do not use the thermometer as a stirring rod!) After the addition is complete, continue stirring, and heat the mixture strongly on the steam bath for 15 min with stirring.

Cautiously pour the hot mixture into 30 mL of ice and water, washing the beaker with a few mL of water. Stir until all the acid has dissolved in the water. Collect the precipitated crude product on a Büchner funnel, washing it with cold methanol, and allow it to air dry on the filter. Store it in your drawer until the next lab period two weeks later.

Recrystallize the crude product from ethanol-water, using about 0.1 g of decolorizing carbon. (Dissolve it in hot ethanol, add the activated carbon, and filter hot. Reheat the filtrate to boiling, and add water to the cloudy point. Add a drop or two of ethanol to redissolve the fine cloudy precipitate, and allow the solution to cool undisturbed. Collect the crystals on a Büchner funnel, and allow them to air dry at room temperature.) Weigh the product, calculate the yield, and obtain its melting point. Sublime a small amount of the recrystallized material under vacuum, and measure the melting point of the sublimate.