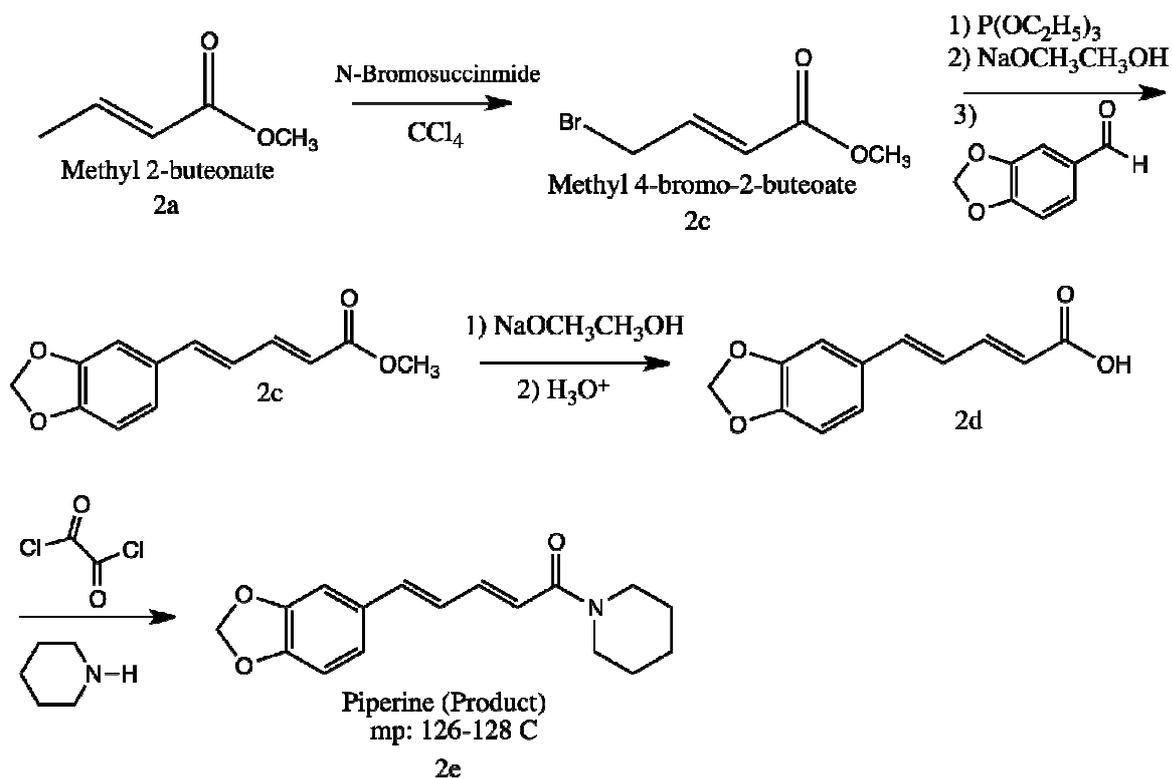


Multistep Synthesis: Synthesis of Piperine

The independent project I chose to do is the synthesis of Piperine. The reason I chose this project was so that I could compare the results I obtained from the isolation of piperine, and see how both techniques compare to one another. The materials and procedure are adapted from the *Microscale Synthesis of the Natural Products Carpanone and Piperine* by Joseph C. Sloop.



Physical Data:

Name of Compound	Mol. Wt. (g./mol)	Color cryst. form	B.P. °C	M.P. °C	Density (g./mL)	Solubility	Hazards
Carbon Tetrachloride (CCl ₄)	153.82		77	-23	1.5940	al, benz, chl, eth	Irritant, poisonous
N-bromosuccinimide	177.98	wh sol.	339	175- 178	2.098	w	Irritant
Benzoyl Peroxide	242.23	-----	103	104.5	1.334	-----	Irritant, Flammable
Triethyl phosphite	166.16	-----	156		0.969	-----	-----
Piperonal	150.13	-----	263	37	1.337	-----	-----

Dry dimethoxyethane	90.12	-----	85	-58	0.8683	-----	Toxic, Flammable
Dry Benzene	78.11	-----	80.1	5.5	0.8787	al,chl,dieth,ace	Toxic
Piperic Acid	218.21	-----	-----	-----	-----	-----	-----
Oxalyl chloride	126.93	-----	64	-12	1.488	Diethyl eth	Toxic, Irritant
Magnesium sulfate	120.38	-----	-----	-----	-----	w	Toxic
Piperidine	85.15	-----	106	-7	0.862	w	Flammable, Irritant
piperine	285.35	Wh cryst.	-----	130	1.193	DCM	Irritant

Materials List: *Compounds*

- (5mL)- Carbon Tetrachloride (CCl₄)
- (3.0 g.)- N-bromosuccinimide
- (1.5mL)- Methyl 2-butenate
- (100 mg.)- Benzoyl Peroxide
- (450 mg.)- Triethyl phosphite
- (400 mg.)- Piperonal
- (10mL)- Dry dimethoxyethane
- (2mL)- Methoxide/Methanol Solution
- (9.0mL)- Dry Benzene
- (250 mg.)- Piperic Acid
- (2.0mL)- Oxalyl chloride
- Magnesium sulfate
- (1.5mL)- Piperidine

Material List: *Equipment*

- Calcium Chloride drying tube
- Sunlamp
- Two-necked round bottom flask
- Dry nitrogen line (for round bottom flask)
- Conical Vial (3mL)

Procedure: *Day 1*

1. Add 5.0mL of Carbon tetrachloride to a 25mL round bottom flask
2. Then add 3g. of N-bromosuccinimide, 1.5mL of Methyl 2-butenate, and 0.1g. of benzoyl peroxide.

3. Attach reflux condenser to flask, stir bar, and calcium drying tube, then reflux for 45-60min under a sunlamp.
4. Once reaction is complete, remove flask from heat and distill off ~4mL of Carbon tetrachloride
5. Next, using a vacuum pump, distill the residue (methyl 4-bromo-2-butenate 93-102 °C)

Day 2

1. To 0.5 g. of methyl 4-bromo-2-butenate, add 0.45 g. of triethyl phosphite in a 3mL conical vial (attach reflux condenser and stir bar)
2. Reflux reaction for ~30min, then transfer reaction mixture via syringe to a two-necked round bottom flask containing 0.4 g. of piperonal and 10mL dry dimethylethane (attach a dry nitrogen line, stir bar, and thermometer)
3. Using a second syringe, add 2.0mL methoxide/methanol solution (stir reaction for 15min. so temperature does not exceed room temp.)
4. Next, add reaction mixture to 40mL of ice cold water in a 100mL Erlenmeyer flask, and stir for ~15min.
5. Then using vacuum filtration, collect precipitate and air dry overnight

Day 3

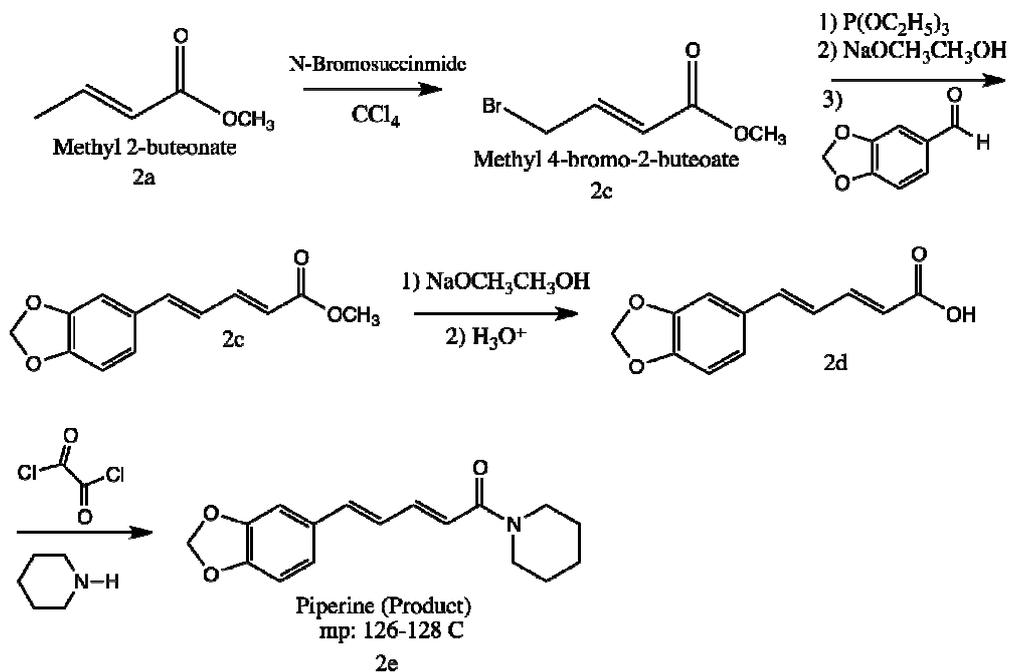
1. To 0.500 g. of collected dried precipitate, add 0.25 g. of NaOH and 6.0mL of methanol (attach reflux condenser and stir bar), and then reflux reaction mixture for ~90 minutes
2. Using rotary evaporation, reduce mixture until pale yellow residue remains, then dissolve this solid in 20mL of water
3. Extract with two-three 5.0mL portions of diethyl ether, and then add concentrated HCl to aqueous solution until pH=1
4. After, vacuum filtrate, and collect the precipitate and air dry for 24h.

Day 4

1. Next, recrystallize the crude acid from methanol (m.p. 145-147 °C)
2. To 0.250 g. of piperic acid (2d), add 5.0mL of dry benzene in a 10mL round bottom flask (add stir bar and calcium drying tube)
3. Next, via syringe, add 2.0mL of oxalyl chloride and reattach drying tube, then stir for ~45min at room temperature
4. Using a rotovap evaporate solvent from mixture until residue forms, and then add 3.0mL of dry benzene to residue, then add 1.5mL of piperidine/2.5mL of benzene
5. Reflux reaction mixture for 30min
6. After, allow reaction to cool to room temperature, then pour mixture into flask containing 10mL of water
7. Next, extract the resulting solution with three 10mL portions of chloroform, then wash the organic extract with 10mL of 0.1 HCl, then 10mL saturated sodium bicarbonate solution, followed by 10mL of saturated NaCl solution
8. Dry organic extracts with magnesium sulfate, and filter the chloroform solution and evaporate in hood.

9. Finally, recrystallize from acetone (m.p. 126-128 °C), to yield piperine, then take an IR spectrum and submit an NMR sample

Multistep Synthesis: Synthesis of Piperine



Introduction:

The multistep synthesis chosen for his experiment was piperine, which is one of the main alkaloids (i.e. contains nitrogen groups) responsible for the pungency and spice of the black pepper. It was first discovered around the 1820s by a Danish physicist and chemist Hans Christian Orsted, and historically has been used in everything from food to medicine. It primarily comes from the *Piper Nigrum* vine, and traditionally was thought to cure a wide range of illnesses from diarrhea to insect bites. Nevertheless, its most common place is in the kitchen where it has been a staple of flavor for over a thousand years [1,3].

Experimental:

Using the various techniques such as refluxing, distilling and extracting as well as some other intermediate techniques (i.e. filtration and recrystallization) generally yields the product piperine. However, in this particular lab only the first product was successfully synthesized during the experiment. The first step of the experiment consisted of an NBS reaction, which was done on methyl 2-butenoate using carbon tetrachloride, benzoyl peroxide and N-bromosuccinimide. The reaction was then refluxed for approximately 60min under a sun lamp, which helps start the reaction through radical initiation of the bromine. Once the reflux was complete 4 mL of CCl_4 was distilled out of the reaction mixture using the simple distillation technique. Following this, the remaining reaction mixture was reduced with a vacuum distillation pump, which left a dark orange-brown crystal precipitate. Once the crystallized product was collected and weighted, an NMR was taken. From there, ~0.5 g. of the product was added to a 3mL conical vial along with triethyl phosphite, and refluxed for ~30min. Once refluxed, the remaining mixture was added to a 3-armed round bottom flask along with

Dimethylethane and piperinal. In order to run this reaction, a nitrogen line was attached to the flask in order to flush out any air, as well as a thermometer and a septum to relieve pressure. As the reaction proceeded, a solution of methanol/methoxide was added via syringe. After ~15min. the mixture was added to a Erlenmeyer flask along with 40mL of cold water to precipitate out the product (E,E)-Methyl-[3 4 (Methylenedioxy) Phenyl] -2,4-pentadienoate. However, no precipitate was recovered upon vacuum filtration due to the small crystal size, so an extraction was done using DCM to try and pull the product out, but unfortunately no product was every recovered from the dark brown liquid residue, so an NMR was taken. Finally, the product from the first step was made a second time to try and remake the second product of the synthesis procedure, however due to time this was never accomplished.

Discussion/Results:

The multistep synthesis of piperine yielded no end product, so the melting point, percent yield, and NMR could not be obtained. However, the first day's product was successfully synthesized twice, and the second day's product was formed, but never isolated out of solution due to some potential errors as will be discussed. The first product synthesized was methyl 4-bromo-2-butenoate with an obtained weight of 1.8403 g. and a percent yield of ~72%. The first product was then synthesized again to try and find any errors in our synthesis, which yielded a weight of 1.8735 g. with a percent yield of about 74%. Although the first day's product was synthesized successfully the overall synthesis of piperine was quite unsuccessful. I would now like to address some potential errors in the overall piperine synthesis and also discuss the results of the products obtained from this experiment.

The first potential error I would like to discuss comes from the seconds day's method of filtering the product (E,E)-Methyl-[3 4 (Methylenedioxy) Phenyl] -2,4-pentadienoate) out of solution. The reason for this is because the precipitated crystals obtained in this synthesis were extremely fine, so the use of vacuum filtration that was suggest caused the crystals to fall right through the filter, which made recovering the product not possible. In order to try and obtain the crystals, an extraction was done, however this turned out to be unsuccessful. Another possible error in this lab was the possibility of unreacted mixture in the second day's synthesis. For example, when stirring the flask containing the previously made product (i.e. methyl 4-bromo-2-butenoate) with piperinal, and methanol/methoxide solution some of the mixture was stuck to the side of the flask, which therefore could have caused the little product that was obtained. Furthermore, during this particular reason a nitrogen line was attached to the flask in order to remove the air from the reaction, however the nitrogen atmosphere was broken during this reaction because of excess pressure build up so there was a chance that this could have had an effect the overall synthesis. Nevertheless, this error seems negligible since the atmosphere was only broken for a short time and the amount of air around the reaction was quite small. Finally, I would like to address the two syntheses of methyl 4-bromo-2-butenoate. When comparing both products from the first day's reactions, there seemed to be a drastic color differences noted between both products (i.e. light yellow-brown and dark red-brown). One possible reason for the color difference could have come from some potential unreacted bromine during the reflux with would have be seen as the dark-red-brown color, since bromine is a dark red-brown. However, when comparing the NMR's of both products they indicated fairy

pure products despite the color difference, but it's worth noting that the starting material is almost identical to the product so it's hard to tell whether there was more product in one than the other.

Upon obtaining the two products of methyl 4-bromo-2-butenate that were synthesized, NMR's were run to check for purity and identity. When analyzing the first product, which was the dark red-brown crystals there were a few characteristic peaks noted. For instance, around the 3.70 ppm range there was a singlet peak which indicated a primary aliphatic carbon and since it was next to an ester it was shifted up to the high 3 range. Also, in the 2.87 ppm range there was a triplet peak around the allylic position where the bromine attaches, which suggest that the product still had some starting material in it, which is why there is a triplet peak and not a doublet. Furthermore, upon analyzing the second product that was the light-brown precipitate the NMR seemed to show almost identical peaks as the first product but instead of a triplet at the allylic position there was a doublet, which suggest that this product when further to completion than the first synthesis. Finally, an NMR was done of the second days product (E,E)-Methyl-[3 4 (Methylenedioxy) Phenyl] -2,4-pentadienoate), which was a dark brown liquid residue, but since the crystals couldn't be isolated out of solution the NMR was extremely hard to analyze. However, a few potential characteristic peaks found were around 5.90-6 ppm, which indicated the presence of a conjugated system, as well as around the 6.80-7.50 ppm, which indicated the presence of an aromatic ring. Unfortunately, there were many other peaks that couldn't be determined, do the product still being in solution as well as the presence of possible impurities, but it can be concluded that there was at least some product in the solution.

Conclusion:

Ultimately, the overall synthesis was unsuccessful, but despite not getting any piperine in the end, there was still a lot to be learned in this lab, which made it fun and successful in its own way. And even though there was no second day product obtained, which halted the experiment; the possible problems and differences found in the experiment were most likely due to some of the errors described in the discussion section. Therefore, we can conclude that although the synthesis was unsuccessful, the techniques and procedure used were most likely correct despite the results obtained.

References

[1] "Black Pepper and Piperine." *Encyclopedia Britannica.com*. Revised March 1999. <<http://www.britannica.com/bcom/eb/article/0/0,5716,15702+1+15499,00.html>>

[2] Microscale Synthesis of the Natural Products Carpanone and Piperine Joseph C. Sloop.
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[3]http://web1.caryacademy.org/facultywebs/gray_rushin/StudentProjects/CompoundWebSites/2000/Piperine/piperin_home_page.htm