

EXPERIMENT 7

REDUCTION OF AN OPTICALLY ACTIVE NATURAL PRODUCT

This experiment demonstrates a general method for the reduction of ketones to alcohols, the use of polarimetry to study the stereochemistry of a reaction and introduces some commonly used tests for the qualitative analysis of alcohols and ketones

A. PRELAB ASSIGNMENTS

1. First Week

- a. Read Jones, Chapter 4, on Stereochemistry.
- b. Prepare a Table of Physical Constants in your notebook. Include structures, formulae, molecular weights, specific rotations, and other relevant physical properties for (+) camphor, (-) camphor, (+) borneol, (-) borneol, (+) isoborneol, (-) isoborneol, methanol, and sodium borohydride. Specify R or S at carbon 1, which is the bridgehead carbon with the methyl group. (Consult the Merck Index and the Aldrich Catalog, in addition to the Handbook of Chemistry and Physics, and if necessary, the Dictionary of Organic Compounds.)
- c. Write a balanced equation for the NaBH_4 reduction of camphor, showing all likely products.

2. Second week prelab assignment

Answer the following in your notebook, before the second week lab lecture:

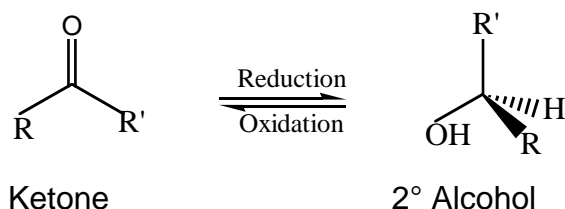
- a. Determine the limiting reagent and calculate the theoretical yield of the product (borneol and/or isoborneol).
- b. Identify all chiral centers in the compounds listed in 1.b. above and label them as (R) or (S). (Use models.)
- c. Identify the products of the reaction (1.c. above) as structural isomers, enantiomers, or diastereomers.
- d. Define the terms "stereoselective" and "stereospecific."

B. THEORETICAL BACKGROUND

Camphor, (1,7,7-trimethylbicyclo-[2.2.1]-2-heptanone) belongs to a diverse family of naturally occurring compounds, known as terpenes, which have carbon skeletons composed of 5-carbon isoprene units. Optically active camphor is isolated from camphor trees found in Java, Brazil, China and Sumatra.

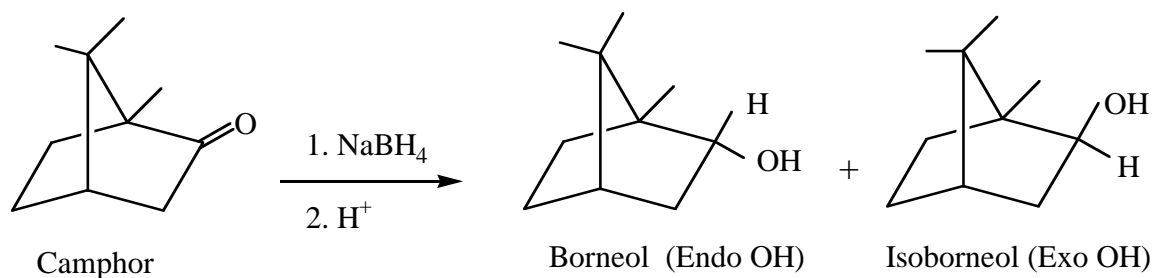
Camphor has many practical and important uses. For example, camphor is used as a preservative in pharmaceuticals, in cosmetics, and even in embalming fluids. Camphor has also been used as an anesthetic, as a mild antiseptic, and as a cardiac stimulant.

The reduction of ketones to 2° alcohols is an example of a **functional group transformation**, i.e., a reaction that changes a group or groups attached to a compound but leaves the carbon backbone unaltered. The reverse reaction, oxidation, converts 2° alcohols back to ketones.



Commonly used reducing agents include complex metal hydrides, such as LiAlH_4 (lithium aluminum hydride) and NaBH_4 (sodium borohydride). In this experiment, we will use sodium borohydride to reduce camphor, an optically active, naturally occurring ketone.

The reduction of the ketone group in camphor can form two products, borneol or isoborneol.



The products differ in the way in which the metal hydride reducing agent delivers a hydride ion to the planar carbonyl group. Stereochemical demands of the substrate, in this case camphor, can direct the addition of metal hydride to one of two faces of the carbonyl. Addition of hydride to exo face of camphor forms borneol, the endo product. Addition of hydride to the other face of camphor forms isoborneol, the exo product. If much more of one product is formed, the reaction can be said to be stereoselective. By determining which (if either) product is preferentially formed, it is possible to determine if and how the stereochemical demands of camphor are controlling the reduction reaction.

Once the product(s) are isolated and identified, it becomes possible to determine if the reduction was stereospecific by measuring the optical rotation of the starting material and product(s). If the reduction was stereospecific, optically pure (+) or (-) camphor should form only (+) or (-) borneol, or only (+) or (-) isoborneol, with no loss of optical purity.

In this experiment, you will start with either (+) or (-) camphor. (The camphor to be used will be assigned by your instructor.) From the sign of the optical rotations of the starting camphor and of the product(s), you can confirm the identity of the product(s) and determine the stereoselectivity, by determining if one of the expected products, borneol or isoborneol, is formed in greater amount. (You could also evaluate the stereospecificity by measuring optical rotation of both the starting material and the isolated purified product(s) and determining the optical purity or enantiomeric excess of each.)

C. EXPERIMENTAL PROCEDURE

The Reduction Reaction

1. Place 0.0132 mole of your assigned camphor in a 50 mL round-bottom flask (RBF). Add 8 mL of methanol and cool the flask in ice in a 250 mL beaker ice bath. While the flask is cooling, weigh 0.016 mole of NaBH_4 in a vial and keep it covered. Crush any large lumps with a spatula.

2. Add the NaBH_4 to the camphor solution in 3 portions with cooling, as described in steps **a-c** below.
 - a. Remove the flask from the ice bath, and add about 2 scoopula-tips full of NaBH_4 . Swirl the mixture for 5-6 minutes. Crush any solid lumps that form with a thin, bent spatula. Whenever the bubbling becomes vigorous and/or the flask no longer feels cool, return it to the ice bath. Continue to swirl and crush lumps.
 - b. After about 6 minutes, cool the flask in the ice bath again; repeat step **a**.
 - c. Repeat step **b**, adding the remaining NaBH_4 .
3. After about 5 minutes, let the solution warm to room temperature. Swirl it occasionally for another 10 minutes. Meanwhile, clamp the flask to a ring stand with the flask in contact with a steam bath (STEAM OFF) and equip it with a reflux condenser. (Cooling water tubing will not be needed for this short reflux time.) When bubbling becomes slow, heat the solution to boiling, and reflux it for about 5 minutes.
4. Put about 30 mL of ice into a 125 mL Erlenmeyer flask, cool the reaction mixture for a minute or two, and pour it with stirring onto the ice. Rinse the reaction flask twice with 2 mL portions of methanol, and add the washes to the reaction mixture.
5. Stir the mixture until the ice melts. Collect the solid by suction filtration. Wash the filtered solid with cold distilled water, and press it dry with a glass stopper.
6. Transfer the crude reaction product to the same 125 mL Erlenmeyer flask. Save a few small crystals of crude product to use as seed crystals, in case the product "oils out" as the recrystallization solution cools.
7. Dissolve the crude product in a minimum volume of 1:1 methanol-water mixture. Then add water dropwise until a permanent turbidity is seen. Add hot methanol again until the solution just becomes clear. Set aside to cool slowly. Then cool in ice, and filter the recrystallized product using suction filtration.
8. Transfer the product to a 100 mL beaker and cover with parafilm.

Second Lab Period

9. Weigh your dry product and determine the yield.

10. Functional Group Tests

Two classical tests will be performed in order to determine whether or not the product is an alcohol and whether or not it is contaminated by unreacted camphor. For **a** and **b** below, record your observations and results in tabular form and give general equations for positive tests.

a. Chromic Acid Test for Alcohols

In the chromic acid test, 1° and 2° alcohols are oxidized by solutions of chromic acid (H_2CrO_4) to form carboxylic acids and ketones, respectively; tertiary alcohols do not react with H_2CrO_4 . A positive test is indicated by the formation of a green-blue precipitate.

Add a match head size of solid or 1 drop of liquid to 1 mL acetone in a test tube. Then add 1 drop of chromic acid reagent and shake the mixture. The appearance of an opaque blue-green precipitate within 2 seconds is a positive test.

Perform the test on 1-butanol, 2-butanol, 2-methyl-2-propanol (t-BuOH), camphor, and your product.

b. 2,4-Dinitrophenylhydrazine (2,4-DNP) Test for Ketones

In the 2,4-DNP test, ketones (and aldehydes) react rapidly with 2,4-dinitrophenylhydrazine to give brightly colored precipitates. Alcohols do not react with this reagent.

Different concentrations of reactants will be used to increase the sensitivity of the test, so that small amounts of unreacted starting material (camphor) can be detected in the product from your reduction reaction.

Knowns

Perform this test on the following substances: isoborneol, camphor, methanol, and acetone. For each test, put 1 mL of 95% ethanol in a small test tube. Add (and mix) a spatula-tip full or 5 drops of the test compound, followed by 1 mL of 2,4-DNP reagent. Mix well. If a precipitate does not form, boil the solution

in the test tube in a steam bath for 1 minute. Cool it in ice. A colored precipitate is a positive test for a ketone.

Reaction product

Repeat the 2,4-DNP test as above, but use about 0.1 g of your product. If a positive test is observed, explain why this occurred.

11. Polarimetry

Work in pairs to measure the optical purity of camphor. Find a partner who used the same starting material, #1 or #2, as yours, and share the data.

- a. Accurately weigh out about 0.2500 g of camphor in a small beaker.
Dissolve the camphor in the beaker in a small amount of 95% ethanol.
Transfer this solution **quantitatively** to a 25 mL volumetric flask, and fill to the mark with 95% ethanol; mix well. Set the polarimeter to 0 with a 95% ethanol blank cell. Fill a 2 dm cell with the prepared camphor solution and measure the optical rotation.
- b. Accurately weigh out about 0.5000 g of your product in a small beaker.
Dissolve and transfer quantitatively to a 25 mL volumetric flask, and fill to the mark with 95% ethanol, as in step **a** above. (If the solution is cloudy or turbid, filter it.) Be sure to rinse the polarimeter cell with a little ethanol, and then pre-rinse it with some of your sample before filling the cell. (The cells require about 18 mL to fill.) Measure the optical rotation as above.
- c. Calculate the specific rotation of both samples.

D. DISCUSSION AND CONCLUSIONS

In addition to your own Discussion and Conclusions, answer the following questions:

1. Does your calculated specific rotation correspond to a single pure alcohol isomer? Which one? If not, determine from the signs of optical rotation of your starting material and product which isomer (if either) was formed in excess and the identity of the other isomer.

2. Calculate the percent composition of your product (if it was a mixture).

Assume that

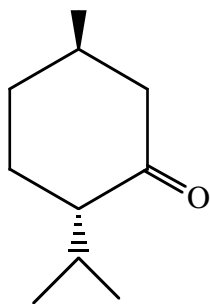
$$[\alpha]_{(\text{specific})} = X_b[\alpha]_b + X_i[\alpha]_i$$

(b = borneol, i = isoborneol expected from your starting material, X = mole fraction)

Was the reaction stereospecific or stereoselective?

E. QUESTIONS

1. If unreacted camphor were not removed from your product by recrystallization, how would this affect your calculation of the proportions of borneol and isoborneol? Explain.
2. Thin layer chromatography would be a more sensitive method than the 2,4-DNP test to detect unreacted camphor in your product. Suggest why this might not work, even though the product mixture can be separated on silica gel with CH_2Cl_2 developing solvent. (Hint: Camphor has a powerful odor and requires a sealed tube for m.p.)
3. Based on your results, determine whether the hydride adds from the exo- or endo- face of the carbonyl group. Does this result satisfy predictions made on the basis of the stereochemistry of camphor? Explain.
4. Write a balanced equation (structural formulae) for the reaction of camphor with 2,4-dinitrophenylhydrazine.
5. Predict the most likely product formed from the reaction of optically pure (+) menthone with sodium borohydride. Give the common name of the product.



(+) Menthone

NOTES