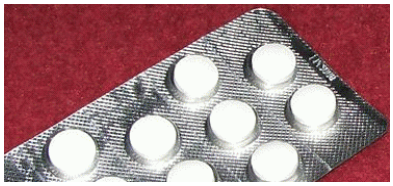
Fig. 38-1



Ibuprofen tablets

Experiment 38

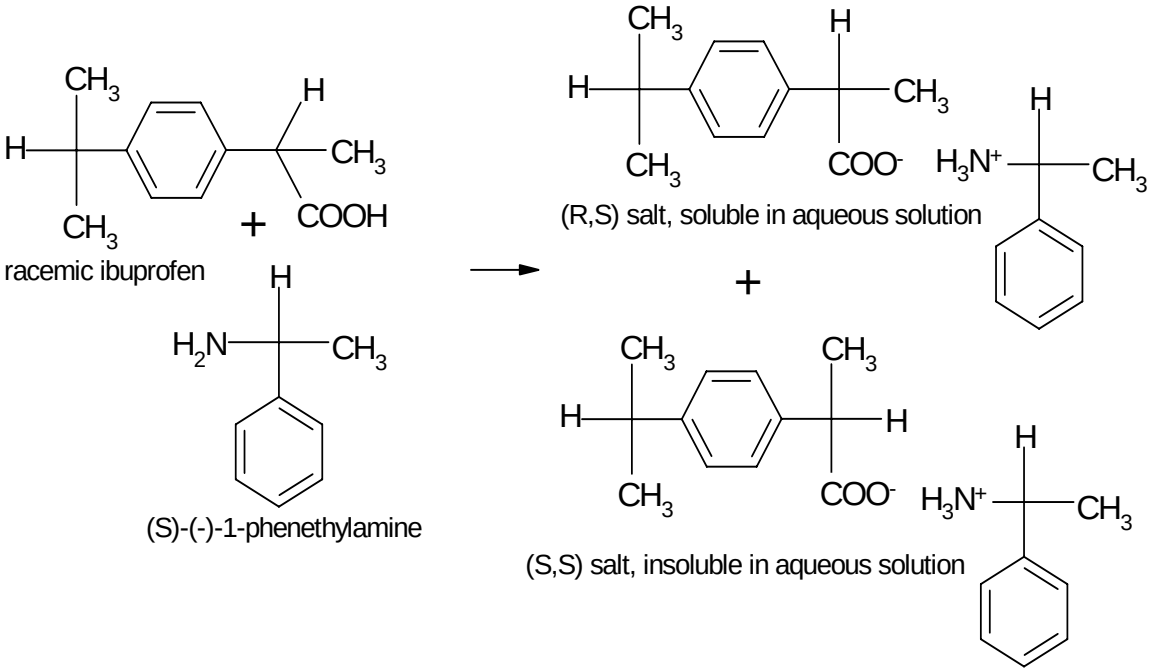
ENANTIOMERS OF IBUPROFEN

Text Topics

Optical activity, enantiomers, resolution, diasteromers.

Discussion

Generally speaking, except for their behavior in polarimetry and in reactions with other chiral molecules, enantiomers have identical physical and chemical properties. To illustrate the concept that enantimers interact differently with other enantiomers, ***Experiment 10*** demonstrated that the enantiomers of carvone, the essence of spearmint and caraway, have different odors. Ibuprofen [2-(4'-isobutylphenyl)propionic acid] has a stereogenic center and is the active component in over-the-counter drugs such as Motrin, Advil and Nuprin. It has been demonstrated that only the (*S*)-(+) enantiomer of ibuprofen has the desired pharmacological properties. As the racemic mixture is much less expensive than the (*S*)-(+) enantiomer and the (*R*)-(-) isomer apparently does not have any harmful pharmacological effects, the drug is usually marketed as the racemic mixture. Because it would be preferential to provide only the active stereioisomer, this experiment involves an attempt to resolve racemic ibuprofen into its enantiomers.



Racemic ibuprofen will be reacted with the commercially available *(S)*-(-)-1-phenethylamine (also named (S)-(-)-α-methylbenzylamine). The two diasteromeric isomers formed have substantially different solubilities in water. With the much lower water solubility, the desired (*S*,*S*)-ibuprofen-phenethylammonium salt precipitates from the solution and is collected, recrystallized and reverted with acid to the (*S*)-(+) enantiomer of ibuprofen and *(S)*-(-)-1-phenethylamine. As an optional experiment, the inactive enantiomer can be recovered also.

Because of the cost of the starting materials, only small amounts of the reagents will be used. Unfortunately, this makes polarimetry measurements to determine the success of the reaction somewhat difficult. One way around this is to have students perform polarimetry measurements on combined products. Fortunately, for this case, there is an alternative method for qualitatively determining the optical purity of the product. As you are aware, impurities normally depress and broaden the melting ranges of compounds. However, the melting points of mixtures of enantiomers are much less predictable. Based on empirical evidence and theory, it could be expected that a racemic mixture should have a melting point that is lower than the melting point of either enantiomer. This prediction is often not realized with racemic mixtures sometimes having melting points higher than the melting points of the enantiomers. This is the case with the enantiomers of ibuprofen. The racemic mixture melts about 78°C and each of the enantiomers melts at about 52°C. Thus you should be able to determine the success of your resolution attempt by measuring the melting ranges of the starting ibuprofen and the product(s) of your experiment.

Procedure

Mount a 3 necked flask equipped with a reflux condenser, a dropping funnel and a magnetic stirrer in a water bath on a heater-stirrer unit. Add 1⅔ g of racemic ibuprofen and 15 mL of 0.25 M KOH to the flask. While wearing gloves, use a calibrated Beral pipet to carefully add 0.5 mL of *(S)*-(-)-1-phenethylamine to the dropping funnel. Heat the water bath to its boiling point. Most of the ibuprofen should dissolve. Now add the amine slowly and dropwise to the heated mixture. A precipitate should form within minutes but continue to heat the mixture for 30 minutes. Remove the hot water bath and allow the solution to cool. Use vacuum filtration to collect the solid. Wash the collected solid with a small amount of ice water.

Add the solid to a 50 mL beaker that contains a boiling stick. Add a few mL of 2-propanol and heat to boiling. Continue to slowly add 2-propanol to the boiling solution until all of the solid dissolves. Allow the solution to cool and immerse it in an ice bath. Vacuum filter and wash the recrystalllized salt with ice water.

Transfer the recrystallized salt to a 50 mL beaker. Add 10 mL of 2 M H_2SO_4 and a stirring bar to the beaker. Stir for a few minutes and transfer the solution to a separatory funnel. Extract the aqueous layer three times with MTBE (methyl-*t*-butyl ether). Combine the organic layers and wash them with 10 mL of water and 10 mL of saturated NaCl solution. Dry over sodium sulfate and rotary evaporate to remove the MTBE. Place the flask containing a thick oily liquid in a freezer and solidification should result. Weigh the solid and determine the melting ranges of the product and the original ibuprofen.

Options: Follow the instructions in the online supplement to the first reference listed below and isolate the inactive enantiomer. Also combine student products (be sure the samples have similar melting points first) and determine the optical rotation and optical purity.

References

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Prelaboratory Preparation - *Experiment 38*

First, be sure to list all the goals of the experiment. Prepare a flow diagram that shows all of the steps that will be followed during the attempted isolation of the (*S*)-(+) enantiomer of ibuprofen. Include names of the enantiomers and diastereomers in your diagram. Prepare a table for insertion of useful and observed data such as molecular mass, mass, moles, melting points and percent yields and recoveries. Use the Internet to determine the pharmacological activities of the enantiomers of thalidomide.

Observations

Report all relevant observations including physical properties and melting ranges.

Conclusions

This section should include the following:

1. Were the goals of the experiment achieved? Explain your answer.
2. Discuss the success of the attempted resolution. Include explanations.
3. How could the percent yield and recoveries have been improved?
4. Should ibuprofen be resolved before it is marketed? Discuss both pharmacological and cost issues.