## **Experiment** 17

Fig. 17-1

# NUCLEOPHILIC SUBSTITUTION WITH SACCHARIN



Ira Remsen 1846 -1927 http://www.jhu.edu/~gazette/2000/sep1100/11remsen.html

### **Text Topics**

Nucleophilic substitution reactions, nucleophilicity.

#### Discussion

The word serendipity has the ring of positive, joyous thoughts. Indeed, serendipity has played a very significant role in scientific discoveries and progress. It is worth repeating four quotations that were included in the discussion of *Experiment 2:* 

"In the fields of observation, chance favors only the mind that is prepared." *Louis Pasteur* "God hides things by putting them near us." *Ralph Waldo Emerson* 

"Man will occasionally stumble over the truth, but most of the time he will pick himself up and continue on." *Winston Churchill* 

"Where we go matters less than what we notice." The is part of a poem that is attributed to Bokonon from *The Lost Book*.

In scientific research, it is very important to make all observations carefully and alertly and to pay special attention to unexpected results. As Pasteur indicated, a person with a prepared mind is much more likely to initiate an investigation of unexpected observations and make significant discoveries. Among the chemically related serendipitous discoveries that have impacted our lives are rubber, teflon and penicillin. Additionally, three of the most commonly used artificial sweeteners, saccharin, cyclamates and aspartame, were discovered when research chemists tasted a strong sweetener on their food or fingers after having synthesized a chemical in the laboratory. While this certainly leads to a critical questioning of their hygienic and safety procedures, the researchers all deserve considerable credit for going back into the laboratory to find what was causing the sweet taste. In 1878, Constantin Fahlberg working with one of the 19<sup>th</sup> century's most famous American chemists (Ira Remsen at Johns Hopkins University) discovered saccharin in this way. Despite a huge controversy regarding potential carcinogenicity in the late 20<sup>th</sup> century, saccharin is still one of the biggest selling artificial sweeteners available today.

It is a common approach in pharmacological research to try to modify the structure of a drug that has bioactive properties to improve desired properties and diminish undesired side effects. Because of its instability in stomach acid, research of this nature led to the modification of penicillin G to ampicillin and amoxycillin.



Substantial efforts have been made to separate the analgesic properties of morphine from its addictive and hallucinogenic properties. Limited success has resulted in the synthesis of drugs like vicodin, darvon and demerol. While these drugs do have analgesic properties, they unfortunately still tend to be addictive if abused. Apparently, the sites in morphine that are responsible for the analgesic properties also are associated with the sites that cause the addictive properties.



For saccharin, it is conceivable that a structural modification could improve its sweetening properties and diminish undesirable properties. It is also possible that the reverse could occur. In today's experiment, you will use the sodium salt of saccharin as a nucleophile to displace the iodide in iodoethane to produce ethyl saccharin. Because tasting is out of the question for safety reasons, you will not be able to answer the question about sweetness. However, another interesting challenge is presented in the synthesis.



As you can observe above, as a result of the dispersal of negative charge illustrated by the resonance structures of the anion of saccharin, attack on the iodoethane can occur by the nitrogen or the oxygen. Fortunately the methylene hydrogens on the carbon attached to either the N or O resonate at different chemical shifts. By comparing the integrations of the quartets of the two methylene groups, you will be able to calculate the ratio and percentage of each isomer produced.

#### Procedure

This reaction should be carried out in a hood. Because of limited hood space, it might be advisable to work with a partner on this experiment. Place a crystallizing dish or beaker appropriately sized to hold a 50 mL Erlenmeyer flask on a hot plate. Fill the dish or beaker about half way with water and heat the water to about 80°C. Add 0.0050 moles of the hydrate of the sodium salt of saccharin and 2.5 mL of dimethylformamide (DMF) to a 50 mL Erlenmeyer flask. Swirl the flask in the heated water bath until the solid dissolves. Now use a calibrated Beral pipet to add 0.40 mL of iodoethane to the flask. Cover the flask with Parafilm and heat the flask in the 80°C water bath with occasional swirling for about 10 minutes (*please see next paragraph*). After the solution has cooled to room temperature, add 30 mL of water and swirl several minutes until solidification is complete. Break the clumps up with a spatula and cool the mixture in an ice bath. Vacuum filter using a Büchner funnel to collect the solid. Wash the solid twice with 5 mL of ice-cold water. Allow the product to air dry at least overnight. Some students find that the product crystallizes in two different looking batches. However, analysis performed in our labs could not distinguish between the two sets of crystals. Do you observe two sets of crystals and can you perform a test to distinguish between them?

Additionally, the product ratio seems to differ from student to student. This could be because one of the products rearranges to the other during the heating process making the ratio dependent on the heating time and the temperature. At the instructors request, divide into groups and heat for different amounts of time (e.g., 5 min., 10 min., 20 min., 30 min., 60 min.) or at different temperatures (60°C, 70°C, 80°C, 90°C) and determine if there is a trend in the product ratio change.

Weigh the dry product and determine the percent yield. Determine a melting range and carefully observe the full melting range. Using CDCl<sub>3</sub> as the solvent, determine the ratio of products using <sup>1</sup>H-nmr.

#### E17-4

#### References

Greenberg, F. H. J. Chem. Educ., **1990**, 67, 611. Lehman, J. W. Operational Organic Chemistry, Prentice-Hall, **2002**, 156-161. Roberts, R. M. Serendipity: Accidental Discoveries in Science, Wiley, **1989**. Ellis, J. W. J. Chem. Educ., **1995**, 72, 671-675.

## **Prelaboratory Preparation - Experiment 17**

First, be sure to list all the goals of the experiment. Compare the structures of the morphine derivatives. Can you determine which structural features are necessary for analgesic properties? Calculate the theoretical yield for the saccharin reaction. Predict which product you expect to predominate. Explain how nmr will be used to determine the product ratio.

## **Observations**

Report all relevant observations including masses, melting ranges and <sup>1</sup>H-nmr.

## Conclusions

This section should include the following:

- 1. Were the goals of the experiment achieved? Explain your answer.
- 2. What was the ratio of products obtained? Was the ratio consistent with your prediction? Explain your answer.
- 3. Was the melting range consistent with your <sup>1</sup>Hnmr results? Explain your answer.
- 4. Would this reaction be a good way to synthesize either N-ethyl saccharin or O-ethyl saccharin? If not, how could you modify the procedure to achieve a good synthesis?
- 5. If you obtained two different crops of crystals, was there a difference between them?
- 6. If different groups of students heated the reaction mixture for different amounts of time or at different temperatures, did the product ratio change and if so was there a trend? If there was a trend, how do you explain it?