TOTAL SYNTHESIS OF QUINOLINE-5,8-DIONE ANALOGS
AND 7-N-BUTYRYLDEMETHYLLAVENDAMycin BENZYL ESTER

AN HONORS 499 THESIS

by

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I. Preface—Introduction for Non-Science Honors Students

It seems that HONRS 499 is encapsulated by a foggy, thick, and not-well-understood mystique that sends the shivers down the spines of even the hardiest of Honors students. There are a thousand and one questions to ask, and acquiring the nerve to search out the answers may seem impossible. Please let me assure you that it is not. A few possible places to begin inquiry include the Honors College Dean, the Honors College Assistant Dean, the Honors College Academic Advisor, Honors College Peer Advisors, past Honors College students, and even present Honors College students. As of 1998, there was also a “Thesis Guide” published by the Honors College that may prove helpful. From this point forward, I will try to be rather general (as you may have already noticed) in hopes that the information in this introduction will not become quickly outdated.

After becoming at least somewhat informed about the nature of this great adventure, it may be advisable to begin searching for a mentor. Ideally, one should find a qualified person who works well with students (with you in particular) and who has extensive knowledge about a subject (or subjects) that interests you. It is usually helpful to begin searching very early. Although it is by no means the standard across all disciplines, beginning work on an Honors thesis in the summer after one’s sophomore year is not uncommon for chemistry majors. Several of us are still writing this last week of our senior year. Don’t let this cause undue panic, though. Chemistry research is generally very time-intensive.

This introduction has probably not told you anything you did not already know, but if anything, perhaps it has reiterated the fact that one should start as early as possible, but within
reason, of course. For example, it would probably have been useless for me to ask Dr. Behforouz, my kind mentor, to start research on the synthesis of anticancer drugs before I took his organic chemistry class. Start as early as possible, but wait long enough to find something you really enjoy and something you are capable of doing.

Please allow me to close with a few personal comments about myself. I am a Chemistry and Premedical Preparation major, and I am a Biology minor. Overall, I have enjoyed my chemistry research, but there were many trying and difficult times. I think it sort of comes with the territory. I must confess, however, that a few of my peers seemed to fair much better than I did in being able to obtain satisfactory results. Maybe that’s just a sign that organic chemistry doesn’t like me as much as I like it. 😊

This is just to say that I wish you the best in all of your endeavors, and especially in the exciting area of research you choose. I am sorry I could not be more helpful, but maybe just knowing that someone else cares enough about you to write a special introduction will make the journey a little easier. I surely hope that is the case, and so long, friends.

-Darric
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III. Acknowledgments

I would like to express my deepest sense of gratitude for Dr. Mohammad Behforouz. He kindly allowed me to be a part of his prestigious research group when he already had a sufficient number of students to fill the laboratory space provided to him by the university. After I joined his group, Dr. Behforouz selflessly took time to explain the concepts that needed clarifying from time to time. Dr. Behforouz also willingly shared his incredible knowledge of so many things besides organic chemistry. And perhaps something I will never forget, Dr. Behforouz gave me words of encouragement when he knew I was despondent about the progress of my project. He has excelled in every aspect of being a mentor, teacher, and a friend to me. Thank you, Dr. Behforouz.

As I already mentioned, Dr. Behforouz performs research that many organic chemists can only dream of doing. His noble goal of finding antitumor compounds that may someday cure you or me alludes to his great character. Dr. Behforouz has an insurmountable desire to aid the advancement of science, and his fortitude and work-ethic have been the tools he has used to reach his goals. Recently, I was honored enough to attend a recognition reception for Dr. Behforouz—he is the first faculty member at Ball State University to earn a patent for his research. This exemplifies Dr. Behforouz’s exceptional quality as an individual and as a scientist.

I also would like to thank Mrs. Wen Cai, who was instrumental in all the research presented in this work, and especially in the synthesis of the lavendamycin analog when success
was so necessary and important for all of us. She was always willing to take time from her busy schedule to help me, even when she was pressured by the work of her own projects. I am grateful to her as a scientist and a friend.

I want to say a great big “Thank You” to all the past, present, and future fellow members of Dr. Behforouz’s research team. The research of past students made my task much easier. The kindness of the present fellow-workers made my experience enjoyable. The work of future members may make my efforts more worthwhile, if my labor will ever become anything. I would especially like to thank Michele Etling, who aided me immensely in the synthesis of all new quinoline-5,8-dione compounds, and the Masters and Honors Thesis authors I cite in the procedures. Also, the format and content for this thesis was patterned after Anthony Rose’s Honors Thesis. Discussion of some of the chemistry was taken from Ervin Walter’s Honors Thesis. Thanks to everyone of you.

The Ball State University Department of Chemistry deserves much credit. All of the rich opportunities provided, all of the knowledge made accessible, and all the financial assistance offered have been very beneficial to me. My temporary home in the Chemistry Department has been quite wonderful.

The work that I have tried to do could not have been possible without the fiscal support of the National Institute of Health, the American Cancer Society, and Eli Lilly. I am thankful to all our financial providers.

Last, but far from least, I would like to thank my family and friends for all their moral support and prayers. It is wonderful to have so many others to care for you.
IV. Abstract

The synthesis of 7-butyramidoquinoline-5,8-dione-2-carboxylic acid, pyrrolidine 7-butyramidoquinoline-5,8-dione-2-carboxamide, and 7-N-butyryldemethyllavendamycin benzyl ester are reported. The carboxylic acid was synthesized from the commercially available 8-hydroxy-2-methylquinoline via nitration, reduction-butyrylation, oxidation to the dione and then to an intermediate aldehyde, followed by final oxidation to the product. Reaction of the acid with N-hydroxysuccinimide and then pyrrolidine afforded the ester. The lavendamycin analog was synthesized by condensation of the intermediate aldehyde and a tryptophan derivative. These three compounds can now be tested for biological activity. This will hopefully aid in the current structure-activity relationship studies being performed on the related quinones and lavendamycin analogs synthesized as chemotherapeutic agents.
V. Background Information on Lavendamycin

In 1981, the researchers at Bristol Laboratories found lavendamycin (1) in the fermentation broth of the aerobic, gram-positive bacterial microorganism \textit{Streptomyces lavendulae}.\textsuperscript{1,2} Isolation of the structurally and chemotherapeutically similar compound streptonigrin (2) from \textit{Streptomyces flocculus} had been reported in 1959 by Rao, \textit{et al.}\textsuperscript{3,4} Both lavendamycin and streptonigrin show potent anticancer and antimicrobial activity, but unfortunately both compounds are also highly cytotoxic.\textsuperscript{4}

\begin{center}
\begin{tikzpicture}
  % Drawing code for lavendamycin (1)
  % Drawing code for streptonigrin (2)
\end{tikzpicture}
\end{center}

In 1984, Kende and Ebetino, researchers at the University of Rochester, were the first to publish the synthesis of lavendamycin methyl ester.\textsuperscript{5,6} Their lavendamycin methyl ester was produced by using a Bischler-Napierski cyclodehydration to obtain a pentacyclic product which was converted to the final ester through a number of transformations. A $\beta$-methyl tryptophan
was used as an intermediate in their condensation. In 1985, Hibino et al were the second to report the synthesis of lavendamycin methyl ester. Their methodology made use of the Pictet-Spengler condensation reaction between a quinoline analog and β-methyl tryptophan to acquire a pentacyclic intermediate. A several-step transformation was performed on the intermediate to give the final product. The same year, Boger’s research group published a third way to synthesize lavendamycin methyl ester. Their synthetic strategy involved twenty steps and gave an overall yield of less than 1%.

Dr. Behforouz reported the highly concise, five-step synthesis of lavendamycin methyl ester (9) in 1993 (Scheme 1). The overall yield of the procedure was 33%, and the methodology far superior since only a small number of stable intermediates are involved. A Diels-Alder condensation of bromoquinone 3 and the novel 1-azadiene 4 produces the AB ring system 5. The methyl group of the quinolinedione 5 is oxidized to aldehyde 6 via selenium dioxide. A Pictet-Spengler condensation of aldehyde 6 and β-methyl tryptophan (7) gives 7-N-acetyllavendamycin methyl ester (8). Sulfuric acid, water, and heat are used to hydrolyze 8 to the end product 9.

In 1996, Dr. Behforouz reported an even better synthesis of lavendamycin methyl ester. The starting material for the production of the AB ring portion of lavendamycin is the commercially available 8-hydroxy-2-methylquinoline (8-hydroxyquinaldine). The method has an excellent overall yield of 40%. The synthesis of 7-N-butyryldemethyllavendamycin benzyl ester utilizes this procedure (Scheme 2).

In addition, many of the lavendamycin analogs currently being synthesized by Dr. Behforouz’s group are made using this superb method. The analogs are then tested for biological
activity. The ongoing structure-activity relationship studies are focused on finding the relationship between the compound's structure and its biological activity.

**Scheme 1**

- Reaction 1: 3 + 4 → 5
  - Reagents: \( C_6H_5Cl \), Heat
  - Products: 5

- Reaction 2: 6 + 7 → 8
  - Reagents: Xylene, Reflux
  - Products: 8

- Reaction 3: 8 → 9
  - Reagents: \( H_2O, H_2SO_4 \)
  - Products: 9
VI. Quinoline-5,8-dione Importance

The 7-aminoquinolinedione segment of the more complex antitumor compounds lavendamycin (1), streptonigrin (2), and streptonigrone is suspected to play the most critical role in determining the anticancer activity of these compounds.\textsuperscript{10,11} The quinoline-5,8-dione compounds (10) in general have a wide spectrum of biological activity as antifungal, antibacterial, antitumor, antiasthmatic, and antiparasitic agents.

![Quinoline-5,8-dione structure](image)

Some new synthetic methodologies dealing with the quinoline-5,8-diones were recently reported by Dr. Behforouz.\textsuperscript{12} The new methods included the replacement of an amino group on a quinone ring by alkoxy groups, and the 1,2-addition of the ethyl group (instead of the expected 1,4-addition of the cyano group) of diethylaluminum cyanide to a quinolinedione.

The quinolinediones have been in the literature for decades, but the C-6- and/or C-7-substituted quinolinediones have been the compounds of most intense study. These substituents include functionalities such as amino, hydroxyl, thiol, and their derivatives, as well as alkyl, halogen, and nitro groups.\textsuperscript{12} Part of the synthesis described herein deals with modifying the C-2 position of the quinolinedione ring. It is hoped that such derivatives will lead to elucidation of the smallest, most potent pharmacophore of the lavendamycin structure.
VII. Biological Activity

As mentioned previously, the quinoline-5,8-dione portion of several antitumor compounds is critical, and perhaps essential, for biological activity. In fact, streptonigrin entirely loses its antitumor activity if the aminoquinone moiety is blocked as in azastreptonigrin.\(^{13}\) This important part of the lavendamycin compound is of particular interest as more data is accrued on the relationship of chemical structure to biological activity.

The cytotoxicity of the quinones, and of streptonigrin in particular, has been studied. Several biological mechanisms of action have been proposed, but there is no complete consensus within the scientific community on any given mechanism. The quinone reduction potential may be important and correlated to the compound’s demonstrated ability to cleave DNA.\(^{14}\) Some research has shown that the quinones may exert their effect through the electron transport system within the mitochondria.\(^{4,13,15,17}\) The hydroxyl radical is thought to be particularly important. A commonly seen mechanism\(^{15}\) is given below:

\[
\begin{align*}
[1] & \quad QQ + \text{NADH} + H^+ \rightarrow QQH_2 + \text{NAD}^+ \\
[2] & \quad QQH_2 + O_2 \rightarrow QQH' + \text{HO}_2' \\
[3] & \quad \text{HO}_2' \leftrightarrow H^+ + \text{O}_2' \\
[4] & \quad 2\text{O}_2' + 2H^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \\
[5] & \quad \text{O}_2' + \text{H}_2\text{O}_2 \rightarrow \text{HO}^' + \text{HO}^- + \text{O}_2 \\
[6] & \quad 2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \text{ (in the presence of the enzyme catalase)}
\end{align*}
\]
Since the biological activity may depend on the quinoline-5,8-dione portion of the lavendamycin molecule, the synthesis of quinolinedione analogs with modifications at the C-2 and C-7 positions was performed. It is hoped that a better understanding of these groups’ importance will be achieved as more and more data become available. Ideally these studies will lead to the synthesis of a small, soluble, potent, nontoxic chemotherapeutic drug.

Structure-activity relationship studies on the larger lavendamycin analogs have become much more feasible because of Dr. Behforouz’s concise synthetic methodologies with good overall yields.

![Chemical Structure](image)

Analogs showing excellent results against oncogene-transformed cell lines

<table>
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<tr>
<th>Analog</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
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<th>K/1</th>
<th>H/1.2</th>
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</tr>
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<td>CO₂C₈H₁₇ - n</td>
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<td>0.25</td>
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<td>9.00</td>
<td>&gt;33</td>
</tr>
</tbody>
</table>

These studies, along with similar studies on quinolinediones, have, in fact, been taking place for several years with collaborators at the National Institute of Health, Eli Lilly, and others.

Certain lavendamycin analogs seem to be especially active against ras<sup>k</sup> tumor cells. A few examples are given above, where compounds 11, 12, 13, and 14 have 3, 9, 18, and 130 fold
activity against \( \text{ras}^K \) oncogene transformed cells.\(^{18} \) To date, the structure-activity relationship studies have shown that the amide and ester functional groups at the C-2' position endow the compound with a great deal of biological activity. The various analogs synthesized by members of Dr. Behforouz's group should aid in the further identification of the particular groups and positions that are most important.
VIII. Total Synthesis of Quinolinediones 21 and 23 and Lavendamycin Ester 26

Quinolinediones 21 and 23

The compounds 21 and 23 were prepared according to Scheme 2.

Scheme 2
8-Hydroxy-2-methylquinoline (8-Hydroxyquinaldine) (15) is commercially available from Aldrich Chemical Company. A nitration of this compound in concentrated nitric/sulfuric acid solution gave dinitro 16. The hydroxyl of 15 is an ortho-para directing activator, so the nitro groups perform an electrophilic attack on the ring via the nitronium cation. The pyridine ring is not nitrated because of its low electron density and because of the nitrogen's electronegativity. The reaction is quite exothermic and should be performed in an ice bath.

The ammonium chloride salt was made by the reduction of dinitro 2 in a Parr hydrogenator with hydrogen gas, palladium charcoal, and HCl for at least 24 hours. The acid was used to convert the free amino groups to ammonium chloride salts (dihydrochloride salts) since the electron donating nature of the amino groups on the aromatic ring make them susceptible to air oxidation. Sodium acetate (NaOAc) and sodium sulfite (Na2SO3) were added directly to the ammonium chloride salt solution. Sodium acetate’s role is to act as a base to liberate the basic amino groups from the salt. In other words, sodium acetate deprotonates the ammonium ion to change the salt into the free amine. The sodium sulfite is both a base and an antioxidant. The basic properties of Na2SO3 allow it to convert the dihydrochloride salt to the
free amine. Sodium sulfite acts as an antioxidant because it is a source for the production of SO₂ in solution, which is rather susceptible to air oxidation; therefore, the SO₂ is oxidized before the compound. The last reagent added to the salt solution is butyric anhydride. The nucleophilic attack of the amino groups on the carbonyl carbons of butyric anhydride give product 18.

A solution of potassium dichromate in glacial acetic acid was used to oxidize 18 to quinolinedione 19. The aqueous reaction mixture was extracted with dichloromethane and the organic extracts were neutralized with a 3-10% sodium bicarbonate (NaHCO₃) solution. The neutralized organic extracts were rotary evaporated to dryness.

Selenium dioxide in a wet dioxane solution was used to oxidize quinolinedione 19 to aldehyde 20. An argon system must be used to protect the reaction mixture, and the complete conversion to 20 may take a day or more. Only the methyl group of the dione is successfully oxidized to the aldehyde. This is accomplished by the formation of an unstable oxide of selenium when the selenium dioxide reacts with water.

Sodium perborate tetrahydrate (NaBO₃•4H₂O) was added to a glacial acetic acid suspension of aldehyde 20. The suspension was heated slightly, and the reaction typically took no longer than a couple of hours to run to completion. The solid carboxylic acid 21 was isolated by vacuum filtration.

The acid was dissolved in DMF and the solution was cooled in an ice bath. Then, DCC (dicyclohexylcarbodiimide) and N-hydroxysuccinimide were added. After several hours in the ice bath, the solution was vacuum filtered to remove the urea and other possible insoluble side
products. The resulting reactive intermediate 22 was not isolated, so the solution was taken to the next step.

The addition of pyrrolidine to the solution containing the N-hydroxysuccinimide ester resulted in an immediate change in color from yellow to red. The amide was then isolated by vacuum pump distillation that took several hours. The red compound could be further purified by column chromatography, but a quick work-up was necessary to avoid formation of other products from the once-pure column fractions.

7-N-Butyryldemethylavendamycin Benzyl Ester (26)

Pentacyclic lavendamycin derivatives may be synthesized by performing a Pictet-Spengler condensation of a quinolinedione aldehyde and a tryptophan, both fully functionalized before the reaction. Care must be exercised to make certain of the purity of the reactants and the solvents. A spiroindolenine intermediate is thought to occur in the reaction pathway of a Pictet-Spengler condensation.19

Lavendamycin ester 26 was synthesized following Scheme 3.

Scheme 3
According to Scheme 3 above, aldehyde 20 was reacted with L-tryptophan benzyl ester (25) through the Pictet-Spengler condensation to produce a lavendamycin analog. The commercially available tryptophan hydrochloride salt (24) was suspended in ethyl acetate (EtOAc). The free amine was liberated by careful addition of 14% NH$_4$OH. The organic layer was washed with water until both it and the washings have a pH of 7. Rotary evaporation initially yields an oil, but a solid, white compound eventually is obtained. This product is dried and reacted with aldehyde 20 to produce 7-N-butyryldemethyllavendamycin benzyl ester (26).
IX. Experimental Section

A. General Information

Reagents: 8-Hydroxy-2-methylquinoline, 5% palladium on charcoal, butyric anhydride, selenium dioxide, N-hydroxysuccinimide, L-tryptophan benzyl ester hydrochloride, and N-dicyclohexylcarbodiimide were purchased from the Aldrich Chemical Company.

Solvents: 1,4-Dioxane and xylene were dried and distilled before use. All other solvents were reagent grade and were not distilled.

NMR Spectra: $^1$H NMR were recorded on a Varian Gemini 200 spectrometer in deuterated chloroform (CDCl$_3$) or dimethyl-d$_6$ sulfoxide (DMSO-d$_6$) with residual chloroform (CHCl$_3$, $\delta$ 7.24 ppm), dimethyl-d$_6$ sulfoxide (DMSO-d$_6$, $\delta$ 2.49 ppm), or tetramethylsilane (TMS, $\delta$ 0.00 ppm) as the internal standards.

Thin-Layer Chromatography: Eastman silica gel thin-layer chromatography strips and sheets with fluorescent indicator were used to monitor reactions and to determine product purity.

B. Solvent Purification

1,4-Dioxane’s tendency to polymerize and to contain free radical impurities made the purification and drying of this solvent necessary. Two similar procedures were used for this process. The older procedure required refluxing the solvent over potassium hydroxide (KOH), filtering or decanting the solvent, and then refluxing it over sodium spheres until the spheres
appeared shiny and metallic. Benzophenone was then added, and if a blue color was achieved, the solvent was simple-distilled. The newer procedure skipped the reflux over potassium hydroxide and the subsequent filtration or decantation step. It is important to note, however, that the solvent should be used the same day it is purified with either procedure for best results.

The solvent used for the condensation reaction, xylene, was dried and purified. First, xylene was refluxed over sodium spheres in a medium-sized still. Then, benzophenone was added. When the mixture turned blue the purified solvent was collected.

C. Procedures

**Preparation of 8-Hydroxy-2-methyl-5,7-dinitroquinoline (16)**

This procedure was similar to that reported by Mark G. Stocksdale.\(^{20}\)

In a 500 ml ice bath-cooled Erlenmeyer flask, equipped with a magnetic stir bar, was placed 210 ml of concentrated nitric acid. While stirring, 90 ml of concentrated sulfuric acid was added slowly. (These steps are equivalent to adding 300 ml of 70% v/v concentrated nitric acid - concentrated sulfuric acid solution to the 500 ml Erlenmeyer flask.) Stirring continued while the solution remained in the ice bath. To this solution, 8-hydroxy-2-methylquinoline (8-hydroxyquinaldine is the trade name for the same compound) (15; 30.00 g, 0.188 mol) was added in small portions over a ten minute period. Upon addition of the 8-hydroxy-2-methylquinoline, a brownish-red gas was evolved. The mixture was continually stirred in the ice bath for three hours and fifteen minutes. The resulting black-red solution was then poured into a 2 L beaker containing 800 ml water and 400 ml of ice and was stirred vigorously with a glass stirring rod. A bright yellow precipitate in an orange solution was obtained after allowing the precipitate to
settle. The precipitate was filtered using a water aspirator and was left on the filter paper in the Buchner funnel overnight. The precipitate was washed with 300 ml 95% ethanol and then was washed with 300 ml diethyl ether two times (600 ml diethyl ether total). The resulting 8-hydroxy-2-methyl-5,7-dinitroquinoline (16) was air-dried on the filter paper in the hood and massed 26.94 g (57.4%): \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 9.65 (1H, d, \(J = 9.1\) Hz, C-4H), 9.19 (1H, s, C-6H), 8.13 (1H, d, \(J = 9.1\) Hz, C-3H), 2.94 (3H, s, C-2CH\(_3\)).

**Preparation of 5,7-Dibutyramido-8-butyroxy-2-methylquinoline (18)**

This procedure was similar to that reported by Mark G. Stocksdale,\(^2\) but was scaled up two times.

In a 500 ml heavy-walled hydrogenation bottle, 8-hydroxy-2-methyl-5,7-dinitroquinoline (16; 10.00 g, 0.04 mol) and 5% palladium on charcoal (3.00 g) were suspended in 200 ml of water and 24 ml of concentrated hydrochloric acid. This mixture shook under 30 psi of hydrogen for about 45 hours, with a decrease in pressure over time. The catalyst was filtered off using a water aspirator, and the filter cake should be washed with some water. The dark red solution (with a yellow tint, especially if it forms a thin film on the glassware) containing the dihydrochloride salt of 5,7-diamino-8-hydroxy-2-methylquinoline (17) was placed in a 1000 ml round-bottomed flask (rinsing the glassware to complete transfer increased the volume to the point the solution would not fit in a 500 ml flask) with a magnetic stir bar. To this stirred solution was added in sequence as quickly as possible, sodium sulfite (Na\(_2\)SO\(_3\); 24.00 g), sodium acetate (NaOAc; 32.00 g), and butyric anhydride [(CH\(_3\)CH\(_3\)CH\(_2\)CO)\(_2\)O; 130 ml)]. The thick
whitish precipitate which continued to form over four hours and forty-five minutes was filtered using a water aspirator and was washed with a total of 800 ml of water in the filtration apparatus. The product was eventually dried between paper towels and left in the hood overnight. The whitish compound (18) massed 14.24 g (88.8%) and had NMR peak values significantly different from those reported by Stocksdale. An error in referencing to the DMSO peak, since the spectrum (see Appendix A) is complex and crowded around δ 2.55 - 2.30, may be part of the reason for the discrepancy (those reported here are for the spectrum in Appendix A). Another contributor to the differences could be the impurity of the sample: \(^{1}\)H NMR (DMSO-d\(_6\)) δ 9.75 (1H, s, C-7NH), 9.50 (1H, s, C-5NH), 8.15 (1H, s, C-6H), 8.09 (1H, d, J = 8.1Hz, C-4H), 7.38 (1H, d, J = 85 Hz, C-3H), 2.71 (3H, s, C-3CH\(_3\)), 2.50 - 2.30 (4H, m, 2NHCOC\(_2\)CH\(_2\)CH\(_3\)), 2.20 (2H, t, J = 7.3 Hz, OCOCH\(_2\)CH\(_2\)CH\(_3\)), 1.80 - 1.60 (4H, m, 2NHCOC\(_2\)CH\(_2\)CH\(_3\)), 1.60 - 1.40 (2H, m, OCOCH\(_2\)CH\(_2\)CH\(_3\)), 1.03 - 0.94 (6H, m, 2NHCOC\(_2\)CH\(_2\)CH\(_3\)), 0.90 (3H, t, J = 7.3 Hz, OCH\(_2\)CH\(_2\)CH\(_3\)).

Preparation of 7-Butyramido-2-methylquinoline-5,8-dione (19)

This procedure was similar to that reported by Mark G. Stocksdale.\(^{20}\)

In a 1000 ml Erlenmeyer flask, equipped with a magnetic stir bar, 5,7-dibutyramido-8-butyroxy-2-methylquinoline (18; 3.29 g, 8.25 mmol) was suspended in 122 ml of glacial acetic acid. Potassium dichromate (K\(_2\)Cr\(_2\)O\(_7\); 8.80 g, 0.03 mol) was added directly to the solution. Both massing dishes were rinsed with water poured from a graduated cylinder that contained 115 ml of water to aid in quantitative transfer of the reagents. The remainder of the 115 ml of water
was added to the reaction solution. A watchglass was placed over the mouth of the Erlenmeyer in order to prevent the solution from splashing out of the container since it was stirred as vigorously as possible. After waiting two hours, 70 ml of CH₂Cl₂ was added to the solution.

The resulting two-phase solution was stirred for 22 hours, and then poured into a 1 L separatory funnel. After the solution separated, the organic layer (bottom layer) was released into a 1000 ml Erlenmeyer flask (which will contain all the organic layers eventually). The water layer was then extracted with CH₂Cl₂ (12 x 50 ml). On extractions 7-12, 50 ml of a saturated NaCl solution was added after the CH₂Cl₂ each time (the order of addition is not important). The combined organic extracts were washed with 3 x 200 ml 10% NaHCO₃ (add 100 g NaHCO₃ to 1000 ml of water to make 1 L of 10% NaHCO₃) and both layers were saved. The water layers were extracted with 2 x 50 ml of CH₂Cl₂ and 50 ml saturated NaCl solution was added on the first extract only. The two approximately 50 ml CH₂Cl₂ extracts were combined, neutralized with 200 ml 10% NaHCO₃, and then added to the original CH₂Cl₂ extracts from the 12 original extractions. This final CH₂Cl₂ solution was dried with MgSO₄, and then filtered with a water aspirator and sintered-glass filter. The filter cake was rinsed with CH₂Cl₂ two times. The resulting orange-yellow solution was rotary evaporated to yield a light yellow solid with an orange-red impurity.

After vacuum drying, the solid (19) massed 1.60 g (75.1%): ¹H NMR (CDCl₃) δ 8.37 (1H, br s, C-7NH), 8.28 (1H, d, J = 8.1 Hz, C-4H), 7.89 (1H, s, C-6H), 7.53 (1H, d, J = 8.1 Hz, C-3H), 2.74 (3H, s, C-2CH₃), 2.48 (2H, t, J = 7.4 Hz, C-7NCOCH₂CH₂CH₃), 1.84 - 1.66 (2H, m, C-7NCOCH₂CH₂CH₃), 0.99 (3H, t, J = 7.4 Hz, C-7NCOCH₂CH₂CH₃).
Preparation of 7-Butyramido-2-formylquinoline-5,8-dione (20)

This procedure was similar to that reported by Mark G. Stockdale.\textsuperscript{20} Yields up to 120\% were recorded, but this procedure is similar to the reference and gives a decent yield.

In a 25 ml round-bottomed flask, equipped with a magnetic stir bar, water-cooled reflux condenser, and an argon filled balloon, recrystallized 7-butyramido-2-methylquinoline-5,8-dione (19; 0.516 g, 2 mmol), selenium dioxide (SeO\textsubscript{2}; 0.255 g, 2.3 mmol), 12 ml of dried distilled 1,4-dioxane, and 0.25 ml of water were stirred and slowly heated to reflux over one hour. The final temperature should be close to 120-130 °C. The solution was refluxed for 65 hours and 45 minutes. The selenium metal was allowed to settle, and the supernatant solution was pipetted off and filtered. Dried, distilled 1,4-dioxane (10 ml) was added to the selenium metal still in the 25 ml round-bottomed flask, and the solution was magnetically stirred and refluxed for ten minutes. The entire mixture was filtered and the selenium on the filter paper was washed with about 10 ml CH\textsubscript{2}Cl\textsubscript{2}. All filtrates were put in a beaker along with the filter paper, and everything was heated on a steam cone until boiling. The solution was then refiltered with a fresh filter paper, and the selenium was washed with CH\textsubscript{2}Cl\textsubscript{2}. (If the next reaction is to be the conversion of this aldehyde to the corresponding acid, the solution can be rotary evaporated and dried under 40-50 °C heat on the vacuum pump for several days.) This solution was diluted with 50 ml of CH\textsubscript{2}Cl\textsubscript{2} and neutralized with 2 x 50 ml 3\% NaHCO\textsubscript{3}. Organic and water layers were both saved. The water layers were combined and extracted with 50 ml of CH\textsubscript{2}Cl\textsubscript{2}. The approximately 50 ml CH\textsubscript{2}Cl\textsubscript{2} extract was neutralized with 30 ml of 3\% NaHCO\textsubscript{3}, and then it was added to the original CH\textsubscript{2}Cl\textsubscript{2} extracts from the first neutralizations. This final CH\textsubscript{2}Cl\textsubscript{2} solution was dried with MgSO\textsubscript{4}, and
then filtered with a water aspirator and a sintered-glass filter. The filter cake was rinsed with 
CH$_2$Cl$_2$. The resulting solution was rotary evaporated to yield a yellow-orange solid. After 
vacuum drying overnight, the solid massed 0.422 g (77.6%): $^1$H NMR (CDCl$_3$) $\delta$ 10.29 (1H, s, 
C-2CHO), 8.62 (1H, d, $J$ = 8.1 Hz, C-4H), 8.39 (1H, br s, C-7NH), 8.31 (1H, d, $J$ = 8.0 Hz, C-
3H), 8.06 (1H, s, C-6H), 2.52 (2H, t, $J$ = 7.4 Hz, C-7NHCOCH$_2$CH$_2$CH$_3$), 1.90 - 1.70 (2H, m, C-
7NHCOCH$_2$CH$_2$CH$_3$), 1.02 (3H, t, $J$ = 7.4 Hz, C-7NHCOCH$_2$CH$_2$CH$_3$).

**Preparation of 7-Butyramidoquinoline-5,8-dione-2-carboxylic acid (21)**

This procedure was similar to that performed in the reference cited below.$^{22}$ Yields up to 
160.3% were recorded, but this procedure gives a more believable yield.

In a 5 ml round-bottomed flask equipped with a miniature magnetic stir bar, 7-
butyramido-2-formylquinoline-5,8-dione (20; 0.1064 g, 0.39 mmol) and 1.0 ml glacial acetic acid 
(AcOH, unpurified) were placed while the silicon oil bath was warming up. When the 
temperature reached 75-85 °C, addition of 0.3016 g sodium perborate tetrahydrate (NaBO$_3$$\cdot$4H$_2$O) 
in four portions over 30 minutes was begun. Compound 20 dissolved partially (the solution 
appears more like a suspension than a solution for the entire reaction) only after addition of the 
first portion of NaBO$_3$. The solution turned from yellow-brown to orange-brown shortly after the 
first portion was added, so the heat was removed but stirring was continued. Almost 
immediately before the addition of the second NaBO$_3$ portion, 0.5 ml AcOH was added. 
Approximately two minutes later, another 0.5 ml AcOH was added. After addition of the final 
sodium perborate portion, the reaction was left stirring for another 1 hour and 30 minutes. At the
end of this time period, since a total of 2.0 ml AcOH was used for the reaction, 2.0 ml H₂O was added to the reaction mixture. After about five minutes of stirring, the solution was filtered using the water aspirator. The filtrate was poured back into the reaction vessel, and a spatula was used to scrape the sides of the round-bottomed flask. This suspension was filtered using the same filtration apparatus as previously (including the same filter paper). Other attempts were made to increase the yield, but seemingly the most significant amount of product is the filter cake. The light, bright yellow compound (21) massed 0.0745 g (66.1%): IR (KBr) 3384, 3315, 3221, 1680, 1654, 1506, 1464, 1414, 1387, 1323, 1204, 894, 800, 724 cm⁻¹; ¹H NMR (DMSO-d₆) δ 10.01 (1H, s, C-7NH), 8.47 (1H, d, J = 8.1 Hz, C-4H), 8.36 (1H, d, J = 8.1 Hz, C-3H), 7.80 (1H, s, C-6H), 2.59 (2H, t, J = 7.3 Hz, C-7NHCOCH₂CH₂CH₃), 1.70 - 1.50 (2H, m, C-7NHCOCH₂CH₂CH₃), 0.90 (3H, t, J = 7.3 Hz, C-7NHCOCH₂CH₂CH₃).

**Preparation of Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide (23)**

All glassware should be oven-dried. Reagents were dried as specified. N,N-Dimethyl formamide (DMF) was dried over 4 Å molecular sieves. About 50 ml pyrrolidine was poured into a 125 ml Erlenmeyer flask and 5.0 g magnesium sulfate (MgSO₄) was added. After shaking and stoppering the flask, it was allowed to sit overnight. The pyrrolidine was decanted into a 100 ml round-bottomed flask with 2.0 g CaH₂, then fractionally distilled (boiling point 87-88 °C). The 100 ml receiving flask was stoppered with a rubber septum and placed under an argon (Ar) system. To a 50 ml round-bottomed flask was added 0.1445 g 7-butyramidoquinoline-5,8-dione-2-carboxylic acid (21; 0.5 mmol), 10 ml DMF, and a miniature stir bar. The reaction flask was
placed under an Ar system, and the solution was stirred and heated at 70 °C until a clear solution was obtained. The heat was then removed, and the flask was allowed to cool under Ar in an ice bath. After more than an hour of cooling, N-hydroxysuccinimide (0.058 g, 0.5 mmol) and 1,3-dicyclohexylcarbodiimide (DCC; 0.110 g) were added and the reaction solution was allowed to stir overnight under Ar and on ice. The solution was then filtered, and the filtrate containing product 22 was poured into a clean, dry 50 ml round-bottomed flask. The product was not isolated. The solution containing 22 was stirred under Ar in an ice bath. Pyrrolidine (about 0.05 ml, 1.1 equivalents) was added, and the solution turned deep red immediately. The reaction was allowed to stir, and then the 50 ml round-bottomed flask containing the red solution was placed on a short-path distillation apparatus equipped for vacuum distillation. This room-temperature distillation took 2-3 hours, after which the compound was placed directly on the vacuum pump to dry. The compound was removed from the vacuum pump and 10 ml diethyl ether was added to the reaction flask. The compound was then scraped against the sides of the flask and filtered with additional ether rinsings. This afforded the dark purple compound 23, which was placed on the vacuum pump to dry for a few days and massed 0.1187 g (69.4%). The dried compound was suspended in a 5% methanol in ethyl acetate solution, and then filtered following concentration with an argon stream. The filtrate was run through a column for further purification (it is important to work up the desired fractions soon after collecting from the column so that impurities do not interfere with purification); the yield after the suspension and column chromatography dropped to 7.0%: IR (KBr) 3377, 3217, 2965, 2875, 2370, 1715, 1679, 1624, 1565, 1543, 1479, 1432, 1306, 1197, 1098, 1023, 802 cm⁻¹; the ¹H NMR spectrum of this
compound located in Appendix A is difficult to interpret, but it appears as though 23 was successfully synthesized; $^1$H NMR (CDCl$_3$) $\delta$ 8.33 (1H, d, $J = 8.1$ Hz, C-4H), 8.03 (1H, d, $J = 8.1$ Hz, C-3H), 7.67 (1H, s, C-6H), 3.80 - 3.50 (4H, m) may be due to CONCH$_2$ of the pyrrolidine ring, 2.44 (2H, t, $J = 7.5$ Hz, C-7NHCOCH$_2$CH$_2$CH$_3$), 2.10 - 1.80 (4H, m) may be due to CONCH$_2$CH$_2$ of the pyrrolidine ring, 1.80 - 1.60 (2H, m, C-7NHCOCH$_2$CH$_2$CH$_3$), 0.99 (3H, t, $J = 7.3$ Hz, C-7NHCOCH$_2$CH$_2$CH$_3$).

**Preparation of L-Tryptophan Benzyl Ester (25)**

Prepared 14% NH$_4$OH by adding 5 ml concentrated NH$_4$OH (assay 28.7%) to a 25 ml Erlenmeyer flask and then diluting with 5 ml water. Added the commercially available L-tryptophan benzyl ester hydrochloride salt (24; 0.9920 g, 3 mmol) to a 2-necked, 250 ml round-bottomed flask equipped with a stir bar. Next, 60 ml ethyl acetate (EtOAc) was added to the flask and stirring was begun. Stirring was continued for a minute or two without successful dissolution of the compound, and then 14% NH$_4$OH (1.7 ml) was slowly added to obtain a clear solution. Upon termination of stirring, a white precipitate was noticed, so 0.5 - 2.0 ml water was added with concomitant dissolution of the precipitate. Since this result was an indicator that the precipitate was NH$_4$Cl, the procedure was continued. Working quickly, the solution was poured into a 125 ml separatory funnel and the bottom aqueous layer was removed. The organic layer was washed with water (7 x 9 ml) until both the organic and aqueous layers had a pH of about 7. The resulting organic layer was dried over MgSO$_4$ in the refrigerator. From this point forward, all glassware was oven-dried before use. The cold MgSO$_4$ solution was filtered through cotton
into a 100 ml round-bottomed flask. A few ml of EtOAc was used to aid in quantitative transfer of the compound. The solution was rotary evaporated—at first an oily substance appeared, but the white, solid compound 25 eventually emerged. After drying on the vacuum pump, the white to off-white 25 massed 0.9351 g (106.0%): $^1$H NMR (CDCl$_3$) $\delta$ 8.01 (1H, br s, N-1H), 7.54 (1H, d, $J$ = 7.7 Hz, C-4H), 7.20 (1H, m, C-7H), 7.30 - 7.12 and 7.06 - 6.98 (5H, m, C$_6$H$_5$), 7.12 - 7.06 (2H, m, C-5H and C-6H), 6.86 (1H, d, C-2H), 5.04 (2H, s, CO$_2$CH$_2$C$_6$H$_5$), 3.80 (1H, m, C-3CH$_2$CH(NH$_2$)CO$_2$), 3.30 - 2.90 (2H, m, C-3CH$_2$CH(NH$_2$)CO$_2$).

**Preparation of 7-N-Butyryldemethyllavendamycin Benzyl Ester (26)**

All glassware was oven-dried prior to use. 7-Butyramido-2-formylquinoline-5,8-dione (20; 0.0693 g, 0.25 mmol), a magnetic stir bar, L-tryptophan benzyl ester (25; 0.0759 g, 0.26 mmol), and 100 ml dry xylene were added to a three-necked 250 ml round-bottomed flask under an argon flow and equipped with a Dean-Stark collector connected to an oil bubbler. The reaction was stirred and heated to 130 °C over an hour. The reaction was monitored by TLC (5 ml CH$_2$Cl$_2$ + 10 drops CH$_3$OH). At about 16 hours, a precipitate started forming in the reaction flask (it was cloudy before this), so the reaction was stopped and left under argon until the solution was transferred to a 24/40-necked, 250 ml round-bottomed flask. The reaction mixture was rotary evaporated to dryness, then about 10 ml acetone (CH$_3$COCH$_3$) was added, and the flask was left open in the hood for approximately 5½ hours. The solution was then filtered using the water aspirator, and the 250 ml round-bottomed flask was rinsed with some acetone. The filtrate and the 25 ml filtration flask were removed and placed open in the hood to dry overnight.
A clean 125 ml filtration flask was connected to the filter funnel containing the filter cake, and the filter cake was rinsed with some acetone and then with hexanes. This filtrate was discarded, but the filter cake was placed in a very small round-bottomed flask to dry on the vacuum pump overnight. After drying, the orange-brown compound 26 massed 0.0306 g (22.0%). After drying in the hood, the saved filtrate was suspended in acetone and refiltered. This filter cake and the dried 26 were placed in separate small vials and stored: IR (KBr) 3377, 3332, 3308, 2964, 2875, 1731, 1704, 1648, 1587, 1500, 1334, 1309, 1263, 1221, 1119, 886, 863, 740, 698 cm⁻¹; the ¹H NMR spectrum of this compound located in Appendix A is difficult to interpret with respect to the CO₂CH₂C₆H₅ hydrogens, but it appears as though they may be in the 7.80 - 7.20 region; due to the complexity and crowding of this area in the spectrum, these five hydrogens are not assigned; ¹H NMR (CDCl₃) δ 11.80 (1H, br s, -NH), 9.17 (1H, d, J = 8.4 Hz, C-4H), 8.95 (1H, s, C-3'H), 8.53 (1H, d, J = 8.4 Hz, C-3H), 8.40 (1H, br s, C-7NH), 8.21 (1H, d, J = 7.8 Hz, C-12'H), 7.99 (1H, s, C-6H), 7.70 (1H, d, J = 4.4 Hz, C-9'H), 7.61 (1H, t, J = 8.4 Hz, C-10'H), 7.44 (1H, t, J = 6.8 Hz, C-11'H), 5.54 (2H, s, C-2'CO₂H₂), 2.53 (2H, t, J = 7.3 Hz, C-7NHCOCH₂CH₂CH₃), 1.82 (2H, m, C-7NHCOCH₂CH₂CH₃), 1.06 (3H, t, J = 7.3 Hz, C-7NHCOCH₂CH₂CH₃).
# Appendix A — Spectra

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Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide (23)  
(\textsuperscript{1}H NMR—Close-up Spectrum of \(\delta 2.20 - 0.60\) with Integration and Labeled Peaks)

Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide (23)  
(IR—Full Spectrum)

Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide (23)  
(IR—Full Spectrum with Labeled Peaks)

L-Tryptophan benzyl ester (25)  
(\textsuperscript{1}H NMR—Full Spectrum with Integration)

L-Tryptophan benzyl ester (25)  
(\textsuperscript{1}H NMR—Close-up Spectrum of \(\delta 8.20 - 6.60\) with Integration and Labeled Peaks)

7-N-Butyryldemethylavendamycin benzyl ester (26)  
(\textsuperscript{1}H NMR—Full Spectrum with Integration)

7-N-Butyryldemethylavendamycin benzyl ester (26)  
(\textsuperscript{1}H NMR—Full Spectrum with Labeled Peaks)

7-N-Butyryldemethylavendamycin benzyl ester (26)  
(IR—Full Spectrum)

7-N-Butyryldemethylavendamycin benzyl ester (26)  
(IR—Full Spectrum with Labeled Peaks)
8-Hydroxy-2-methyl-5,7-dinitroquinoline
5,7-Dibutylamido-8-butyroxy-2-methylquinoline
7-Butyramido-2-methylquinoline-5,8-dione
7-Butyramido-2-formylquinoline-5,8-dione

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COHNN}^+\text{CHO}
\]
7-Butyramidoquinoline-5,8-dione-2-carboxylic acid
7-Butyramidoline-5,8-dione-2-carboxylic acid
7-Butyramidoquinoline-5,8-dione-2-carboxylic acid
Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{COHN} \quad 23
\]

\[
\text{Py} \quad \text{rr} \quad \text{ol} \quad \text{di} \quad \text{ne} \quad 7-\text{Bu} \quad \text{ty} \quad \text{ram} \quad \text{i} \quad \text{do} \quad \text{qu} \quad \text{in} \quad \text{o} \quad \text{l} \quad \text{i} \quad \text{ne} \quad 5,8-\text{dione} \quad 2-\text{carboxamide}
\]
Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide
Pyrroolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide
Pyrrolidine 7-Butyramidooquinoline-5,8-dione-2-carboxamide

CH₃CH₂CH₂CONH
N

O

O
Pyrroldine 7-Butiramidoquinoline-5,8-dione-2-carboxamide
Pyrrolidine 7-Butyramidoquinoline-5,8-dione-2-carboxamide

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{COHN} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{N} \]

IR Spectra

\%T vs. cm\(^{-1}\):

- 3376.71
- 3217.47
- 2964.93
- 2874.98
- 2369.86
- 2259.96
- 1812.65
- 1781.42
- 1714.85
- 1678.77
- 1624.49
- 1542.22
- 1431.88
- 1304.45
- 1298.45
- 1260.84
- 1252.37
- 1196.55
- 1125.32
- 1097.69
- 1063.28
- 1022.53
- 1000.00

Wavenumber range: 600.00 to 600.0 cm\(^{-1}\)
L-Tryptophan benzyl ester
L-Tryptophan benzyl ester
CH₃CH₂CH₂COH-CH₃

7-N-Butyryldemethyllavendamycin benzyl ester
7-N-Butyldemethylavendamycin benzyI ester
7-N-Butyryldemethyllavendamycin benzyl ester
7-N-Butryrydemethyllavendamycin benzyl ester
Appendix B — Research Presentations

Some of the material in this thesis has been presented to various audiences. A presentation was made for the Ball State Chemistry Department in the Summer Research Program for two consecutive years. The work was also presented at the Indiana Academy of Science’s 113th Annual Meeting held at Saint Joseph’s College on October 30-31, 1997.
X. Works Cited


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