Total Synthesis of 7-N-Succinyldemethyllavendamycin Esters

An Honors Thesis

by

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Abstract

7-N-Succinyl demethyl lavendamycin esters—analogs of the naturally occurring, anti-tumor, anti-microbial agent lavendamycin—were synthesized by a six step pathway. These analogs were chosen for their possible biological activity and their solubility in pharmaceutical solvents. NMR spectra, mass spectra, TLC, and melting point studies were performed on the final products and on each intermediate to verify structure and physical properties.
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1 Background

1.1 Lavendamycin

1.1.1 Discovery and Activity

In 1981, Doyle and associates reported the isolation of the compound known as lavendamycin (2) from a fermentation broth of *Streptomyces lavendulae* at Bristol Laboratories [6],[1]. The purified product was a dark red solid, mp > 300° dec. The compound exhibited very limited solubility in organic solvents. Consequently, an x-ray analysis was not possible. Through the use of UV spectroscopy, elemental analysis, mass spectroscopy, and NMR spectroscopy, the structure shown in figure 1 was determined. Lavendamycin (2) is closely related to streptonigrin (1) in structure and activity (figure 1). The reported isolation procedure for 2 was significantly complex and yielded only a small amount of crude product. Over 3000 liters of growth medium and bacteria were incubated for 170 hours. After extraction and several washings, 135 grams of crude product was isolated. Biological assays showed that lavendamycin demonstrated antimicrobial activity similar to streptonigrin but less potent. In addition, lavendamycin showed slight activity against a type of leukemia in mice.

![Figure 1: Streptonigrin and Lavendamycin](image)

1.1.2 Total Synthesis

After the discovery of lavendamycin by Doyle’s group, several groups began attempts at total synthesis. The total synthesis of lavendamycin methyl ester was first published by Kende’s group at the University of Rochester in 1984 [8], [9]. Their synthesis was composed of two key elements: a Friedländer condensation to synthesize the A and B rings of the final product, and a Bischler-Napieralski cyclodehydration to produce the skeleton of the pentacyclic product.

The next group to achieve the total synthesis of lavendamycin methyl ester was the Hibino group. In contrast to Kende’s group, Hibino used a Pictet-Spengler condensation
between β-methyl tryptophan methyl ester and an analog of quinoline [7]. Following the condensation, the additional functionality to the A ring. At the same time, several other groups were also continuing research with similar goals [4], [11].

Behforouz's group decided to take up this research using a slightly different approach. They would ultimately use the Pictet-Spengler condensation to form the full five-ring laven­
damycin, but the intermediate quinoline ring was synthesized via a Diels-Alder condensa­tion [3]. Additionally, the quinoline ring system was completely functionallized before entering the Pictet-Spengler condensation. This method rivaled previous syntheses in effi­ciency, conciseness, and practicality. Since then, Behforouz's group has developed an even more efficient pathway for the synthesis of the quinoline moiety (7) (figure 2 on the following page).

1.2 7-N-Acetyllavendamycin Esters

During the lavendamycin research, it was discovered that the 7-N-acyllavendamycin inter­mediate (9) was a more selective antitumor agent than 2 itself. This discovery prompted Behforouz's group to begin an in depth study of other lavendamycin analogs [2]. This was for two reasons. First, it was hoped that further activity increases would arise when other analogs were synthesized. Second, it was hoped that an in depth study of analogs and their activity would provide some insight into the mechanism by which 2 and its analogs function. Only through a complete structure-activity relationship study (SAR), could the active subunits of 2 be determined. The novel research discussed in this paper is a part of this ongoing study.

1.2.1 Total Synthesis

The central feature of the efficient synthesis used by Behforouz's group is the Pictet-Spengler condensation shown in figure 3 on page 4. By carefully choosing different tryptophan and quinoline components, a large number of lavendamycin analogs with a variety of functional characteristics can be synthesized. The following section discusses some of the results from biological testing of such compounds. These results appear to be quite promising.

1.2.2 Biological Activity

Since the start of the project, Behforouz's group has synthesized many different analogs of 2. Of these, several have shown excellent biological activity [2]. Specifically, acetyl analogs of 2 with methyl, i-amyl, and n-octyl esters showed 9-, 20-, and 130- fold selectivity against rasK transformed cells. This is extraordinary when compared with lavendamycin's 0.5 fold selectivity against the same cells.
Figure 2: Total Synthesis of Lavendamycin Methyl Ester
2 7-\textit{N}-SuccinylDemethyllavendamycin Esters

The novel research discussed in this paper deals with succinyl analogs of 2. Those are analogs in which \( R^1 = \text{NHCO(CH}_2\text{)_2CO}_2\text{H} \). This class of analogs was specifically chosen for two reasons. First, it is hoped that analogs of this type will exhibit even higher selective activity as anti-tumor agents. Second, it is hoped that the carboxyl group on the A ring of the lavendamycin will increase the solubility in polar solvents like water. This is because one of the main problems with the previous active analogs was their low solubility in common pharmaceutical solvents. Succinyl analogs may remedy that problem.

2.1 Total Synthesis

The overall pathway to the total synthesis of 7-\textit{N}-succinylDemethyllavendamycin esters is similar to the pathway for lavendamycin methyl ester shown in figure 2 on the preceding page with a few changes. The first step is a double nitration of 8-hydroxyquinaldine (3), a commercially available compound. Next, the aromatic nitro groups on 4 are reduced to amino groups and complexed with hydrogen chloride via a hydrogenation. Third, the 5,7-diamino-8-hydroxy-2-methylquinoline dihydrochloride salt (10) is reacted with succinic anhydride to form a disuccinamido quinoline (11). Fourth, 11 is oxidized with \( \text{K}_2\text{Cr}_2\text{O}_7 \) to the quinoline dione (12). Next, the methyl side chain of 12 is oxidized to an aldehyde with selenium dioxide. Finally, this aldehyde (13) is condensed with a tryptophan ester to form the lavendamycin analogs.

The complete pathway is shown in figure 4 on the next page. Differences between this pathway and the original synthesis of lavendamycin include substituting succinic anhydride for acetic anhydride in the acylation step. Additionally, the hydrogenation and Succinylation
Figure 4: Total synthesis of 7-\textit{N}-Succinyl\textit{demethyl}lavendamycin
are performed separately unlike in the synthesis of 2. This change was made because the succinylation must be performed in a different solvent than the hydrogenation. This requires that the intermediate be isolated. In the original pathway, the two steps were done one after the other in the same reaction flask.

During this research, two different 7-N-succinyldemethyllavendamycin esters were synthesized. First, 7-N-succinyldemethyllavendamycin i-amyl ester (16) was synthesized using 13 and tryptophan i-amyl ester. The tryptophan ester (14) in this case is not commercially available. It was synthesized via a standard Fischer esterification. The second analog synthesized was 7-N-succinyldemethyllavendamycin n-butyl ester (17). The tryptophan ester for this condensation is available from Aldrich in the form of a hydrochloride salt.

The two lavendamycin analogs and their intermediates were characterized using a variety of methods such as \(^{1}H\) NMR, \(^{13}C\) NMR, thin layer chromatography, and mass spectroscopy. Each intermediate demonstrated characteristics that agree with expectations. Biological testing of these compounds will take place in the future.

### 2.2 Selected Mechanisms

In this section, several of the reactions of the overall pathway will be discussed. The reaction that will not be discussed is the oxidation of 8-hydroxy-2-methyl-5,7-disuccinamidoquinoline by \(K_2Cr_2O_7\). That mechanism is not fully understood by the chemical community at this time. Other mechanisms come from standard organic textbooks, chemical literature, and the mind's of the author and other Ball State students.

#### 2.2.1 Nitration of 8-Hydroxyquinaldine

The nitration of 8-hydroxyquinaldine with HNO\(_3\) and H\(_2\)SO\(_4\) is a very standard reaction. The mechanism consists of two electrophilic attacks on the aromatic ring by NO\(_3^+\) (figure 5 on the following page). The first step in this mechanism is the protonation of nitric acid by sulfuric acid. Next, the protonated nitric acid loses water to form the nitronium cation. Electrophilic attack on the activated para- position followed by abstraction of a proton yields the singly substituted quinaldine. A second attack at the ortho- position yields the final product.

The attacks occur at the ortho- and para- positions because of the resonance electron donating effect of the hydroxyl group at position 8. Figure 6 on the next page shows the resonance structures of 8-hydroxyquinaldine. It is because the second and third cannoical forms have negative charges at the ortho- and para- positions that electrophilic attack is favored there. Once the first nitro group attaches to the aromatic ring, its meta- directing, combined with the ortho- para- directing of the hydroxyl group, guides the second nitro group to the 7 position.

The pyridine ring is not nitrated in this case because of the electron withdrawing effect of the nitrogen atom. The electron density of the pyridine ring is significantly reduced.
Figure 5: The mechanism of the nitration of 3

Figure 6: Activity of the quinaldine ring
and the ring has very low reactivity towards electrophilic attack. Additionally, the electron withdrawing of the nitrogen atom positively polarizes the pyridine ring further lowering its reactivity towards electrophiles. Figure 6 (b) shows this polarization [10].

2.2.2 Hydrogenation of 8-Hydroxy-2-methyl-5,7-dinitroquinoline

The reduction of 8-hydroxy-2-methyl-5,7-dinitroquinoline to 5,7-diamino-8-hydroxy-2-methylquinoline dihydrochloride salt is accomplished by reaction with hydrogen gas in the presence of palladium charcoal and acid. Figure 7 shows the mechanistic pathway. Each nitro group

![Mechanism of the hydrogenation of 8-hydroxy-2-methyl-5,7-dinitroquinoline](image)

is reduced in a similar manner. A nitrogen first abstracts a hydrogen atom from the surface of the catalyst. This leaves one oxygen bound to the surface of the catalyst. A hydrogen attacks this oxygen and frees it from the surface of the catalyst. Loss of a water, at this point, leaves NO. From here, addition of two more moles of hydrogen yields the free amine. Exactly which path the addition goes through is unknown. Finally, the free amino groups are protonated and complex with chloride ions in solution to produce 10.

2.2.3 Succinylation of 5,7-Diamino-8-hydroxy-2-methylquinoline Dihydrochloride Salt

The succinylation of 5,7-diamino-8-hydroxy-2-methylquinoline dihydrochloride salt is another standard reaction. The reaction is an amine acylation by an acid anhydride. The reaction mechanism contains several tetrahedral carbon intermediates (figure 8 on the next page). The NaOAc's role in the mechanism is to deprotonate the ammonium ion in order to convert the dihydrochloride salt into the free amine. The Na₂SO₃ has a dual role in the mechanism. Besides its function as a base in a similar manner as NaOAc, the Na₂SO₃ serves as an anti-oxidant to protect the free amine from oxidation. The hydroxyl group at position
Figure 8: The mechanism of the succinylation of 10

8 of the diamine may be converted to OR via a similar pathway, but this substitution does not effect the success of the next reaction.

2.2.4 Oxidation of 2-Methyl-7-succinamidoquinoline-5,8-dione

The oxidation of the methyl group of the 2-methyl-7-succinamidoquinoline-5,8-dione is an interesting reaction. The oxidizing reagent in the reaction is selenium dioxide. In 1960, Corey and associates studied the mechanism of oxidations similar to this one [5]. While their article mostly concerns the oxidation of methylenes to aldehydes in the presence of an α ketone, they also discuss to application of these reactions to the oxidation of methylated quinoline derivatives. The mechanism they proposed is shown in figure 9 on the following page. This reaction also produces water and elemental selenium as by products.

2.2.5 Pictet-Spengler Condensation

The Pictet-Spengler condensation is the key reaction in the total synthesis of 7-N-succinyl-demethylavendamycin. In 1978, the mechanism of this class of reactions was studied at the University of Wisconsin-Milwaukee [12]. That group proposed the existence of a spiroindole-nine intermediate during the condensation. The mechanism for the condensation based on their proposal is shown in figure 10 on page 11.
Figure 9: The mechanism of the oxidation of 12
Figure 10: The mechanism of the Pictet-Spengler condensation
2.3 Experimental Procedures

2.3.1 General Information

Reagents 8-Hydroxyquinaldine, succinic anhydride, selenium dioxide, and tryptophan n-buty1 ester ammonium chloride salt were purchased from the Aldrich Chemical Company. Tryptophan i-amyl ester was prepared previously by Nasrin Olang via the Fischer esterification method.

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

Melting Points Reported melting points were obtained on a Thomas-Hoover Capillary melting point apparatus and are uncorrected.

NMR Spectra $^1$H and $^{13}$C NMR Spectra were obtained on a Varian Gemini 200 spectrometer in $d$ - DMSO using the residual DMSO peak at 2.49 ppm as the standard.

Low Resolution Mass Spectra Low resolution MS were obtained in house on an Extrel ELQ 400 quadrupole instrument using EI ionization.

Thin Layer Chromatography TLC was used to determine qualitative purity of products and reaction completion. Eastman silica gel sheets with fluorescent indicator were used.

2.3.2 8-Hydroxy-2-methyl-5,7-dinitroquinoline (4)

To an ice-cooled erlenmeyer flask equipped with a magnetic stir bar was added HNO$_3$ (210 mL) and H$_2$SO$_4$ (90 mL). To this mixture, 8-hydroxyquinaldine (30.00 g, 0.188 mol) was added slowly. The reaction flask was cooled and stirred for 90 minutes and then added to 600 mL of ice water. The bright yellow precipitate was filtered and dried giving 35.37 g (75%) of product. $^1$H NMR ($d$-DMSO) $\delta$ 2.95 (s, 3 H), 8.16 (d, $J = 9.2$ Hz, 1 H), 9.22 (s, 1 H), 9.67 (d, $J = 9.0$ Hz, 1 H).

2.3.3 5,7-Diamino-8-hydroxy-2-methylquinoline Dihydrochloride Salt (10)

In a hydrogenation flask was placed crushed 8-hydroxy-2-methyl-5,7-dinitroquinoline (15.00 g, 0.060 mol) mixed with Pd – C 5% (2.5 g). To this mixture was added water (225 mL) and concentrated HCl (25 mL). The reaction mixture was placed on a Paar Hydrogenator for 18 hours with 38 psi of hydrogen gas. The reaction mixture was filtered, the solvent was removed from the filtrate, and the bright orange product was dried. The reaction produced 12.05 g (76%) of product.
2.3.4 8-Hydroxy-2-methyl-5,7-disuccinamidoquinoline (11)

To 80 mL of stirring DMF under argon was added NaOAc (2.00 g), Na2SO3 (2.00 g), and 5,7-diamino-8-hydroxy-2-methylquinoline dihydrochloride salt (1.00 g, 3.81 mmol). Succinic anhydride (3.05 g) in 30 mL of DMF was added drop-wise, and the reaction was stirred for 18 hours. The reaction mixture was filtered. To the filtrate was added 3 mL of water. After 1 hour, CH2Cl2 (500 mL) was added. After 36 hours, the orange-brown precipitate (1.17 g, 79%) was filtered and dried. 1H NMR (d-DMSO) δ 2.56–2.76 (m, 11 H), 7.37 (d, J = 8.8 Hz, 1 H), 8.07 (s, 1 H), 8.20 (d, J = 8.4 Hz, 1 H), 9.49 (s, 1 H), 9.76 (s, 1 H). EIMS (rel. intensity) M+ (3.8) (M - 18)+ (38.0) (M - 37)+ (17.4) (M - 91)+ (30.9) (M - 200)+ (100).

2.3.5 2-Methyl-7-succinamidoquinoline-5,8-dione (12)

To K2Cr2O7 (1.36 g) in water (18 mL) and glacial acetic acid (21 mL) was added 8-hydroxy-2-methyl-5,7-disuccinamidoquinoline (0.68 g, 1.75 mmol). The reaction was stirred for 20 hours. The reaction mixture was extracted 7 times with CH2Cl2 (420 mL). The extracts were combined and dried with anhydrous MgSO4. After filtering, removal of solvent from the filtrate gave 0.22 g (44%) of yellow solid. 1H NMR (d-DMSO) δ 2.56–2.90 (m, 7 H), 7.71 (s, 1 H), 7.73 (d, J = 8.3 Hz, 1 H), 8.24 (d, J = 7.9 Hz, 1 H), 9.98 (s, 1 H). EIMS (rel. intensity) M+ (21.7) (M - 74)+ (12.3) (M - 98)+ (70.8) (M - 100)+ (86.5) (M - 127)+ (100).

2.3.6 2-Formyl-7-succinamidoquinoline-5,8-dione (13)

To 2-methyl-7-succinamidoquinoline-5,8-dione (225.1 mg, 0.781 mmol) was added dioxane (4.00 mL), water (0.10 mL), and SeO2 (167.9 mg). The reaction was stirred and refluxed under argon at 115°C for 11 hours. The reaction was filtered and the filter cake was returned to the flask and refluxed with 5 mL more dioxane. This was repeated once more, and all filtrates were combined. Removal of the dioxane gave 130.0 mg (55%) of yellow-orange product. 1H NMR (d-DMSO) δ 2.88 (t, J = 6.1 Hz, 2 H), 2.53 (t, J = 6.1 Hz, 2 H), 7.81 (s, 1 H), 8.29 (d, J = 7 Hz, 1 H), 8.55 (d, J = 6.8 Hz, 1 H), 10.16 (s, 1 H), 10.24 (s, 1 H). EIMS (rel. intensity) (M - 1)+ (4.0) (M - 16)+ (12.1) (M - 98)+ (81.0) (M - 100)+ (81.1) (M - 127)+ (60.8).

2.3.7 Tryptophan n-Butyl Ester (15)

To 50 mL of ethyl acetate was added tryptophan n-butyl esterhydrochloride salt (334 mg, 1.25 mmol). This mixture was stirred and 14% NH4OH was added drop-wise until the solution reached pH 10. The solution was extracted 3 times with 30 mL of ethyl acetate and was dried with anhydrous MgSO4. The mixture was filtered, and removal of the solvent gave 290 mg (97%) of light yellow oil.
2.3.8 7-N-Succinyldemethylavendamycin i-Amyl Ester (16)

To 200 mg (0.662 mmol) of 2-formyl-7-succinamidoquinoline-5,8-dione under argon was added anisole (250 mL) and tryptophan i-amyl ester (218 mg, 0.798 mmol). The reaction was stirred and refluxed at 120°C for 11 hours. The reaction mixture was filtered, and the filtrate was concentrated until a red precipitate formed (31 mg, 8%). m.p. > 200° decomposed. \(^1\)H NMR (d-DMSO) \(\delta 1.05 (d, J = 6.2 \text{ Hz}, 6 \text{ H}), 1.25 (m, 1 \text{ H}), 1.76 (m, 2 \text{ H}), 2.60 (m, 2 \text{ H}), 2.90 (m, 2 \text{ H}), 4.46 (t, J = 6.7 \text{ Hz}, 2 \text{ H}), 7.44 (m, 1 \text{ H}), 7.72 (m, 2 \text{ H}), 7.81 (s, 1 \text{ H}), 8.59 (d, J = 6 \text{ Hz}, 1 \text{ H}), 8.56 (d, J = 8 \text{ Hz}, 1 \text{ H}), 8.91 (d, J = 8 \text{ Hz}, 1 \text{ H}), 9.10 (s, 1 \text{ H}), 10.36 (s, 1 \text{ H}), 11.98 (s, 1 \text{ H}).

2.3.9 7-N-Succinyldemethylavendamycin n-Butyl Ester (17)

To 80 mg (0.265 mmol) of 2-formyl-7-succinamidoquinoline-5,8-dione under argon was added anisole (100 mL) and tryptophan n-butyl ester (79 mg, 0.305 mmol). The reaction was stirred and refluxed at 120°C for 9 hours. The reaction mixture was filtered, and the solvent was removed from the filtrate. The brown-red solid was recrystallized in ethyl acetate to give 28 mg (20%) of an orange-red solid. \(^1\)H NMR (d-DMSO) \(\delta 1.04 (t, J = 7.2 \text{ Hz}, 3 \text{ H}), 1.55 (m, 2 \text{ H}), 1.84 (m, 2 \text{ H}), 2.59 (t, 2 \text{ H}), 2.93 (t, 2 \text{ H}), 4.45 (t, J = 6.6 \text{ Hz}, 2 \text{ H}), 7.45 (m, 1 \text{ H}), 7.73 (m, 2 \text{ H}), 7.82 (s, 1 \text{ H}), 8.54 (d, J = 8 \text{ Hz}, 1 \text{ H}), 8.60 (d, J = 8.7 \text{ Hz}, 1 \text{ H}), 8.95 (d, J = 8.3 \text{ Hz}, 1 \text{ H}), 9.10 (s, 1 \text{ H}), 10.29 (s, 1 \text{ H}), 11.97 (s, 1 \text{ H}).

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Appendix A - IAS Presentation

On November 3, 1995, the author went to the Indiana Academy of Science annual meeting. At that meeting, he gave a presentation of the material discussed in this paper to the members of the academy and to his peers. The experience was an important part of his education as presentations will undoubtedly be part of the requirements he will face in graduate school and in the work place.
Appendix B - Spectra

The following spectra are included in this section:

1. $^1$H NMR spectrum of 8-hydroxy-2-methyl-5,7-dinitroquinoline
2. $^1$H NMR spectrum of 8-hydroxy-2-methyl-5,7-disuccinamidoquinoline
3. $^1$H NMR spectrum of 2-methyl-7-succinamidoquinoline-5,8-dione
4. $^1$H NMR spectrum of 2-formyl-7-succinamidoquinoline-5,8-dione
5. $^1$H NMR spectrum of 7-$N$-succinyldemethylavendamycin $i$-amyl ester
6. $^1$H NMR spectrum of 7-$N$-succinyldemethylavendamycin n-butyl ester
7. Low Resolution MS of 8-hydroxy-2-methyl-5,7-disuccinamidoquinoline
8. Low Resolution MS of 2-methyl-7-succinamidoquinoline-5,8-dione
9. Low Resolution MS of 2-formyl-7-succinamidoquinoline-5,8-dione
(Succ)HN

COO-/amyl
7-\text{SUCCINYL} \text{AVAMYCIN BUTYL ESTER (AVAMY))}

**EXPERIMENTAL**

**SAMPLE**

**PROCEDURE**

![Diagram of molecular structure and NMR spectrum](image)
References


