Hemisuccinate Synthesis: Investigation of Dibutyltin Oxide as an Esterification Catalyst

Julia A. Pfaff

Candidate for the degree

Bachelor of Science

Submitted in partial fulfilment of the requirements for

College Honors

Departmental Distinction in Chemistry & Biochemistry

Pamela G. Artz, Ph.D.

Robert D. Rapp, Ph.D.

Kathy M. Ozment, M.A.

F. Wilbur Gingrich Library
Special Collections Department
Albright College

Release of the Senior Thesis

I hereby deliver, give, and transfer property, rights, interest in and legal rights thereto which I had, have, or may have concerning the Senior Honors Thesis described below to the Special Collections Department of the F. Wilbur Gingrich Library at Albright College as an unrestricted gift. While copyright privileges will remain with me, the author, all privileges to reproduce, disseminate, or otherwise preserve the Senior Honors Thesis are given to the Special Collections Department of the Gingrich Library. I place no restrictions on this gift and hereby indicate this by signing below.

Title: Hemisuccinate Synthesis: Investigation of Dibutyltin Oxide as an Esterification Catalyst

Signature of Author: Julia A Pfaff Date: 4 May 2006

Printed Name of Author: Julia A. Pfaff

Current Home Address: 129 Edgewood Rd

City, State, Zip Code: St. Marys PA 15857

Julia Pfaff

Fall 2005/Spring 2006
The Senior Thesis

Hemisuccinate Synthesis: Investigation of Dibutyl Tin Oxide as an Esterification Catalyst

Abstract: Studies have led to recent developments in the use of natural compounds to produce extended-release agents. Such agents have been known to play integral roles in the formation of chemical agents involved in HIV and tumor therapy. The use of natural products, however, is hindered by their decomposition when subjected to aggressive chemical environments. This decomposition of the natural products has led to decreases in product yield, decreases in effectiveness, and, in some cases, toxicity of the compounds. In an effort to suppress some of this decomposition, catalysts are used to conduct the syntheses under milder conditions. Because of its proposed ease of purification and its mild reaction conditions, dibutyltin oxide has been suggested to serve as the catalyst in hemisuccinate synthesis. Various primary, secondary, and tertiary alcohols were selected and reacted with succinic anhydride and with dibutyltin oxide serving as the catalyst. The hemisuccinate products were analyzed primarily by infrared spectroscopy. While the primary and secondary alcohols demonstrated the expected trends on their respective IR spectra, the tertiary alcohol did not. It is suggested that the tertiary alcohol was decomposed into its alkene and acid derivatives during reflux. This shows that tertiary alcohols may decompose even under fairly mild conditions. This illustrates the sensitivity of the compounds to the reaction conditions, which is a key focus of the proposed synthesis.

Introduction: Hemisuccinates are very important in generating an extended release of chemically active agents in chemical compounds. Hemisuccinates are linked to polymers through an ester or amide linkage to achieve this sustained release of agents. This is most commonly seen in the sustained release of HIV inhibitors in HIV treatment, sustained release of anti-tumor agents in chemotherapy, and in the sustained release of odorants in laundry detergents.

In previous work, acid and base catalysts have also been frequently used in esterification reactions. However, current methods of hemisuccinate synthesis often include typically unfavorable reaction conditions. For example, one method of synthesis which involves the treatment of triterpenes with acid anhydride "requires reagents in at least 2.5-10 times molar excess for completion of the reaction" and another method was found to be unsuccessful "even under drastic conditions." (Hashimoto, *et al,* 1997) A typical method of synthesis involves several hours of refluxing succinic anhydride and the active agent with a strong base catalyst, such as triethylamine (Rapp, 2005). Unfortunately, many natural products will begin to decompose when exposed to these strong basic conditions and high temperatures.

In the case of anti-AIDS agents, acid derivatives have been synthesized and evaluated with regard to their methods of synthesis and their overall inhibitory affects against HIV. However, these agents have been shown to have many adverse side effects which limit the effectiveness and the benefits of the agents and their methods of synthesis. Due to such adverse side effects of the currently used agents, recent research approaches have engaged in discovering "diverse anti-HIV agents with novel structures or

mechanisms of action." (Hashimoto, *et al,* 1997) Natural products have been suggested to serve as these new diverse agents with novel structures. Therefore, there has been much focus on discovering "novel plant-derived natural products" as potential compounds involved in the synthesis of anti-HIV agents. Furthermore, it has been suggested that these new natural compounds can be modified such that they will produce agents of greater potency. However, a hindrance in this proposed synthesis of anti-AIDS agents is the decomposition of such natural products under aggressive chemical conditions, as previously discussed. Upon experimentation with several proposed natural products, some degree of decomposition was observed. Therefore, some of the resulting acid derivatives of the agents used in synthesis were found to exhibit decreased potency against HIV, while others displayed relatively strong cytotoxicity, which yielded toxic or inactive compounds. (Hashimoto, *et al,* 1997)

With this in mind, it has been the goal of scientists to propose reaction pathways that occur under milder conditions and therefore minimize such decomposition of natural products. Several reaction catalysts involving tin oxide have been investigated in previous studies. Similarly, the investigation of dibutyl tin oxide as an esterification catalyst has been suggested due to the ease of purification of the products and the mild reaction conditions. This investigation will consist of using dibutyl tin oxide as a catalyst in the formation of hemisuccinates of several proposed "natural products" (various primary, secondary, and tertiary alcohols). The proposed alcohols include menthol, (+) β-citronellol, geraniol, α-terpineol, and borneol.

Experimental: The reagents used in the synthesis of various hemisuccinates include the following:

The succinic acid used to generate the succinic anhydride was obtained from Fisher Scientific Company of Fair Lawn, New Jersey. Chemical formula $(CH_2COOH)_2$, F.W. 118.092g, m.p. 187-188°C. Catalog number A-294, Lot number 733877.

The menthol [89-78-1] was obtained from the Aldrich Chemical Company of Milwaukee, Wisconsin. F.W. 156.27g, b.p. 216°C, m.p. 34-36°C, d 0.89g/mL

The β-Citronellol, 95% [106-22-9] was obtained from the Aldrich Chemical Company of Milwaukee, Wisconsin. F.W. 156.27g, b.p. 222°C, n_D^{20} 1.4556, d 0.857. Catalog number C8, 320-1, Lot number 00311MM.

The [(1S)-*endo*]-(-)-Borneol, 97% [464-45-9] was obtained from Sigma-Aldrich Inc. F.W. 154.25g, b.p. 210°C/760mmHg, m.p. 206°C. Lot number 16412LA.

The Geraniol, 98% [106-24-1] was obtained from Sigma-Aldrich Inc. F.W. 154.25g, b.p. 231-232°C, n_D^{20} 1.4760, d 0.879. Catalog number 16, 333-3, Lot number 08107HC.

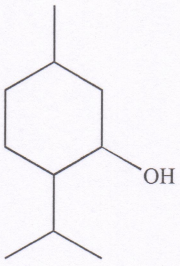
The α-terpineol, tech., 90% [10482-56-1] was obtained from Sigma-Aldrich Inc. F.W. 154.25g, b.p. 217-218°C/760 mmHg, m.p.31-35°C, n_D^{20} 1.4820, d 0.935. Catalog number 43, 262-8, Lot number 07601PC.

The dibutyltin oxide, 98% [818-08-6] was obtained from the Aldrich Chemical Company, Inc. Chemical formula $[CH_3(CH_2)_3]_2Sn{=}O$. F.W. 248.92g. Catalog number 18, 308-3, Lot number 10731KU.

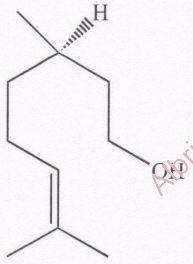
Succinic anhydride was prepared according to the procedure found in *Organic Syntheses* (1). The described procedure was modified such that the succinic anhydride product would be one-fourth of the amount produced by the original procedure. From the amounts listed in the procedure (118g succinic acid, 215cc acetyl chloride) it was determined that the components would produce a 4.65M solution. With respect to this value, the two components were reduced such that their respective amounts would produce a solution of equal molarity. In preparation of the succinic anhydride, 25.02g of succinic acid and approximately 45mL of acetyl chloride were used. 18.61g (87.8%) of succinic anhydride was obtained.

Using the succinic anhydride and the alcohols depicted below, dibutyl tin oxide was used as a catalyst in the synthesis of hemisuccinates. Each hemisuccinate was prepared according to the same procedure, outlined below.

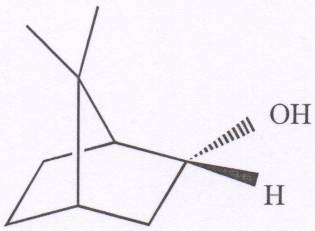
Proposed alcohols for hemisuccinate synthesis:



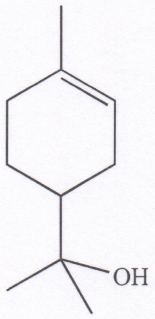
Menthol



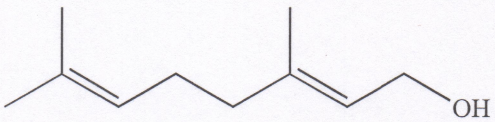
(+) β - Citronellol



(+) d - Borneol

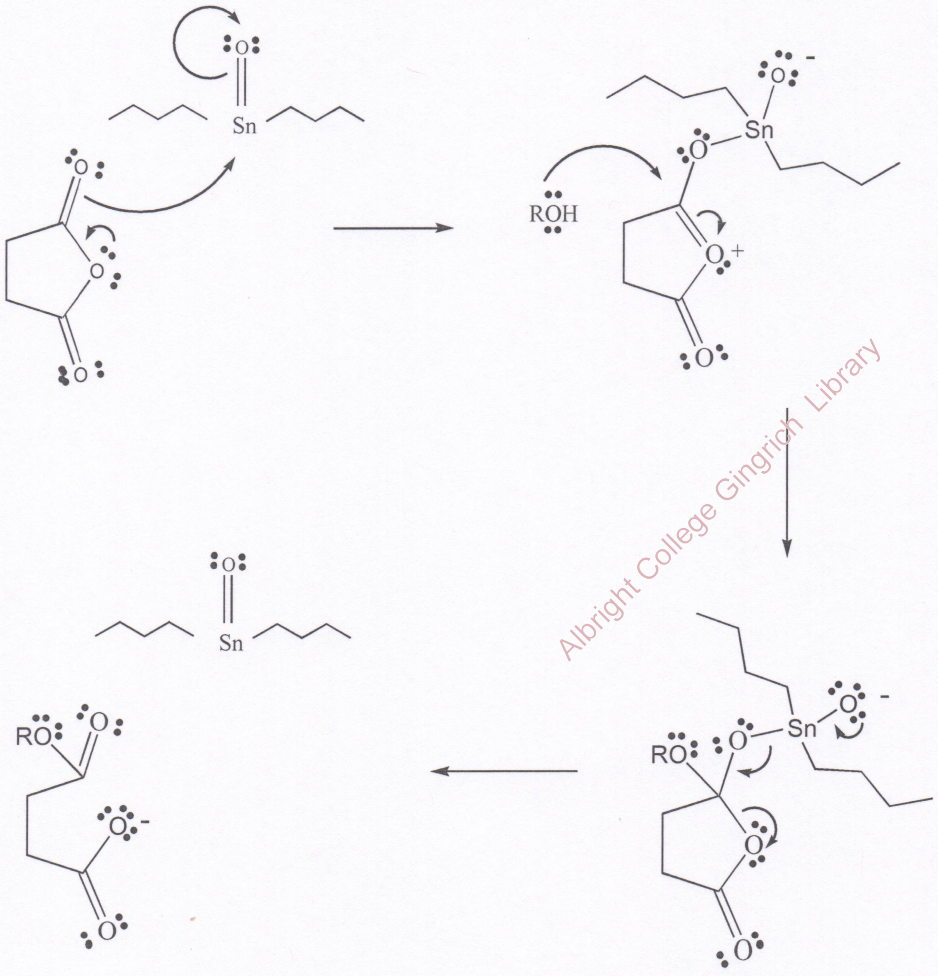


α -Terpineol



Geraniol

Proposed mechanism of Hemisuccinate synthesis:

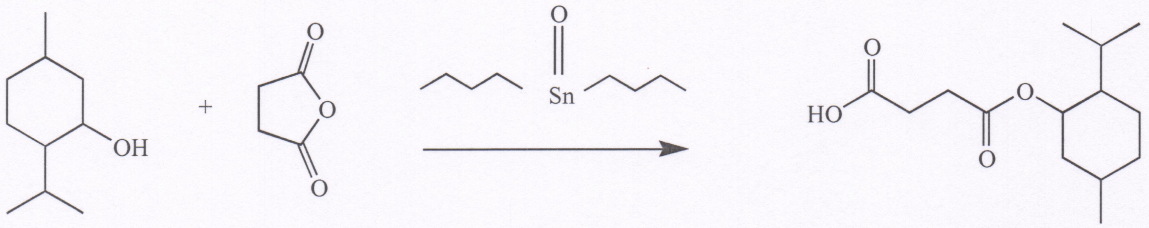


General procedure for hemisuccinate synthesis:

In a 25mL round bottom flask, 2.00mmol of the proposed alcohol was combined with 624mg(6.24mmol) of succinic anhydride, 400mg(1.60mmol) of dibutyl tin oxide, and 10mL of toluene. A stirbar was added and the flask was fitted with a reflux condenser. The reaction was heated to 100°C and held at this temperature overnight. The following day, the reaction was cooled in an ice bath. To remove the unreacted succinic anhydride, the solution was filtered using a water aspirator. The precipitate was washed with several portions of cold toluene. The filtrate and the toluene washes were quantitatively transferred to a 100mL round bottom flask and the toluene was removed from the solution using a rotary evaporator. After evaporation, 20mL of hexane was added to the residue and the solution was allowed to stir overnight at room temperature. After stirring overnight, the insoluble dibutyl tin oxide was removed from the solution by filtration as before. The hexane filtrate and washes were transferred to a 100mL round bottom flask and the hexanes were removed using a rotary evaporator under reduced pressure. After rotary evaporation, the crude hemisuccinate products were obtained as yellow viscous oils.

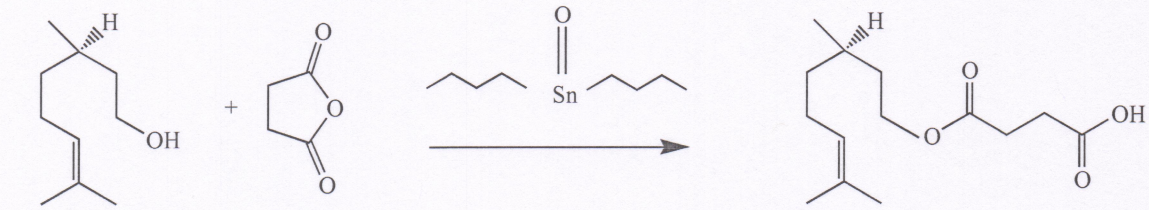
Reaction schemes of the hemisuccinate products:

I. Menthol hemisuccinate



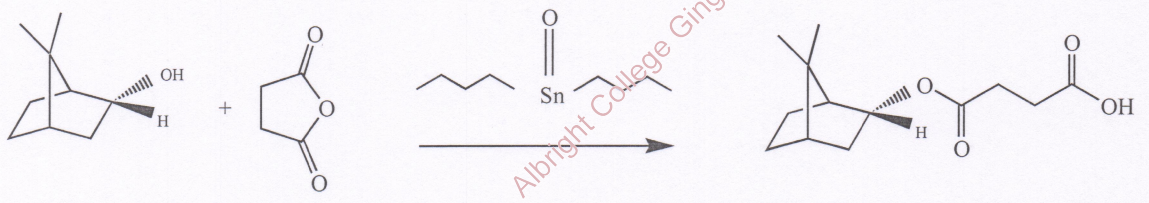
Menthol + Succinic Anhydride → Menthol Hemisuccinate

II. β-citronellol hemisuccinate



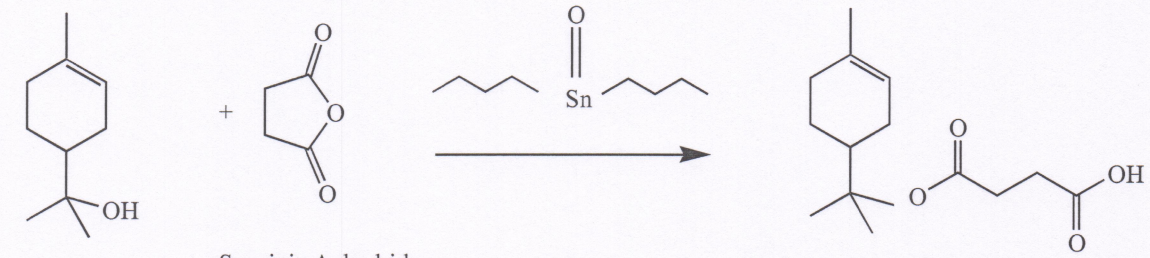
(+) β - Citronellol + Succinic Anhydride → (+) β - Citronellol Hemisuccinate

III. Borneol hemisuccinate



(+) d - Borneol + Succinic Anhydride → [(1S)-*endo*] - (-) - Borneol Hemisuccinate

IV. α-terpineol hemisuccinate



α -Terpineol

Succinic Anhydride

α -Terpineol Hemisuccinate

Yield data for each of the hemisuccinate products is as follows:

I. Menthol hemisuccinate

crude yield: 0.87g

II. β-citronellol hemisuccinate

crude yield: 0.84g

III. Borneol hemisuccinate

crude yield: 0.96g

IV. α-terpineol hemisuccinate

crude yield: 0.34g

Geraniol was also used in effort to generate a fifth hemisuccinate, geraniol hemisuccinate. According to the procedure followed to produce the hemisuccinates, a 2mmole equivalent of geraniol was added to a round bottom flask containing 624mg(6.24mmol) of succinic anhydride, 400mg(1.60mmol) of dibutyl tin oxide, and 10mL of toluene. A stirbar was added and the flask was fitted with a reflux condenser. The reaction was heated to 100°C and held at this temperature overnight. Unfortunately,

after refluxing overnight, the reaction mixture was a chalky white liquid. The mixture was inseparable via vacuum filtration. The unreacted succinic anhydride and dibutyl tin oxide could not be filtered out of the reaction mixture. This led to ineffective IR spectroscopic analysis, and no definitive conclusions were drawn with respect to this particular synthesis.

The other four alcohols used were successful in generating a hemisuccinate product. After rotary evaporation, the crude hemisuccinate products were analyzed by Infrared and proton NMR spectroscopy. Infrared spectroscopy was performed on a Perkin-Elmer Spectrum One FT-IR spectrophotometer and proton NMR spectroscopy was performed on a Varian Unity INOVA at 300MHz. The results of the spectral analysis of the crude products are as follows:

I. Menthol hemisuccinate

IR(neat) 3500-2600, 2956.27, 2870.14, 1734.07, 1370.26, 1173.04 cm^{-1}.

^1H NMR (300MHz, $CDCl_3$) was uninterpretable. (Figure 5)

As illustrated in Figure 1, attached, the strong peaks on the spectrum that appear at 2956.27 and 2870.14cm^{-1} lie within the characteristic range (2850-2970cm^{-1}) of the C-H bond of alkane compounds. The broad band that is seen superimposed on the C-H stretching frequencies is characteristic of carboxylic acid compounds. The strong peak on the spectrum that appears at 1734.07cm^{-1} is characteristic of the carbonyl function of an ester compound (1735cm^{-1}). Also visible on the spectrum are several unidentified peaks that appear around 1400cm^{-1}. These peaks most likely correlate to the methylene groups

adjacent to the carbonyl functions. The characteristic value of such peaks is listed as 1410cm^{-1}. Two peaks on the spectrum fall within the range of 1300-1050cm^{-1}. These peaks represent the symmetric and antisymmetric stretch of an ester function. The peaks appear on the spectrum at 1370.26cm^{-1} and 1173.04cm^{-1}.

II. β-citronellol hemisuccinate:

IR (neat) 3600-2500, 2958.36, 2925.99, 2870.76, 1735.36, 1606.50, 1378.67, 1168.28cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) was uninterpretable. (Figure 6)

As illustrated in Figure 2, attached, the strong peaks on the spectrum that appear at 2958.36, 2925.99, and 2870.76cm^{-1} lie within the characteristic range (2850-2970cm^{-1}) of the C-H bond of alkane compounds. The broad band that is seen superimposed on the C-H stretching frequencies is characteristic of carboxylic acid compounds. The strong peak on the spectrum that appears at 1735.36cm^{-1} lies within the characteristic range (1675-1760cm^{-1}) of the carbonyl function of carboxylic acid esters. The peak that appears at 1606.50cm^{-1} lies within the characteristic range (1600-1660cm^{-1}) of the C=C bond of an alkene compound. Again, visible on the spectrum are several unidentified peaks that appear around 1400cm^{-1}. These peaks most likely correlate to the methylene groups adjacent to the carbonyl functions. The characteristic value of such peaks is listed as 1410cm^{-1}. Two peaks on the spectrum fall within the range of 1300-1050cm^{-1}. These peaks represent the symmetric and antisymmetric stretch of an ester function. The peaks appear on the spectrum at 1378.67cm^{-1} and 1168.28cm^{-1}.

III. Borneol hemisuccinate

IR (neat) 3600-2300, 2955.18, 2872.53, 1736.70, 1415.16, 1382.64, 1356.83, 1283.61, 1231.60, 1160.32, 1113.72, 1080.81 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) was uninterpretable. (Figure 7)

As illustrated in Figure 3, attached, the strong peaks on the spectrum that appear at 2955.18 and 2872.53cm^{-1} lie within the characteristic range (2850-2970cm^{-1}) of the C-H bond of alkane compounds. The broad band that is seen superimposed on the C-H stretching frequencies is characteristic of carboxylic acid compounds. The strong peak on the spectrum that appears at 1736.70cm^{-1} lies within the characteristic range (1675-1760cm^{-1}) of the carbonyl function of carboxylic acid compounds. The peak that appears at 1415.16cm^{-1} most likely correlates to the methylene groups adjacent to the carbonyl functions, which are listed to characteristically appear at 1410cm^{-1}. The peaks that appear at 1382.64 and 1356.83cm^{-1} are characteristic of methyl groups. More specifically, in the case of Borneol hemisuccinate, these peaks correlate to two methyl groups which are bound to the same carbon atom. These are listed to characteristically appear at 1385 and 1365cm^{-1}. Several peaks on this spectrum fall within the range of 1300-1050cm^{-1}. These peaks represent the symmetric and antisymmetric stretch of an ester function. The peaks appear on the spectrum at 1283.61, 1231.60, 1160.32, 1113.72, and 1080.81cm^{-1}, which lie within the suggested range (1050-1300cm^{-1}).

IV. α-terpineol hemisuccinate

IR (neat) 3390.98, 2964.78, 2923.60, 1712.26, 1605.09, 1376.46, 1287.68, 1221.95, 1157.82, 1132.51, 1077.03, 913.57, 836.48, 799.70, 774.80, 739.38 cm^{-1}

^1H NMR (300MHz, $CDCl_3$) was uninterpretable. (Figure 8)

As illustrated in Figure 4, attached, the strong peak that appears at 3390.98 clearly lies within the characteristic range (3200-3600cm^{-1}) of an alcohol. This could possibly suggest that some unreacted a-terpineol remains in the crude product. The strong peaks that appear at 2964.78 and 2923.60cm^{-1} lie within the characteristic range(2850-2970cm^{-1}) of the C-H bond of alkane compounds. The strong peak on the spectrum that appears at 1712.26cm^{-1} lies within the characteristic range (1675-1760cm^{-1}) of the carbonyl function of carboxylic acid compounds. The peak that appears at 1605.09cm^{-1} lies within the characteristic range (1600-1660cm^{-1}) of the C=C bond of alkene compounds. The peak that appeats at 1376.46cm^{-1} is characteristic of methyl groups, which characteristically appear at 1375cm^{-1}. There are several peaks on the spectrum thatt fall within the range of 1300-1050cm^{-1}. These peaks represent the symmetric and antisymmetric stretch of an ester function. The peaks appear on the spectrum at 1287.68, 1221.95, 1157.82, 1132.51, and 1077.03cm^{-1}. Finally, specific to a-terpineol hemisuccinate, there are several peaks on the spectrum, 913.57, 836.48, 799.70, 774.80, and 739.38cm^{-1}, which lie within the characteristic range (675-995cm^{-1}) of cis-1,2-disubstituted alkene.

Gas chromatography was also a proposed means of analysis of the hemisuccinate products. However, due to the size of the hemisuccinate products, the temperature of the instrument had to be significantly elevated in order to vaporize the compounds.

Unfortunately, the elevated temperature resulted in a decomposition of the hemisuccinates. This rendered the GC analysis useless in the analysis of the purity of the hemisuccinate products.

The four crude hemisuccinate products were purified via vacuum distillation. Menthol hemisuccinate was distilled at 150-170°C and 0.015mmHg. The distillation resulted in 147mg of menthol hemisuccinate product, giving a final product yield of 28.7%. α-terpineol hemisuccinate was distilled at 50-60°C and 0.03mmHg. This resulted in 138.21mg of α-terpineol hemisuccinate product, giving a final product yield of 27.2%. The distilled products were then analyzed via IR spectroscopy. When the spectra were compared to the respective spectra of the crude hemisuccinate products, it was noted that the spectra of the crude and distilled products were nearly identical. They demonstrated the same characteristics, differing only in intensity (Figures 9-10).

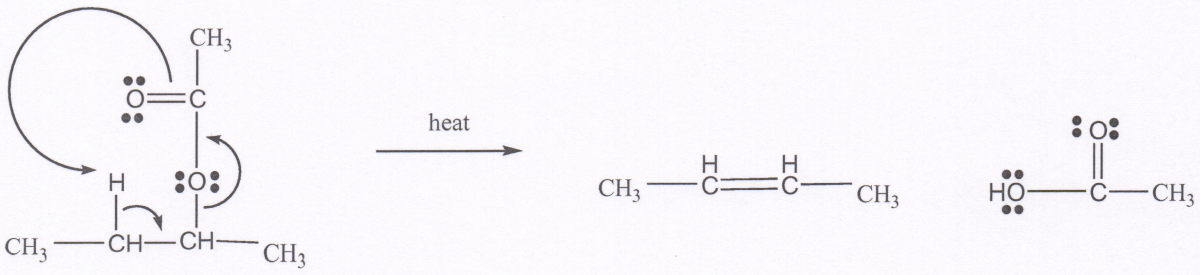
Discussion:

Upon comparison of the IR spectra of the four hemisuccinate products (Figures 1-4), the spectra of β-citronellol hemisuccinate, menthol hemisuccinate, and [(1S)-*endo*]-(-)-Borneol hemisuccinate share similar characteristics (Figures 1-3). For instance, the most notable characteristic of these three spectra is their strong peaks in the region of 1735cm^{-1}, representing the carbonyl function. Also, although the spectra vary in intensity, they show similarities in the region of 3000-2800cm^{-1}. However, the IR spectrum for α-terpineol hemisuccinate looks considerably different than the IR spectra of the other three hemisuccinate compounds. The most significant difference is the peak representing the

carbonyl function. This peak has a surprisingly weak intensity on the α-terpineol hemisuccinate spectrum (Figure 4). We expect a very intense peak in the region of the carbonyl function, and this weakness in intensity suggests that the α-terpineol and succinic anhydride did not efficiently form a hemisuccinate product. Further evidence of this inefficiency lies in the region of 3000-2800cm^{-1}. This region of the α-terpineol hemisuccinate spectrum is also much different than that of the other three spectra. In the α-terpineol hemisuccinate spectrum, this region strongly resembles the characteristics we would expect of a carboxylic acid. Also, the spectrum clearly lacks the peaks that represent the symmetric and antisymmetric stretch of an ester function. We would expect to see strong peaks in the range of 1300-1050cm^{-1}. This provides further evidence that α-terpineol produced less hemisuccinate product than the other alcohols.

A possible explanation of these results can be derived from DePuy *et al,* 1960. His work illustrates the decomposition (pyrolysis) of an ester when exposed to heat. The tertiary ester readily reacts with mild heating due to the stability of the tertiary carbon to which the ester function is attached. The trend is illustrated in the following mechanism, in which a tertiary ester is decomposed into its alkene and carboxylic acid derivatives.

Mechanism; Pyrolysis of Esters:



Upon comparing the IR spectra of the crude (Figure 4) and distilled (Figure 10) α-terpineol hemisuccinate products, the characteristics are nearly identical, as previously mentioned. This suggests that the aforementioned decomposition took place prior to the analysis of the crude product. The most likely explanation is that the decomposition occurred during reflux. The elevated temperature at which the reaction mixture was refluxed overnight must have been a temperature high enough to begin decomposition of the ester function, as illustrated in the DePuy mechanism.

With respect to the attempt to synthesize geraniol hemisuccinate, a reasonable explanation for the outcome of the reaction is unclear. Based on the structures of the proposed alcohols, we would expect that the [(1S)-*endo*]-(-)-Borneol would be the most hindered and therefore the most unlikely to readily react. However, as the experimental data shows, the [(1S)-*endo*]-(-)-Borneol reacted efficiently and produced results similar to menthol and β-citronellol. Geraniol, however, did not react as expected and the results did not resemble those of the other alcohols. With this in mind, a reasonable explanation of this observation could be attributed to some possible steric effect or steric preference when comparing geraniol to the other alcohols.

Additional pathways to pursue would include refluxing the α-terpineol and succinic anhydride mixture under a milder temperature. This would allow further investigation of the stability and reactivity of the tertiary alcohol function. This would also provide evidence to support or contradict the proposition based on DePuy's mechanism and the tertiary ester function.

With respect to geraniol, the white and chalky mixture that resulted after reflux could be separated through a column to more thoroughly analyze the components of the reaction.

Also, with respect to all of the hemisuccinate products that have been synthesized, additional means of purification to consider include fractional distillation and flash chromatography. Finally, in order to more effectively evaluate yield data, the synthesis should be carried out using greater molar equivalents of the starting materials. Working with such small amounts of material magnifies the effect of product/material lost in transfers.

References

1. Blatt, A. H., Ed. Organic Syntheses. John Wiley & Sons, Inc., NY; 1943. Vol 2; pp560-561.
2. DePuy, C.H.; King, R.W. *Pyrolytic Cis Eliminations.* Chemistry Review. 1960. 60; pp431-445.
3. Hasimoto, F.; Kashiwada, Y.; Cosentino, L. M.; Chen, C.; Garrett, P.; Lee, K. *Anti-AIDS Agents – XXVII. Synthesis and Anti-HIV Activity of Betulinic Acid and Dihydrobetulinic Acid Derivatives.* Bioorganic and Medicinal Chemistry. Elsevier Science Ltd, 1997. Vol 5, No 12; pp2133-2143.
4. Rapp, R. D. Department of Chemistry and Biochemistry. Albright College, 2006.
5. Sun, I.; Shen, J.; Wang, H.; Cosentino, M.; Lee, K. *Anti-AIDS Agents. 32.[1] Synthesis and Anti-HIV Activity of Betulin Derivatives.* Bioorganic & Medicinal Chemistry Letters. Elsevier Science Ltd, 1998. Vol 8; pp1267-1272.