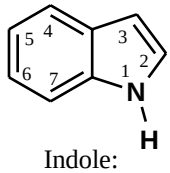
Exp't 15

Fisher Indole Synthesis of 2-Phenylindole

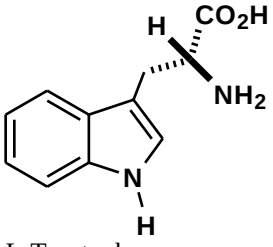
Adapted by Modi, Monarch, Perriello, Pohland, and Minard (PSU '92) from A.I. Vogel's *Elementary Practical Organic Chemistry*, Longman Group Ltd., London (1966). Revised 4/9/01

Introduction:

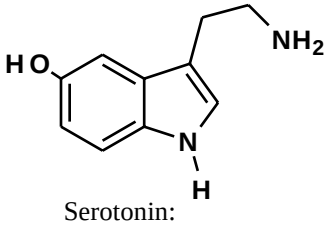
Indoles are a very important class of heterocyclic compounds that play a major role in cell physiology. The parent structure and three examples are:



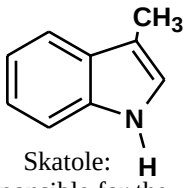
Indole:
the parent heterocycle



L-Tryptophan:
an essential amino acid

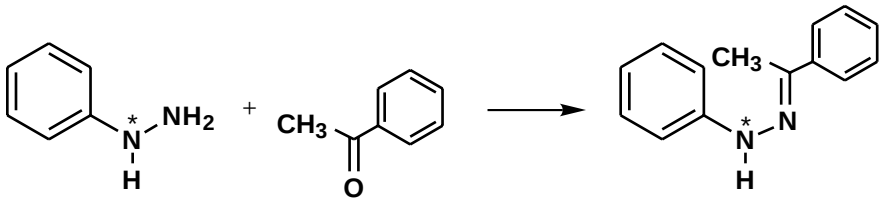


Serotonin:
a potent vasoconstrictor

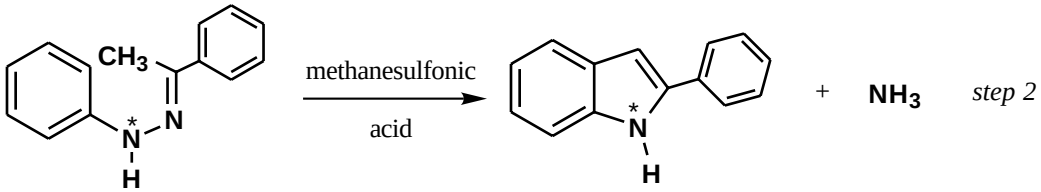


Skatole:
Responsible for the unpleasant odor of feces.

Indoles with various substituents in the 2 and 3 position can be synthesized via the Fisher indole synthesis which involves two steps and utilizes a phenylhydrazine and an aliphatic or aromatic aldehyde or ketone as starting materials. The synthesis of the 2-phenyl derivative prepared in this experiment involves the reaction of phenylhydrazine with the ketone acetophenone to produce a phenylhydrazone as shown in step 1 below. Cyclization with subsequent loss of one of the nitrogens as ammonia is catalyzed by the addition of a strong acid as shown in step 2.



phenylhydrazine acetophenone acetophenone phenylhydrazone



acetophenone phenylhydrazone 2-phenylindole mp 188-189

Various acid catalysts, such as zinc chloride, sulfuric acid, boron trifluoride and polyphosphoric acid have been used to catalyze the second reaction. However, a group of four Chem 36 honors students (see citation above) tried methanesulfonic acid and found this to be an easy-to-handle and quite effective acid catalyst.

Although Emil Fisher reported the discovery of this type of indole synthesis in 1883, it was not until 1943 that Allen and Wilson answered the fascinating mechanistic question: Which nitrogen in the phenylhydrazone intermediate is spit out as ammonia? This was done by labeling the α nitrogen of the phenylhydrazine with the stable isotope, ^{15}N, then carrying out the reaction and examining the products for the presence of the ^{15}N isotope. The result is shown above, i.e. the labeled nitrogen (marked with an *) shows up in the indole product, so it is the β nitrogen that is expelled as ammonia.

The most common use of 2-phenylindole is as a photoconductor in electrophotography.

Prelaboratory Exercises:

^{15}N is not radioactive; how is its presence in a molecule determined?

Write an arrow-pushing mechanism for the formation of the hydrazone in step 1.

Cautions:

Phenylhydrazine is a suspected cancer-causing agent; therefore, gloves should be worn whenever you are in contact with this compound. Methanesulfonic acid is very corrosive. Avoid skin contact with these chemicals. If you should spill either on your skin wash immediately with soap and water.

Synthesis:

Into a 4-mL reaction tube, place 0.56 g of acetophenone and 0.50 g of phenylhydrazine. Mix well and heat this solution on a boiling water bath for one hour. Pour this phenylhydrazone intermediate into a 25-mL Erlenmeyer flask containing 6.0g of methanesulfonic acid which has previously been heated in a hot water bath for 10 min. Heat and stir with a stirring rod for an additional 10 min.

Isolation and Purification:

The hot reaction solution is added to 25 mL of ice/water and stirred. The 2-phenylindole is insoluble in water and therefore will precipitate out. Collect the product by vacuum filtration using a Hirsch funnel and wash the crystals several times with distilled water. After drying, obtain the weight and melting point of the crude product. If you do not observe a melting point between 185 to 189°C, recrystallize the solid from an ethanol/water mixed solvent system. Determine the final weight and % yield and mp.

Cleaning Up:

Filtrates from the reaction can be disposed of by flushing down the drain with water.

Analysis:

Analyze your product by the method described in your experimental assignment sheet.

Final Report:

Write the structure and spectral interpretation on the spectrum. Give yields and mp's of crude and recrystallized product. Answer this questions at the end of your report:

1. Indole is not as basic as an aliphatic amine. Explain why, based on indole's structure.
2. Read the short section in the Lab Guide (Chapter 3) on solvent pair recrystallization. What is a solvent pair recrystallization, how was ethanol and water chosen, and suggest a second pair that should work comparably well.