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An attempt to reduce 2-methyl-1, 4-Naphthalenedione (menadione) to 1, 4-dihydro-2- methyl-1, 4-Naphthalenediol

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Southern Scholars Honors Program
Senior Project Proposal Information Sheet

Name: Alexandria Cooke
Major: Biochemistry

A significant scholarly project, involving research, writing, or special performance, appropriate to the major in question, is ordinarily completed the senior year. The project is expected to be of sufficiently high quality to warrant a grade of "A" and to justify public presentation.

Under the guidance of a faculty advisor, the Senior Project should be an original work, should use primary sources when applicable, should have a table of contents and works cited page, should give convincing evidence to support a strong thesis, and should use the methods and writing style appropriate to the discipline.

The completed project, to be turned in in duplicate, must be approved by the Honors Committee in consultation with the student's supervising professor four weeks prior to the last day of class for the semester the project is turned in. Please include the advisor's name on the title page. The 2-3 hours of credit for this project is usually done as directed study or in a research class.

NOTE: Senior Project Proposal Due Date: The senior project proposal is due in the Honors Program Director's office two weeks after the beginning of the semester the project will be completed. The proposal should be a detailed description of the Honors Project's purpose and proposed methodology.

Keeping in mind the above senior project description, please describe in as much detail as you can the project you will undertake. Attach a separate sheet of paper.

Signature of faculty advisor: ____________________________

Expected date of completion: 4/1/09

NOTE: An advisor's final project approval does not guarantee that the Honors Faculty Committee will automatically approve the project. The Honors Faculty Committee has the final vote.

Approval to be signed by faculty advisor when the project is completed:

This project has been completed as planned (date): 4/2/09

This is an "A" project: ____________________________

This project is worth 2-3 hours of credit: ____________________________

Advisor's Final Signature: ____________________________ Date: 4/2/09

Chair, Honors Committee: ____________________________ Date Approved: 5/15/09

Dear Advisor,

(1) Please write your final evaluation on the project on the reverse side of this page. Comment on the characteristics that make this "A" quality work.

(2) Please include a paragraph explaining your specific academic credentials for advising this Senior Project.
An attempt to reduce 2-methyl-1, 4-Naphthalenedione (menadione) to 1, 4-dihydro-2-methyl-1, 4-Naphthalenediol.

Alexandria S. Cooke

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In fulfillment of Southern Scholars senior project under the supervision of Dr. Brent Hamstra

April 2, 2009
ABSTRACT

In the following report, menadione is used as the starting material of a multi-step Aldol synthesis to yield a derivative. Menadione, a known precursor of vitamin K, is proposed to be combined with safranal, from the saffron plant, to generate a product with possible benefits in the food and medical industries. The target derivative compound is a highly conjugated structure with three 6-membered rings. Current findings show that menadione is highly insoluble in water and difficult to hydrate using a typical acid and water hydration method. Hydration was attempted and unsuccessful with H₃PO₄ and H₂SO₄, thus a new method was implemented. This new method involved the reduction of menadione. The reduction of menadione with LiAl₄ proved to be more successful than the previous trial of hydration of menadione.

INTRODUCTION

Menadione, a vitamin K precursor, was once thought to have many potential uses but has proved harmful to humans and some animals. Once thought to be candidates for a cancer fighting drug, menadione derivatives proved to be toxic and were replaced with vitamin K₂ agents.¹ Derivatives such as menadione sodium bisulfite (MSB) have been used in the feeding of animals such as dogs and salmon as a vitamin K supplement, however, addition of menadione derivatives to both diets exhibited unwanted and harmful effects on these animals.²,³ MSB and vitamin A used in research done on salmon proved to put the salmon at a higher risk for stress factors.³ Currently menadione and its existing derivatives seem to have no beneficial uses, but could prove to be valuable if the correct derivative was synthesized.

The currently proposed research involves addition of a compound called safranal to the menadione piece to create a new derivative of menadione. Safranal is a compound derived from the spice saffron and contributes to the smell of the saffron plant.⁴ Previously safranal has been
found to have anti-nociceptive, pain blocking, activity and has been used in folk medicine; recent studies have shown that safranal may potentially be useful as an anti-tumor agent, as well as a learning and memory agent. Since safranal has proven to be of medicinal value in the past, there is a possibility that with the addition of the safranal piece, the derivative could be of use in the medical and food industry.

The proposed synthetic scheme, as shown in Figure 1, is a multi-step organic synthesis, with the main step being an Aldol reaction. The first step, the reduction of menadione, was added halfway through the experiment when the original first step failed to produce the desired results. After the reduction, the product is hydrated and re-oxidized. The following step is an alcohol protection reaction using dihydropyran (DHP). Following the protection is a deprotonation and Aldol reaction, which will attach the safranal compound to the altered menadione compound. The final steps involve an oxidation of the secondary alcohol on the safranal piece to a ketone, deprotecting the alcohol formed in the first step by removing the DHP, and finally a dehydration (elimination) reaction to restore the double bond in the ring.

EXPERIMENTAL DETAILS

In the first step, a hydration of the double bond was attempted using the following procedure. Into a 250 mL flask was put 0.5160 grams (0.002997 moles) of the pale yellow menadione powder. 30 mL of deionized water (DI H₂O) was added with mixing, creating a frothy yellow mixture. 15 drops of 85% H₃PO₄ were added to catalyze the hydration of the menadione. No change occurred and 35 mL more water was added to assist the dissolving of the menadione. The mixture was placed on low heat for 45 minutes. After 10 minutes of heat and stirring, the mixture turned from a frothy yellow liquid to a clear yellow liquid and showed clumping of a solid, which associated with the top layer of froth. An additional drop of H₃PO₄
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was added, and immediately a small amount of oil-like substance formed, which turned to a brown-colored solid. Diethyl ether (20 mL) and a solution of 0.1 M NaHCO₃ (3 mL) were added to the liquid and poured into a separatory funnel to extract the menadione mixture from the water. The menadione-ether mix was then rotary evaporated (Rotovapor Büchi RE111) and a melting point test was done by heating a small amount of the solid and recording the melting temperature (MELTEMP). The solid product had a melting point of ~96.5°C; menadione has a melting point of 102°C.

The solid was fully re-dissolved using 10 mL of 95% ethanol, and the mixture was heated. After the solid was fully dissolved, 15 ml of DI H₂O was added and the liquid mixture was put on low heat for about 30 minutes. Small brown clumps formed in the bottom of the flask and precipitate formed, possibly because some ethanol evaporated. A reflux apparatus was set up and 24 mL ethanol and 3 mL of DI H₂O was added to the flask. The mixture was left to reflux overnight on low heat; the following day the reflux was stopped, and the flask was cooled to room temperature. After sitting in a drawer for four days, crystals formed. The crystals were long, needle-like, and golden-yellow in color; a yellow liquid remained in the flask with the crystals. The crystals were vacuum filtered and dried using a Buchner funnel; the filtrate was kept. An IR spectrum (Nicolet IR 200 FT-IR) was measured for both the starting menadione compound and the crystalline product.

A second trial was started using 0.5109 g (0.002967 moles) of menadione, 40 mL of ethanol and 20 mL of DI H₂O to fully dissolve the starting compound; a warm water bath was used to encourage dissolving. After the menadione fully dissolved, 1 mL DI H₂O was added at a time until the mixture was saturated with water (50 mL), and 5 mL 85% H₃PO₄, along with boiling chips (Boileezers nonvolatile granules) were added to a round bottom flask. This mixture
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was allowed to reflux overnight. The mixture remained a cloudy yellow-color and yielded a soft paste-like solid after vacuum filtration. The solid was dried in a desiccator for two days. IR spectrum taken of the solid showed no hydroxyl peak. The hydration procedure was started again using the same method but substituting concentrated H₂SO₄ for 85% H₃PO₄. 45 mL of 95% ethanol was used to dissolve the solid and a total of 62 mL of DI H₂O used; drops of ethanol were added between the additions of water. 2.5 mL of concentrated H₂SO₄ was slowly added to the mixture, gas production was observed through the formation of bubbles. This yellow mixture was refluxed overnight. When the reflux was stopped, the liquid mixture was red in color.

To rid the mixture of any unreacted H₂SO₄, it was placed in a separatory funnel and washed three times with 20 mL portions of water, along with 14 mL 0.1 M NaHCO₃. Upon addition of the NaHCO₃, the funnel was shaken and vented to release any built-up gas. 60 mL of diethyl ether was added, separating the mixture into two phases. The lower aqueous layer was discarded, and the dark red organic layer was transferred to a round bottom flask then rotary evaporation was performed. A red-brown solid remained and the melting point was tested (MELTEMP) and found to be 95°-96°C. Methanol (8 mL) was used to re-crystallize and filter the solid, yielding a fine brown solid which was left to dry in the desiccator.

The step which is now first in the above reaction mechanism was added to the scheme because menadione was not able to be hydrated directly. This additional step makes use of LiAlH₄ as the reducing agent which will change the two ketones in menadione into two alcohols. 0.4917 g of menadione was dissolved in 40 mL of diethyl ether, forming a transparent yellow solution. 0.5821 g of LiAlH₄ was added to the liquid, turning it an olive green color. LiAlH₄ is a gray powdery solid that is very reactive, thus the addition was done with extreme caution under the fume hood with a window separating the experimenter from the chemicals. The green liquid
was set to reflux for an hour, after which the liquid was a brown color. The reflux apparatus was removed and the liquid was allowed to cool. During the reflux a brown-black layer of solid formed on top of the liquid. After an extraction and separation of the product an IR spectrum was taken.

The procedure was started again using 0.4559 g of menadione in 25 mL of diethyl ether; adding 0.4440 g LiAlH₄. The procedure was carried out as previously done, except the green liquid was not refluxed. Instead the liquid was transferred to a separatory funnel and an aqueous extraction was performed as follows: water was added drop-wise until bubbling stopped, after which enough water was added to saturate the solution for extraction. Approximately 30 mL of water was added in total. Upon addition of the water, the solution turned black and was warm to the touch, indicating an exothermic reaction occurred between unreacted LiAlH₄ and water. The pH of the solution after the addition of water was 12. To ensure that the alcohol was not deprotonated 6M HCl was added drop-wise until the pH was more acidic at a pH of 5. After this the solution was left in a separatory funnel to separate. Two layers formed, first a clear top layer and brown bottom layer containing the product. The brown layer was drained into a round bottom flask and rotary evaporation was performed until the liquid evaporated, leaving behind a brown-black solid which had a clumpy consistency.

To purify the solid product, a re-crystallization was carried out using warm methanol to dissolve the brown-black solid. The dissolved solid was transferred to a flask to create more surface area; it was cooled to room temperature then placed in an ice bath for 3 minutes. The product was vacuum filtered and a black solid was collected and left to dry in a desiccator. All the liquids, including the red layer from the separatory funnel, were saved. IR spectra were taken of the solid as well as the liquids. Another analysis was performed on the solid using the Gas
Chromatography mass Spectrophotometer (Agilent Technology 6890N GC System). An attempt was made to determine the melting point of the product, as done on previous products, but failed because the melting point is higher than can be tested with the provided laboratory equipment.

RESULTS AND DISCUSSION

In the first trial the melting point of the product was 95.6°C, it was assumed that the starting material was still present with impurities because menadione has a melting point of 102°C. Accordingly the solid was re-dissolved as explained earlier. The crystals formed were analyzed using IR spectroscopy, a distinctive hydroxyl peak at 3416 cm\(^{-1}\) was observed on the spectrum of the product. This peak was not found in spectra recorded later; it was assumed that the original crystalline sample contained water. It is possible that the golden-yellow crystals were a crystallized form of menadione.

The product from the second trial was analyzed using IR spectroscopy and determined not to be the desired hydrated menadione product. Because the spectrum lacked a hydroxyl peak in the 3500 cm\(^{-1}\) region and had a different fingerprint region than that of the menadione spectrum, it can be assumed that the product formed was not hydrated menadione.

In the third trial, using LiAlH\(_4\) and reflux, nothing substantial was found in the IR spectrum to indicate that the desired alcohol was formed. It is possible that the reflux may have heated the solution too much thus preventing the proper reaction from occurring.

From the final trial all the products, liquid and solid, were analyzed. All the spectra had broad peaks in the hydroxyl region, around 3400 cm\(^{-1}\), indicating that the reaction may have been successful. The peaks seen in the spectra of the liquids are probably a result of traces of product left behind in the liquid or the remains of the methanol that was used earlier. The melting point of the product was not able to be determined. However, some information about the desired
product, 4-dihydro-2-methyl-1, 4-Naphthalenediol, was found on SciFinder. The theoretical melting point is 366.2°C, but an experimental value was unable to be determined in the laboratory. The results from the GC-MS, showed a small peak at 172.0 g indicating there are trace amounts of menadione left in the product. The other peaks on the GC-MS were inconclusive and require further analysis and testing.

Although incomplete, experimentation thus far has shown that menadione is highly insoluble in water proving the hydration step of the synthetic scheme to be difficult to carry out. In the early trials menadione proved to be insoluble in water even when saturated with water, shaken well, and heated. However, menadione dissolves easily in ether and alcohols, such as methanol and ethanol. The organic characteristics of ether and alcohol may account for why menadione, also organic, dissolves well in such solvents; in comparison to water, which is not organic. Menadione also appears to be resistant to hydration by H₃PO₄ even when dissolved in ethanol, requiring the use of a harsh acid such as H₂SO₄, which menadione is also resistant to. This resistance to hydration is possibly due to the fully conjugated system present in menadione. The alternating double bonds in the compound form a system in which it is difficult to break even one of the double bonds because the neighboring double bonds stabilize each other. Menadione’s insolubility and resistance to strong acids caused the most difficulty in the initiation of this proposed research. It is because of this resistance that the new first step of reducing menadione was added to the reaction scheme, in hopes of breaking the conjugation of the compound before hydrating it.

IR spectra obtained prior to the third trial with reduction step can be considered invalid because none of the spectra exhibited characteristics of the desired hydrated product, but all the products were similar to the starting material. Menadione’s IR spectrum shows no distinctive
peaks until 1700 cm\(^{-1}\), which is the fingerprint region. Had the initial attempts to hydrate menadione been successful, the desired product from step \(b\). of the proposed scheme would have presented a characteristic broad hydroxyl group peak around 3500 cm\(^{-1}\), the theoretical value for hydroxyl functional groups.

It appears that menadione was more susceptible to reduction using LiAlH\(_4\). As stated earlier IR spectra presented the desired hydroxyl peak, which would be present if the ketones were reduced to alcohol functionality. If menadione was indeed successfully reduced, it should be less difficult to hydrate since the conjugation of the second ring is broken with the absence of the ketones. Unlike previous IR spectra, this final spectrum had a very strong and broad peak at 3400 cm\(^{-1}\). Also, the product sat in a desiccator drying for 3 days before the spectrum was taken, ensuring that no water was in the product.

**CONCLUSIONS AND SUMMARY**

With further analysis of the final product it would be possible to characterize it completely and determine whether theoretically the product should be solid or liquid. It is suggested for future work that the reduction step be performed carefully and on a larger scale to ensure menadione is fully and correctly reduced. Less LiAlH\(_4\) could be used, since it is very strong and reactive. When using heat during a reaction, it should be applied moderately, especially closer to the beginning of the experimentation when the product is more like menadione. It was observed during the various trials that menadione did not always act favorable when heated vigorously. Also if future work were to proceed beyond the first step, one should consider whether re-oxidizing the alcohols to ketones, as outlined in step \(c\). of Figure 1, will cause difficulty proceeding through the remainder of the experiment. Re-oxidizing the alcohols
will replace some of the lost conjugation and stability and may prove to be a hindrance to subsequent reactions as it was in the attempted hydration of menadione.

As observed, menadione does not dissolve in water, but prefers polar organic solvents such as alcohols and ethers. This property of menadione makes it a difficult chemical to work with for organic synthesis, especially when the synthesis involves hydration. However, once it is understood how menadione operates chemically it is a less difficult compound to work with. As science progresses, more work with menadione will be done making it less of a complicated mystery compound in terms of synthesis.

ACKNOWLEDGEMENTS

Both Dr. Brent Hamstra and Dr. Loren Barnhurst are greatly appreciated for their guidance and suggestions throughout the course of this research project.

REFERENCES


7 SciFinder www.scifinder.cas.org (accessed March 30, 2009)
Proposed Mechanism for Synthesis of Menadione Derivative
IR Spectra: Product of Menaquinone Reduction

% Transmittance

Wave numbers (cm⁻¹)
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C:\MSDCHEM\1\DATA\PENALOZA\2ND SEMESTER TRIAL\Snapshot\n
## Data File
MENADIONE REDUCTION.D

## Acq On
31 Mar 2009 16:35

## Operator
Alex's

## Sample
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ALS Vial : 1 Sample Multiplier: 1

## Integration Parameters
Integration Parameters: events.e
Integrator: ChemStation

## Method
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Title : 

## Signal
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highmw.M Tue Mar 31 17:02:42 2009

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- **Menadione**: 11.168

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