STEREOSPECIFIC APPROACHES TO THE SYNTHESIS OF ALKALOIDS

WILLIAM LAWRENCE MANCINI

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STEREOSPECIFIC APPROACHES TO THE SYNTHESIS OF ALKALOIDS

Keywords
Chemistry, Organic
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STEREOSPECIFIC APPROACHES TO THE 
SYNTHESIS OF ALKALOIDS

by

WILLIAM L. MANCINI

B. A., St. Michael's College, 1967; 
M. S., University of New Hampshire, 1969

A THESIS

Submitted to the University of New Hampshire 
In Partial Fulfillment of 
The Requirements for the Degree of 
Doctor of Philosophy

Graduate School 
Department of Chemistry 
January, 1972
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Finally, the author wishes to dedicate this thesis to his wife. Her encouragement, support and sacrifices were an influencing factor in this work.
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF TABLES.................................................................vii</td>
</tr>
<tr>
<td>LIST OF FIGURES.................................................................viii</td>
</tr>
<tr>
<td>ABSTRACT.................................................................x</td>
</tr>
<tr>
<td>I.  INTRODUCTION.................................................................1</td>
</tr>
<tr>
<td>II.  HISTORICAL.................................................................3</td>
</tr>
<tr>
<td>III. DISCUSSION AND RESULTS................................................8</td>
</tr>
<tr>
<td>A.  The Classical Approach..................................................8</td>
</tr>
<tr>
<td>B.  The Oxazolidine System................................................11</td>
</tr>
<tr>
<td>C.  The Oxazolidinone Ring System........................................15</td>
</tr>
<tr>
<td>D.  The Erythro-Aminoalcohol.............................................23</td>
</tr>
<tr>
<td>E.  Reactions with Optically Active Aminoalcohol.................30</td>
</tr>
<tr>
<td>IV.  EXPERIMENTAL..............................................................36</td>
</tr>
<tr>
<td>General.................................................................36</td>
</tr>
<tr>
<td>Melting Points.................................................................36</td>
</tr>
<tr>
<td>Infrared Absorption Spectra...............................................36</td>
</tr>
<tr>
<td>Nuclear Magnetic Resonance Spectra....................................36</td>
</tr>
<tr>
<td>Analytical Data.................................................................36</td>
</tr>
<tr>
<td>Optical Rotation Data........................................................36</td>
</tr>
<tr>
<td>Circular Dichroism Spectra................................................37</td>
</tr>
<tr>
<td>A.  Studies in the threeo-1,2-Diarylethanolamine Series............38</td>
</tr>
<tr>
<td>(+)-threeo-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol........38</td>
</tr>
<tr>
<td>Resolution of (+)-threeo-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol........38</td>
</tr>
<tr>
<td>(+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine............39</td>
</tr>
<tr>
<td>(-)-trans-4,5-Bis(3,4-methylenedioxyphenyl)-oxazolidine..........40</td>
</tr>
</tbody>
</table>
Attempted Alkylation with Bromoacetaldehyde
Diethylacetal of the (+)-trans-4,5-Bis-(3,4-methylenedioxyphenyl)oxazolidine...........40

Attempted Alkylation with Bromoacetaldehyde
Diethylacetal of the (+)-trans-4,5-Bis-(3,4-methylenedioxyphenyl)oxazolidine in Weak Base.................................................41

Attempted Alkylation with Bromoacetaldehyde
Diethylacetal of the (+)-trans-4,5-Bis-(3,4-methylenedioxyphenyl)oxazolidine........41

Attempted Alkylation with Ethyl Bromoacetate of the (+)-threeo-2-Amino-1,2-Bis(3,4-methylene-dioxyphenyl)ethanol..........................42

Attempted Alkylation with Bromoacetaldehyde
Diethyl acetal of the Sodium Salt of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)-oxazolidine..............................................42

Attempted Alkylation with Bromoacetaldehyde
Diethylacetal of the Lithium Salt of the (+)-trans-4,5-Bis-(3,4-methylenedioxyphenyl)oxazolidine at Room Temperature....................43

Attempted Alkylation with Bromoacetaldehyde
Diethylacetal of the Potassium Salt of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)-oxazolidine at Elevated Temperature.............44

(+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)-oxazolidinone.................................44

(+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)-oxazolidinone..............................45

Preparation of (+)-trans-3-Ethoxycarbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone..............................................45

Attempted Cyclization of (+)-trans-3-Ethoxy-carbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone at Elevated Temperature..................................................46
Attempted Cyclization of (+)-trans-3-Ethoxy-
carbonylmethylene-bis(4,5-methylenedioxy-
phenyl)oxazolidinone at Cold Temperature.....47

B. Attempts to Prepare the Erythro-1,2-Diaryl-
ethanol Amine.................................48
2-Benzamido-1,2-bis(3,4-methylenedioxyphenyl) -
ethanol.............................................48
Treatment of N-Benzoyl-(+)—threo—Aminoalcohol 
with Hydrochloric Acid in Chloroform.........48
Oxidation of N-Benzoyl-(+)—threo—Aminoalcohol...49
Reduction of α-Benzamido-(+)—deoxypiperoin.....49
Attempted Hydrolysis of the N-Benzoyl-(+)—
threo—aminoalcohol with Acid..................50
Attempted Hydrolysis of the N-Benzoyl-(+)—
erythro—aminoalcohol with Acid................50
Attempted Hydrolysis of the N-Benzoyl-(+)—
threo—aminoalcohol with Base...................51
Preparation of Piperoin...........................51
Preparation of Piperoin Oxime....................51

BIBLIOGRAPHY.............................................62
LIST OF TABLES

TABLE I ................................................................. 5
TABLE II ............................................................... 13
TABLE III ............................................................. 17
LIST OF FIGURES

Figure 1. Ultraviolet Spectra of (−)-N-Ethoxycarbonylmethylene-(+)-trans-oxazolidinone (17) and (−−) 2,3-Dihydro-(+)-trans-oxazolo-4(1H)-isoquinolone (18) ........................................21

Figure 2. The Circular Dichroism and Ultraviolet Absorption Curves of (−)-threo-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (9b) ..........31

Figure 3. The Circular Dichroism and Ultraviolet Absorption Curves of (−)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13a) ........33

Figure 4. The Circular Dichroism and Ultraviolet Absorption Curves of the (−)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (16b) ..................................................35

Figure 5. Infrared Spectrum of (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (16) as a potassium bromide pellet ..................53

Figure 6. Infrared Spectrum of (+)-trans-N-Ethoxymethylene-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (17) as a potassium bromide pellet ..................................................54

Figure 7. Infrared spectrum of N-Benzoyl-(+)-threo-1,2-Bis(3,4-methylenedioxyphenyl)ethanol (29) as a potassium bromide pellet ........55

Figure 8. Infrared spectrum of α-Benzamido-(+)-dexoypiperin (30) as a potassium bromide pellet ...56

Figure 9. Infrared spectrum of N-Benzoyl-(+)-erythro-1,2-Bis(3,4-methylenedioxyphenyl)ethanol (31) as a potassium bromide pellet ..........57

Figure 10. NMR spectrum of (+)-trans-N-Ethoxycarbonylmethylene-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (17) in deuteriochloroform........58
Figure 11. NMR spectrum of 2,3-Dihydro-({trans}-oxazolo-4(1H)-isoquinolone (18) in deuteriochloroform........................59

Figure 12. NMR spectrum of N-Benzoyl-({threo}-1,2-bis-(3,4-methylenedioxyphenyl)ethanol (29) in dimethyl sulfoxide d₆.................................60

Figure 13. NMR spectrum of α-Benzamido-(+)−deoxypiperoin (30) in deuteriochloroform.........................61
ABSTRACT

STEREOSELECTIVE APPROACHES TO THE SYNTHESIS OF ALKALOIDS

by

WILLIAM L. MANCINI

The synthesis of a chiral tricyclic molecule incorporating an isoquinolin-4-one ring system is described. The heterocyclic five-membered ring, while being incorporated into the ring system of the phthalideisoquinoline, aporphine, or other alkaloid structures, is designed to protect the stereochemistry at the vicinal asymmetric carbon atoms.
Starting with the *three*-diarylethanolamine (9) of known absolute configuration, the functional groups were protected from adverse reactions by incorporation into a heterocyclic five-membered ring. The oxazolidine ring system (13) failed to undergo alkylation at nitrogen under a variety of conditions or alkylation agents, possibly because of ring-chain tautomerism. The oxazolidinone ring system (16), however, gave N-alkylation with ethyl bromoacetate. PPA-Catalyzed cyclization yielded a tetrahydroisoquinolin-4-one (18) having the correct spectral data.

Conversion of the *three*- to the *erythro*-diarylamino-alcohol (9E) was attempted by a sequential oxidation-reduction procedure. The conversion of the *three* stereochemistry to the *erythro* was accomplished with the N-benzoyl derivatives of these compounds. The chiroptical properties of the optical isomers of the *three*-oxazolidines (13) and oxazolidinones (16) are described. The heterocycle (18) is a useful intermediate which may be converted by relatively simple reactions to a variety of alkaloids.
I. INTRODUCTION

For many years the main source of alkaloids, especially the phthalideisoquinolines, has been isolation from plant extracts. The amounts of substances obtained were small and structural determinations were slow and tedious. Through synthesis and resolution, some optical properties of the alkaloids have been gathered. The assignments of absolute configuration have been based primarily on comparison of the chiroptical spectra of these compounds with similar substances.

Assignments of configuration done in the above manner, however, cannot always be considered absolute. Stereospecific syntheses are now being employed, not only to obtain unequivocal assignments of configuration, but also to make available larger amounts of these alkaloids. These syntheses generally start with a compound of known configuration. Care must then be exercised that at no time does reaction occur at the chiral centers.

It is the purpose of this thesis to establish a stereospecific route to (+)-threeo-1-(α-Hydroxy-3',4'-methylene dioxybenzyl)-N-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (1), a possible precursor to the synthesis of phthalideisoquinolines, particularly one of the isomers of bicuculline (2). In this synthetic scheme proof of retention of optical activity must also be demonstrated. Intermediate (1) might possibly be converted to two previously unprepared alkaloids, N-methylovigerine (3), and neolitsine (4). If successful this synthesis will provide these alkaloids in amounts adequate for extensive pharmacological testing.
NCH

1
O

NCH-

O

Methyllovinine (3)

Bicuculline (2)

Neolitsine (4)
II. HISTORICAL

The term phthalideisoquinoline\(^1\) is applied to a group of eleven known alkaloids which are all derived from the parent substance \((5)\) by substitution of a hydroxyl or methoxyl group at C-8, and/or methoxyl and methylenedioxy groups at carbons 6,7,4' and 5'. All the compounds isolated from plants contain an N-methyl group. These compounds are identified in Table I and include narcotine, narcotoline, hydastine, bicuculline, capnoidine, adlumidine, \(\delta\)- and \(\lambda\)-adlumine, corlumine, corlumidine and cordrastine. Corlumidine differs from the other compounds since it contains a hydroxyl group at C-7. All of the phthalideisoquinolines are found in plants of the \textit{Papaveraceae} family, except for hydastine which has been found only in plants of the families \textit{Ranunculaceae} and \textit{Berberidaceae}.

![Chemical structure (5)](image)

Only four of these compounds, adlumine, bicuculline\(^2\), hydastine\(^3\) and narcotine\(^4\), have been synthesized. In all of these early syntheses, the compounds were formed by the condensation of two parts of the total molecule, usually the isoquinoline and phthalide moieties. Any attempt at the synthesis of any of these phthalideisoquinolines employing
this procedure would be nonstereospecific and would probably yield a mixture of diastereomers. To date no stereospecific synthetic procedures have been developed starting with compounds of known configuration. If such a method were developed, the unequivocal determination of the absolute configuration could be achieved. For example, the absolute configuration of bicuculline\(^5\) has been assigned by comparison of its ord and cd curves with those of hydastine and narcotine (Table I).

The aporphines\(^6\) are another family of alkaloids which contain an isoquinoline ring. All of the aporphine alkaloids are based on the 4H-dibenzo[de, g]isoquinoline structure or its N-methyl derivative (6). Most of these alkaloids have been isolated from plants.

\[
\text{(6)}
\]

Within the last few years, aporphines have been synthesized via four major processes: phenolic oxidative coupling\(^7\), a Pschorr cyclization\(^8\), a modified Ullman condensation\(^9\), and a photochemical cyclization.\(^10\) The Pschorr cyclization route is illustrated by the synthesis of nuciferine.\(^11\)
<table>
<thead>
<tr>
<th>Compound</th>
<th>C-6</th>
<th>C-7</th>
<th>C-8</th>
<th>C-4&lt;sup&gt;t&lt;/sup&gt;</th>
<th>C-5&lt;sup&gt;t&lt;/sup&gt;</th>
<th>Configuration C-1</th>
<th>C-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adlumidine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>H</td>
<td></td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>S</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>Adlumine</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td></td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Bicuculline</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>H</td>
<td></td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Capnoidine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>H</td>
<td></td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>R</td>
<td>R</td>
<td></td>
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<tr>
<td>Cordiastine</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>unknown</td>
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<tr>
<td>Corlumidine</td>
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<td>H</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>S</td>
<td>R</td>
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<tr>
<td>Corlumine</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>H</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>S</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>α-Hydrastine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>H</td>
<td></td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R</td>
<td>R</td>
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<td>β-Hydrastine</td>
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<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>α-Narcotine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R</td>
<td>S</td>
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<tr>
<td>β-Narcotine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Narcotine</td>
<td>-O-CH&lt;sub&gt;2&lt;/sub&gt;-O-</td>
<td>OH</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>R</td>
<td>R</td>
<td></td>
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There exists only one aporphine, ushinsunine, which contains an alcohol function at C-7. This novel aporphine base has been found in *Michelia alba*, *Michelia champaca*, and *Michelia compressa*. This compound has a methylenedioxy function at C-1,2. On the other hand, neolitsine (3)\textsuperscript{12} and N-methylovigerine (4)\textsuperscript{13} are the only aporphines known to contain two methylenedioxy functions. However, both of these compounds are devoid of any oxygen function at C-7.
In all the aporphine syntheses known at the present time, no stereospecific syntheses have been employed. Most aporphines contain only one asymmetric center; however, ushinsunine has two chiral centers, one at C-6a, and the other at C-7.

A stereospecific, synthetic pathway which could go through a common intermediate and yield not only aporphines, but also phthalideisoquinolines, would be desirable. From such a synthetic sequence the synthesis of some aporphines and phthalideisoquinolines as well as the determination of their absolute configuration could be realized. The relatively poor yields in aporphine syntheses and the lack of adequate quantities from natural sources have precluded extensive pharmacological testing. A combination of these limiting factors led to the study of stereospecific approaches to the synthesis of these classes of alkaloids.
III. DISCUSSION AND RESULTS

A. The Classical Approach

In designing a stereospecific synthesis careful planning and intense thought must be exercised at every step. Each reaction of the proposed route becomes a most important venture. Besides retaining optical activity each step must result in good yields.

An earlier attempt at the stereospecific synthesis of bicuculline (2) was made by Durand.\textsuperscript{14} In his route it was essential that a compound of known configuration be prepared from which the synthesis could proceed. The threo-isomer of a diarylaminoalcohol (9) was prepared in good yield and resolved. Piperonal (7) was condensed with glycine in basic media to yield the Schiff base (8). Hydrolysis of 8 with hydrochloric acid yielded the desired threo-aminobcohol (9). From the ord spectra of the enantiomers of this compound and those of the known\textsuperscript{14} 1,2-diphenylethanolamine the absolute configurations were assigned. The erythro-isomer which was difficult to prepare was not employed in this sequence. It was felt that a synthetic sequence could be devised employing the racemic threo-isomer (9) and then this route could be applied to the optically active enantiomers of the threo- and erythro-diastereomers.

*The dotted lines indicate relative stereochemistry but do not imply any absolute configuration. Unless otherwise stated the racemic mixture is employed.
Alkylation of the amino function of 9 followed by cyclization would lead to the isoquinoline ring system found in bicuculline. The amine was acylated with oxalyl chloride (10) and cyclized under a variety of conditions. Lewis acid catalysis produced a dioxo compound (11) which was assumed to be the isoquinolin-3,4-dione (12), but the poor yield (3%) destroyed the usefulness of this classical approach.
\[ (9) + \text{Cl-C-C-Cl} \rightarrow (10) \]

LEWIS ACID

\[ (11) \rightarrow (12) \]
B. The Oxazolidine System

In examining the steps of this synthesis one fact becomes immediately obvious. The poor yields of the cyclization reaction probably result from the interference of the hydroxyl group. Thus, if the aminoalcohol (9) is to be employed and ultimately cyclized, the hydroxyl group must be protected so that no N-O migration will occur once the amine has been alkylated or acylated. Of equal concern is dehydration of this alcohol with acid, especially during the cyclization step. A third reason for further exploration of these syntheses was that the steric factors warranted additional study. If, for example, the amine could be hindered from free rotation or fixed rigidly, cyclization to the isoquinoline ring system would proceed perhaps in greater yield.

With these objectives in mind, incorporation of the two functional groups in a single, relatively rigid oxazolidine ring system was employed. The oxazolidine system affords many advantages. Besides fulfilling all of the above requirements, this system is stable to both acid and base. This ring can be opened by lithium aluminum hydride\textsuperscript{15}, catalytic hydrogenation, and Grignard reagents. In each case the bond between carbon-2 and oxygen is broken resulting in the N-substituted aminoalcohol.

The preparation of the oxazolidine (13) was carried out by condensation of formaldehyde with the aminoalcohol (9) in toluene using a Dean Stark separator to remove the water formed. The five-membered ring was readily obtained in 79% yield as previously described.\textsuperscript{16}
To achieve cyclization to an isoquinoline ring system the oxazolidine nitrogen must be alkylated with an ethylene or ethyl substituent. Various alkyl halides were employed for this purpose, however, no success was obtained. Glycidol was condensed with this ring system and was ultimately cyclized to a dihydriodoisoquinoline. However, due to the low yield (2%), this reaction sequence was not utilized further. All attempts at alkylation with ethyl bromoacetate or acetaldehyde diethylacetal proved futile. The alkylation conditions were also varied in basicity, but no success was achieved (Table II). One interesting aspect of these reactions is that starting material was not recovered in greater than fifty percent yield. One of the reasons for the failure of the oxazolidine to N-alkylate was probably the fact that the system undergoes ring-chain tautomerism. The spectral data below substantiated this hypothesis.

The nmr spectrum of the oxazolidine compound (13) showed one-half of an AB quartet for the benzylic protons at 5.2 $\tau$ ($J_{AB} = 4$ Hz). The other half of the quartet, however, was intermingled in a complex multiplet centered at 5.6 $\tau$. There also appeared to be another half of an AB quartet at 6.9 $\tau$ ($J_{AB} = 8$ Hz). The methylene carbon of an oxazolidine
TABLE II

<table>
<thead>
<tr>
<th>Alkylation Group</th>
<th>Conditions</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrCH₂CH(OEt)₂</td>
<td>KOH</td>
<td>CH(OC₂H₅)₂</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Piperidine</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NaH</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n-Butyllithium</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K, PhCH₃, 30° or 110°</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boiling 110° bath</td>
<td>CH₂CH₂OH</td>
<td>2%</td>
</tr>
</tbody>
</table>
ring system which is $\beta$ to a chiral center should appear as a simple AB quartet. The presence of a multiplet suggested that a structure other than the expected oxazolidine ring might have been present. The infrared spectrum of the oxazolidine (13) taken as a potassium bromide pellet exhibited the expected absorption bands of this ring system. In chloroform the infrared spectrum showed a weak absorption band at 1670 cm$^{-1}$, characteristic of an imine (14). An absorption band at $\lambda_{\text{max}}$ 320 nm, characteristic of a Schiff base and consistent with (15), was observed.

Since the oxazolidine is undergoing this equilibrium to form the imine (14), then the base is prevented from abstracting the amine proton. Thus, any subsequent reaction will take place between the base and the alkyl halide. The overall result is that no reaction occurs.
C. The Oxazolidinone Ring System

The failure of the alkylation reaction and possible loss of stereochemical control made it obvious that a different system had to be employed. A system which would give most, if not all, of the advantages of the oxazolidine ring was sought. The 2-oxazolidinone ring system is useful in that it also prevents N-O alkyl migrations. This system also yields the N-methyl carbinol upon reduction with lithium aluminum hydride. The critical disadvantages of the oxazolidinone ring are that it is very sensitive to hydroxy bases and mineral acids. In both cases the ring is decarbonylated. It is easy to see that if mineral acid or any hydroxy base is employed during alkylation or in the cyclization, the possibility of ring opening and N-O alkyl migration occurring prior to cyclization becomes prominent.

The 2-oxazolidinone ring system can easily be formed by condensation of the threo-aminoalcohol (9) with diethylcarbonate.\(^\text{24}\) The infrared spectrum exhibits the expected absorption bands, two carbonyl absorption bands at 1740 and 1780 cm\(^{-1}\) and the lone amide absorption band at 3350 cm\(^{-1}\). It has also been reported that 2-oxazolidinones exhibit a characteristic absorption band between 1029-1059 cm\(^{-1}\) which is consistent with the spectrum of 16.

\[(\text{EtO})_2\text{CO} \quad \text{NaOMe} \]

\[(9) \quad (16)\]
The 2-oxazolidinone ring system comprises an amido function which is also a urethane, and all attempts to alkylate a nitrogen in this type of environment require the use of strong base. Marvel and Moyer\(^{19}\) successfully alkylated lactams by using sodium hydride and an alkyl halide. Following this procedure, the amido proton was removed with NaH and bromoacetaldehyde diethyl acetal was added as the alkylating agent, but no product was obtained. In fact, starting material was not recovered and a better alkyl halide was sought (Table III).

Ethyl bromoacetate was again employed as it was for the oxazolidine compound. The results, however, were quite different. A viscous oil was obtained whose structure (17) was assigned on the basis of its spectral and analytical data. The purification of this oil proved to be a major task. The oil was soluble in a wide variety of organic solvents. Various methods such as heating and/or freezing of the oil (neat) failed to result in either a pure oil or solid. One method ultimately proved successful. Hot petroleum ether was added to the oil and the mixture was stirred before immersion in a Dry Ice-acetone bath. Repeating this procedure several times resulted in a glass-like solid, mp 51-52°. Inspection of the infrared spectrum revealed no amide proton absorption and a broadening of the carbonyl absorption region. The high yield (80%) of a single product was encouraging.

The nmr spectrum of 17 proved to be informative. The benzylic protons appeared as the expected AB quartet (\(J_{AB} = 8\) Hz), centered at 5.0 \(\tau\). The ethyl ester portion of the compound was revealed as a triplet 8.7 \(\tau\) (\(J = 7\) Hz) and as a quartet at 5.8 \(\tau\) (\(J = 7\) Hz). The protons of the methylene carbon of the side chain on nitrogen appeared as an AB quartet
TABLE III

<table>
<thead>
<tr>
<th>ALKYLATED GROUP</th>
<th>CONDITIONS</th>
<th>R</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrCH₂ CH(OEt)₂</td>
<td>NaH, Toluene</td>
<td>CH(OEt)₂</td>
<td>0%</td>
</tr>
<tr>
<td>BrCH₂ COOEt</td>
<td>NaH, Toluene</td>
<td>COOEt</td>
<td>80%</td>
</tr>
</tbody>
</table>
centered at 6.1 τ (J_{AB} = 18 Hz) with a chemical shift difference of 57.6 cycles. The fact that an AB quartet was observed for these protons is not surprising since this methylene group is situated close to a chiral center.

The large chemical shift difference can best be understood if a model of this compound is examined. One of the methylene protons is situated over the 2-oxazolidinone ring and hence is in much different magnetic environment than the other proton which seems to be situated outside of the five-membered ring system. The large coupling constant is not unique. Cahill, Cookson and Crabb\textsuperscript{25} studied geminal coupling constants of methylene groups α to both a nitrogen and a carbonyl function and generalized that the coupling constants were usually 17-18 Hz. Westley and Weinstein found that a number of methylene groups in various dipeptides had chemical shifts between 6.1 and 6.4 τ and that their geminal coupling constants were either 17 or 18 Hz.

All attempts at forming derivatives of this substituted 2-oxazolidinone with acid, base\textsuperscript{26}, and hydrazine hydrate\textsuperscript{27} were in vain. A qualitative ultraviolet absorption spectrum of this oil was also obtained. The value of this spectrum will be shown shortly.

Since, as stated earlier, the method of purification and crystallization of the N-alkylated-2-oxazolidinone was laborious and at times seemed futile, it was thought that one way to circumvent this problem was to effect cyclization of this crude material. Care and thought had to be applied here due to the susceptibility of this ring system to hydrochloric acid and hydroxy bases. Diethylacetyl derivatives of amines had been cyclized previously to 4-isoquinolones using sulfuric acid\textsuperscript{17}, but the presence of the methylenedioxy functions prohibited the use of this acid. These same
authors do imply, however, that polyphosphoric acid worked as well as sulfuric acid.

Kametani and Fukumoto$^{28}$ in the preparation of isoquinolines employed this acid. Care must be taken that this reaction is run under the correct conditions. PPA cyclizations can be run hot, cold, or at room temperature. The first attempt to cyclize the N-substituted 2-oxazolidinone (17) with this acid by warming in a hot water bath resulted in tars. The reaction was also attempted cold, but no results were obtained. The single success in this cyclization procedure was obtained by starting the reaction cold and allowing it to warm to room temperature slowly.

Since impure starting material was used and in very small quantity, only a small amount of oil was recovered from the last reaction. The best way to identify this residue was with nmr and qualitative ultraviolet spectroscopy. The time averaged nmr spectrum of an extremely dilute solution of the reaction product revealed that a reaction had occurred. A change in the aromatic proton region both in shape and integration was observed. The integration of five for the aromatic protons is one less than that of starting material. The lack of the ethyl ester protons was encouraging. The benzylic protons appeared again as an AB
quartet at $5.2 \tau$ ($J_{AB} = 6$ Hz) compared to $5.0 \tau$ ($J_{AB} = 8$ Hz) for the starting material. The largest change was observed for the geminal protons of the methylene group $\alpha$ to the amine. An AB quartet was again observed, this time centered at $6.3 \tau$ ($J_{AB} = 17$ Hz), and the chemical shift difference decreased from 57.6 Hz to 13.6 Hz. These figures become significant when compared with a similar study by Chow and Colon.\textsuperscript{29} These authors prepared a number of $\alpha$-piperidinyl acetophenones. With the $\alpha$-(2-methyl)piperidinyl acetophenone, the methylene protons of the acetophenone portion appeared as an AB quartet centered at $6.1 \tau$ ($J_{AB} = 17$ Hz) with a chemical shift difference of 26 Hz. When the piperidine was unsubstituted at the 2-position, the methylene protons appeared as a singlet at $6.3 \tau$. From the above information it is apparent that the methylene group at C-3 of the isoquinoline moiety could quite possibly be situated between an amine and aromatic ketone as in \textsuperscript{18}.

A qualitative uv spectrum of this oil revealed four bands at $\lambda_{\max}$ 233-234, 261, 285, and 315 nm. The uv spectrum of the starting material revealed only two bands at $\lambda_{\max}$ 238-239 and 287 nm. Even though no correlation can be made on the basis of extinction coefficients since the concentrations are unknown, one can compare the results with the data of Grethe\textsuperscript{3} and coworkers who had prepared a number of 4-isoquinolones. A check of the uv spectrum of one of the compounds that they prepared, 2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone, which was closest to the presumed 4-isoquinolone (\textsuperscript{18}), revealed that it too had four major absorption bands, $\lambda_{\max}$ 226-227, 264, 277-278, and 318 nm. From the above similarities in spectral data, it is proposed that cyclization has resulted in the formation of the ketone \textsuperscript{18}, but improvements in the reaction conditions are necessary.
Figure 1. Ultraviolet Spectra of \((-\))-N-Ethoxycarbonylmethylene-(\(\pm\))-trans-oxazolidinone (17) and \((-\))-2,3-Dihydro-(\(\pm\))-trans-oxazolo-4(1H)-isoquinolone (18).
Since the way is apparently open to the synthesis of the substituted tricyclic derivative (18) which reduction will readily convert to the desired tetrahydroisoquinoline (1), attention was directed to the other isomers possible in this series of compounds.
D. The Erythro-Aminoalcohol

If a stereospecific synthetic route leading to an intermediate which might be capable of yielding aporphines and phthalideisoquinolines is to be complete, all isomers of the starting material must be included. Since all of the previous work had been performed with the threeo-aminoalcohol (9), it would be necessary to obtain the erythro-isomer (19) and then to subject it to the same reactions. The erythro-isomer has been shown to be the more significant in a variety of ethanolamines used in medicine.

Ephedrine (20) and pseudoephedrine (21) are significant drugs, the former having the erythro structure and extensive use as a sympathomimetic, vasoconstrictor, and anti-allergic agent. In veterinary medicine it is useful as an antidote to morphine and barbiturate overdose. The threeo-isomer, pseudoephedrine (21), has less pharmacological significance but has been used as an appetite depressor. A similar difference in physiological activity has been noted in many cases of drugs, e.g., quinine (22) which has a similar ethanolamine structure and is used to fight malaria while epiquinine (23) has no significant, known pharmacological action. The threeo-isomer of an ethanolamine, however, has some very important activity in another series, D-(-)-chloramphenicol (24), having excellent antimicrobial activity.

In many cases, the type of activity varies with the absolute configuration, both erythro isomers being active. Quinine (22) cited above for antimalarial activity has a diastereomer, quinidine (25), which is enantiomeric at C-8, C-9. These two chiral centers are the site of enzyme action, and in contrast to 22, quinidine (25) is extensively used as a cardiac depressant (antiarrhythmic), but all isomers have some amount of antimalarial activity. This suggests that
the configurations may be altered in the body, a relatively easy chemical change taking place.

\[
\text{Ph} \quad \begin{array}{c}
\text{HO-C-H} \\
\text{CH}_3\text{NH-C-H} \\
\text{CH}_3
\end{array}
\]  \hspace{1cm} \begin{array}{c}
\text{Ph} \\
\text{H-C-CH} \\
\text{CH}_3\text{NH-C-H} \\
\text{CH}_3
\end{array}
\]  

(20) \hspace{1cm} (21)

\[
\begin{array}{c}
\text{CH}_3\text{O} \\
\text{H-C-OH}
\end{array}
\]  \hspace{1cm} \begin{array}{c}
\text{CH}_3\text{O} \\
\text{HO-C-H}
\end{array}
\]  

(22) \hspace{1cm} (23)

\[
\begin{array}{c}
\text{NO}_2 \\
\text{HO-C-H} \\
\text{H-C-\text{NHCCHCl}_2} \\
\text{CH}_2\text{OH}
\end{array}
\]  

(24)
In order to understand more fully the pharmacology of alkaloids and synthetic drugs modeled on these natural products, much more detailed comparison of isomers is essential. The lack of significant quantities of particular isomers [e.g., epiquinine (23) and epiquinidine (26)] has prevented such studies. In the synthesis of the phthalideisoquinoline alkaloids, it is necessary to consider routes to all isomers, especially to the erythro isomers. The erythro-isomer (9E) of the aminoalcohol system may be obtained in one of two possible ways, direct synthesis or through conversion from the threo-isomer.

Direct synthesis of the erythro-aminoalcohol was attempted; however, this procedure proved to be both lengthy and impractical. Piperonal (7) was condensed with potassium cyanide as catalyst to yield piperoin (27). The oxime derivative (28) was prepared (53%) and reduction was attempted in ethanol employing Adams catalyst; however, no success was achieved.
Pines and coworkers had shown that it was possible to convert three-aminoalcohols to the erythro-isomers by an oxidation-reduction sequence of reactions. The N-benzoyl derivative (29) of the three-aminoalcohol was prepared in order to protect the primary amine function. This compound gave spectral and analytical data consistent with the expected structure (29).

Oxidation of 29 with Jones reagent yielded the amido carbonyl (30). The infrared spectrum revealed an amido-ketone absorption at 1645 cm\(^{-1}\) and an aromatic ketone absorption band at 1680 cm\(^{-1}\). In the nmr spectrum the benzylic proton appeared as a doublet at 3.4 \(\tau\) (\(J = 7\) Hz) and the amine proton also appeared as a doublet at 3.3 \(\tau\) (\(J = 3\) Hz).
Upon addition of D$_2$O to the nmr sample, the two doublets collapsed into a singlet at 3.4 $\tau$. Reduction of 30 was accomplished with sodium borohydride while bubbling carbon dioxide (to avoid retroaldolization) through the reaction medium. A mixture of the threo- and erythro-amides was obtained which was separated by dry column chromatography. Spectral and analytical data were consistent with the proposed structure and literature data.\textsuperscript{30}
The hydrolysis of 31 proved to be quite a difficult task. It had been reported\textsuperscript{14} that the N-benzoyl-three-amine-alcohol (29) in the presence of hydrochloric acid resulted in N-O migration of the benzoyl group yielding 32. Treatment of the O-benzoyl compound (32) with base yielded the N-benzoyl compound (29) by the reverse reaction.
The N-benzoyl-erythro-isomer (31), however, upon similar treatment yielded the N-benzoyl-threo-compound (29) via the O-benzoyl-threo-aminoester (32). The hydrolysis was attempted according to the procedure of Pines and coworkers. Employing various concentrations of hydrochloric acid in methanol, the reaction condition yielded either starting material (29) or the O-benzoyl compound (32). Probably an intermediate such as proposed by Durand converted the erythro to threo product. Base hydrolysis with sodium hydroxide gave no results. McCasland and Smith reported that hydrolysis of esters of 2-aminocyclopentanols can be achieved by refluxing in 1N hydrochloric acid. This method did not produce the desired erythro-aminoalcohol (9E). It was apparent that if a total stereospecific synthetic scheme was to be completed, this obstacle had to be overcome.
E. Reactions with Optically Active Aminoalcohol (9).

In the design of a stereospecific synthetic scheme the first objective is to devise a reasonable route to the desired compound. The second and most important requirement is to maintain the optical activity without change. The reactions by which the aminoalcohol (9) would ultimately be converted to the key intermediate (1) should not alter the stereochemistry at any step in order to maintain a stereospecific synthesis. Formation of the five-membered ring, however, could affect the chiral centers if a mechanism intervened with dehydration and tautomerism (a) or an internal $S_{N}^{2}$ (b) rather than the direct elimination of water to maintain the stereochemistry (c).

\[ (9) + CH_{2}O^{*} \rightarrow (12) \rightarrow (13) \]

The resolution of 9 was accomplished in good yield and in relatively facile fashion as reported previously.\textsuperscript{30} The absolute configuration had been assigned to the enantiomers of 9 by Lyle and Durand\textsuperscript{30} on the basis of the ord curves.
Figure 2. The Circular Dichroism and Ultraviolet Absorption Curves of (-)-\textit{threo}-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (9b).
The comparison of the curves covered only the spectral region above 290 nm, and verification was sought by the use of circular dichroism measurements. The cd curve showed two major bands with fine structure, the long wave length substituted aromatic band at 292-294 nm, [θ] -19,500°, and the second band at 239-240 nm, [θ] -26,000. These aromatic bands reflected the uv absorption bands at 285 (log ε 3.90) and 237 nm (log ε 3.94). The (+)- and (-)- enantiomers of 9 showed mirror image curves.

The cd curve of (-)-9 agrees with the ord curve obtained previously in that the long wave length Cotton effect has the negative sign. On comparison of the ord curves of 9 with those of threo-2-amino-1,2-diphenylethanol (34) of known configuration, the absolute configuration of (-)-9 was assigned (1S:2S) and of (+)-9 as (1R:2R).

![Structures](34a) ![Structures](34b)

In order to verify that the reactions did not alter the stereochemistry, the cd curves of the five-membered ring derivatives were compared. The levorotatory trans-oxazolidine (13), [α]^{D}_{25} -126°, was prepared and its uv and cd curves were obtained. The possibility of an equilibrium occurring in this system had been discussed earlier (see page 14) and from the cd curves, one could see that a decrease in the number of degrees of rotation had occurred. This was further evidence for an equilibrium which was affecting the
Figure 3. The Circular Dichroism and Ultraviolet Absorption Curves of (-)-trans-4,5-Bis(3,4-methylenedioxy-phenyl)oxazolidine (13a).
chiral center in view of the fact that incorporation of the asymmetric carbons into a ring usually results in an increase in optical rotatory power.\(^{34}\)

In order to prepare the optically active oxazolidinone, the dextrorotatory aminoalcohol (9a) was reacted in the manner described above for the racemate and the resultant oxazolidinone (16a) was purified by recrystallization. Monitoring the reaction by the optical rotation, \([\alpha]^D_{25}=+195^\circ\), showed clearly that the optical activity at the chiral centers was not affected by the reaction conditions. From the uv and cd curves it was obvious that the optically active aminoalcohol (9a) and oxazolidinone (16a) gave very similar curves with somewhat greater amplitude for the latter. Epimerization did not appear to result from this reaction. The cd data provide strong evidence for the assigned absolute and relative configurational assignments. The early hypothesis of Lyle and Lacroix\(^{35}\) that ord curves of the diastereomers would be useful diagnostic tools has been supported by the more recent studies of Mitscher et al.\(^{36}\) The remainder of the reactions in this synthetic scheme occurred away from the chiral centers and, therefore, the danger of loss of optical activity or epimerization was minimal.

The ultimate repetition of each reaction with the optically active aminoalcohol will produce a stereospecific synthesis of one of the four possible isomers of bicuculline (2). At present all the data suggest that the (+)-three-aminoalcohol (9a) used as starting material in this research will produce the rare three-isomer, epibicuculline, having the (1R:9R) absolute configuration, and the (-)-enantiomer (9b) will produce the isomer having the (1S:9S) configuration. Similarly the erythro isomers (9E) will lead to the (1R:9S) and (1S:9R) configurations of bicuculline (2).
Figure 4. The Circular Dichroism and Ultraviolet Absorption Curves of the (-)-trans-4,5-Me(3,4-methylene-dioxyphenyl)oxazolidinone (16b).
IV. EXPERIMENTAL

General

Melting Points. Melting points were determined using a Hoover capillary melting point apparatus and are corrected. In a number of instances the melting points here are slightly higher than literature values. This may be due to the fact that the values reported here are corrected.

Infrared Absorption Spectra. The infrared absorption spectra were determined using Perkin-Elmer Models 337 and 700 spectrophotometers. The positions of the absorption bands are given in cm⁻¹. Unless otherwise indicated, the spectra of solids were determined as potassium bromide pellets.

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton resonance spectrometer. Unless otherwise indicated, the spectra were obtained in deuteriochloroform, and the chemical shifts are given in ppm relative to tetramethylsilane, an internal standard.

Analytical Data. Microanalyses were obtained with an F and M Model 180 carbon, hydrogen, and nitrogen analyzer.

Optical Rotation Data. Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter using a mercury vapor lamp as a light source. The specific rotations, [α] (g/100 ml, solvent), are given for each measurement.
Circular Dichroism Spectra. Circular dichroism spectra were obtained on a Cary Model 6001 Circular Dichroism accessory for the Cary Model 60 Recording Spectropolarimeter. The spectra were determined in 1.0 and .2 cm cells, and the initial concentration and solvent (g/cc, solvent) are indicated for each spectrum. Data are given as the molecular ellipticities, [θ].
A. Studies in the threo-1,2-Diarylthanolamine Series.

(±)-threo-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)-ethanol (9). The synthesis of the (±)-threo-aminoalcohol (9) was accomplished according to the procedure of Lyle and Durand. Starting with piperonal (7, 150 g, 1 mol), 48 g (34%) of the intermediate Schiff base (8) was obtained, mp 182-183°, lit. mp 181-182°. Hydrolysis of the intermediate with 0.5 N hydrochloric acid yielded 12 g (85%) of the aminoalcohol (9), mp 161-162°, lit. mp 161-162°. The nmr spectrum in formic acid displayed the benzylic protons as an AB quartet at 5.0 \( \tau \) \( (J_{AB} = 9.3\ Hz, 1H) \) and at 5.6 \( \tau \) \( (J_{AB} = 9.3\ Hz, 1H) \). The methylenedioxy protons appeared at 4.1 \( \tau \) \( (s, 2H) \) and 4.2 \( \tau \) \( (s, 2H) \) and the aromatic protons at 3.3 \( \tau \) \( (m, 6H) \).

Anal. Calcd for \( C_{16}H_{15}NO_5 \): C, 63.76; H, 5.02; N, 4.65. Found: C, 63.70; H, 5.00; N, 4.61.

IR Spectrum: \( \tilde{\nu}_{\text{max}} \) 3420, 3400, 3250, 3030, 2900, 1590, 1500(s), 1480(s), 1420, 1360, 1300, 1250(b), 1190, 1120, 1045(b), 980, 945, 920, 870, 810, 790, 760, 740 cm\(^{-1}\).

UV: Figure 2.

Resolution of (±)-threo-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (9). The (±)-threo-aminoalcohol (9, 5.00 g, 0.0166 mole) which was prepared according to the method of Lyle and Durand \(^{30}\) was dissolved in 300 ml of hot methylated spirits (90% ethanol:10% methanol). In a separate container (±)-tartaric acid (2.49 g, 0.0166 mol) was dissolved in hot methylated spirits. The two hot solutions were mixed together with immediate formation of white crystals. After all precipitation ceased, the first fraction was separated by filtration and dried. The filtrate was left standing overnight, during which a second fraction precipitated.
The first fraction was recrystallized from water several times yielding a white solid, mp 203-205° (lit. 30 mp 203.5-205°) [α]$_D^{25}$ +102.9° (c 0.84, water). (-)-threeo-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)ethanol hydrogen- (+)-tartrate (4.0 g) was dissolved in 250 ml of hot water, and ammonium hydroxide was added until the solution became basic yielding a white product (2.7 g) which was filtered hot. After several recrystallizations, the white crystals melted at 161-162° (lit. 30 mp 161.5-162.5°), [α]$_D^{25}$ -195° (c 0.48, ethanol) (lit. 30 [α]$_D^{25}$ -200.1°, c 0.48, ethanol).

(+)-threeo-2-Amino-1,2-bis-(3,4-methylenedioxyphenyl)-ethanol (9a) was analogously prepared from its hydrogen (+)-tartrate salt. The (+)-salt (2.1 g) was made basic with ammonium hydroxide. After cooling, the solid was removed by filtration, washed with water, and dried, yielding 1.2 g of material, mp 159-162° (lit. 30 mp 162-163°) [α]$_D^{25}$ +180.2° (c 0.41, ethanol) (lit. 30 +192° (c 0.41, ethanol)).

The cd spectrum in 95% ethanol (c 0.06) was [θ]$_{330-310}^{291}$ +17,100°, [θ]$_{275}^{275}$ +6,000° (sh), [θ]$_{255}^{255}$ +3,900°, [θ]$_{238}^{238}$ +26,000°, [θ]$_{225}^{225}$ +17,800°, [θ]$_{215}^{215}$ +21,600°. The curve is almost the mirror image of that of the (-)-enantiomer (Figure 2).

(+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13). To the (+)-threeo-aminoalcohol (9, 4.5 g, 0.015 mol) was added formaldehyde (10 ml of a 37% solution) in a 100 ml round-bottomed flask. A Dean-Stark trap using benzene was employed to remove excess formaldehyde and water by azeotropic distillation. The solution was heated under reflux for 6 hr during which time a total of 10 ml of aqueous solution was collected. The benzene solution was concentrated under reduced pressure and the resulting oil crystallized from ethanol. Recrystallization yielded 3.76 g
(80%) of a white crystalline solid, mp 137-138.5°, lit.\textsuperscript{16} mp 137-138.5°.

\textit{(-)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13a).} The (-)-enantiomer was prepared from (-)-\textit{three-}
aminoalcohol (9b), $[\alpha]_{D}^{25} -126.3^\circ$ (c 0.95, water), $[\alpha]_{D}^{25} -125.5^\circ$ (c 0.47 ethanol). The cd spectrum (Figure 3) in 95% ethanol (c 0.09) was $[\theta]_{330} 0^\circ$, $[\theta]_{315} -400^\circ$(sh), $[\theta]_{298}$

\textit{-1120°}, $[\theta]_{294} -1020°$, $[\theta]_{285} -540^\circ$(sh), $[\theta]_{280-265}$ 0°,

$[\theta]_{248} -1360^\circ$, $[\theta]_{246} -1440^\circ$, $[\theta]_{243} -1060^\circ$(sh), $[\theta]_{230} -80°$,

$[\theta]_{218} -1060^\circ$. The spectral data were identical with the racemate (13).

The nmr spectrum in deuteriochloroform showed aromatic
protons at 3.60 $\tau$ (m, 6H), methylenedioxy protons at 4.47 $\tau$
(s, 2H) and 4.5 $\tau$ (s, 2H). The benzylic and C-2 protons of
the oxazolidine ring appeared at 5.2 $\tau$ (d, $J = 4.0$ Hz, 1H),
5.6 $\tau$ (m, 2H), and 6.9 $\tau$ (d, $J = 8.0$ Hz, 1H). The amine
proton appeared as an unresolved broad band at 6.6 $\tau$ (1H).

\textit{Anal. Calcd for C}_{17}H_{15}NO_{5}: C, 65.17; H, 4.83; N,
4.47. Found: C, 65.08; H, 4.58; N, 4.21.

\textit{IR Spectrum:} $\lambda_{max}$ 2900, 1490, 1440, 1380(w),
1250(s), 1190, 1040, 980, 940, 875, 840, 825, 800 cm$^{-1}$.

\textit{UV Spectrum:} Figure 3.

\textbf{Attempted Alkylation with Bromoacetaldehyde Diethyl-
acetal of the (\textit{+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)}-
oxazolidine (13).} A modification of the procedure of
Bobbitt and SiH\textsuperscript{18} was employed. The (\textit{+)-trans-oxazolidine}
(13, 6.30 g, 0.02 mol) was dissolved in 135 ml of benzene.
Bromoacetaldehyde diethylacetal (3.90 g, 0.02 mol) was added
and the resultant solution was stirred (magnetically) over-
night. The solution was then heated to reflux for 5.5 hr.
The benzene was removed under reduced pressure yielding a
viscous oil which solidified upon standing. Recrystallization from ethanol yielded a white solid, mp 126-131°. The infrared spectrum showed no carbonyl absorption and the nmr showed the amine proton at 6.6 τ (1H). A total recovery of 3.1 g (50%) was obtained which gave an analysis identical with starting material (13).

**Attempted Alkylation with Bromoacetaldehyde Diethylacetal of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13) in Weak Base.** The (+)-trans-oxazolidine (13, 6.30 g, 0.02 mol) was dissolved in 135 ml of benzene containing crushed potassium hydroxide (1.30 g, 0.02 mol). Bromoacetaldehyde diethylacetal (3.90 g, 0.02 mol) was added and the resultant mixture was heated to reflux for 5.5 hr. The cooled mixture was separated by filtration and the filtrate was concentrated under reduced pressure yielding a viscous oil. Crystallization from ethanol yielded a white solid, mp 133-135°. From all spectral and analytical data it was determined that no reaction had occurred and 3.2 g (50%) of starting material (13) was obtained.

**Attempted Alkylation with Bromoacetaldehyde Diethylacetal of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13).** A modification of the procedure of Schlittler and Müller37 was employed. The (+)-trans-oxazolidine (13, 3.00 g, 0.01 mol) was dissolved in 40 ml of freshly distilled toluene and four drops of piperidine were added. The bromoacetaldehyde diethylacetal (2.80 g, 0.01 mol) was added and the solution was heated to reflux for 8 hr. The cooled orange mixture was separated by filtration and the filtrate was concentrated under reduced pressure to yield a viscous oil. Again crystallization from ethanol yielded 1.50 g (50%) of a white solid, mp 135-137°. The infrared spectrum
failed to show any carbonyl absorption and the nmr was identical with starting material (13).

**Attempted Alkylation with Ethyl Bromoacetate of the (+)-threo-2-Amino-1,2-Bis(3,4-methylenedioxyphenyl)ethanol (13).** A modification of the method of Grethe, Lee, Uskokovic and Brossi17 was employed. The (+)-threo-aminoalcohol (13, 6.9 g, 0.023 mol) was placed into 40 ml of benzene (stored over sodium metal). Sodium carbonate (anhydrous, 4.0 g, 0.038 mol) and ethyl bromoacetate (3.8 g, 0.023 mol) were added and the mixture was stirred and heated to reflux overnight. The mixture was separated by filtration and the clear yellow solution was concentrated under reduced pressure and with steam heat. The orange oil obtained was dissolved in chloroform-d and an nmr obtained. The spectrum showed peaks at 5.78 τ (m), 5.87 τ (m), 6.18 τ (s), 8.74 τ (t), and 8.80 τ (t). From the integration data, it appears that a mixture of mono- and di-alkylated products has resulted.

**Attempted Alkylation with Bromoacetaldehyde Diethyl acetal of the Sodium Salt of (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13).** A modification of the procedure of Fones38 and Bobbitt18 was employed. The (+)-trans-oxazolidine (13, 3.00 g, 0.010 mol) was placed in 120 ml of toluene dried over sodium metal. To the stirred mixture was added sodium hydride (0.50 g, 0.010 mol) in 120 ml of toluene. After stirring for 1 hr, the mixture was heated to reflux for 3.5 hr. The mixture was stirred overnight while cooling. Bromoacetal (3.20 g, 0.016 mol) was added dropwise to the mixture which was then heated to reflux for 5 hr. The mixture was separated by filtration and a yellow solid was obtained (inorganic). The yellow solution was concentrated under reduced pressure and with steam heat. A yellow oil was obtained which was dissolved in chloroform-d. The nmr
of the oil revealed starting material (13).

**Attempted Alkylation with Bromoacetal of the Lithium Salt of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13).** The (+)-trans-oxazolidine (13, 3.00 g, 0.010 mol) was placed in 100 ml of freshly distilled benzene (stored over sodium metal). A constant stream of nitrogen gas was kept flowing over the stirred solution. To this stirred solution was added 7.4 ml of a 1.35 M n-butyllithium solution (0.010 mol) via a syringe. The previously cloudy solution cleared on addition of the base and after a few minutes recloaked. The cloudy solution was stirred for 0.5 hr after which bromoacetal (2.00 g, 0.010 mol) was added. The solution turned orange in color and was allowed to stir with heat for 5 hr. After stirring at room temperature overnight, the cloudy solution was separated by filtration yielding a gelatinous, brown substance (inorganic). The solution was concentrated under reduced pressure and with steam heat. A yellow oil was obtained which crystallized upon standing. The solid, mp 115-127°, upon spectral analysis, was shown to be starting material (13).

**Attempted Alkylation with Bromoacetaldehyde Diethylacetel of the Potassium Salt of the (+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13) at Room Temperature.** The (+)-trans-oxazolidine (13, 4.00 g, 0.01 mol) was dissolved in 100 ml of benzene (stored over sodium metal). A constant stream of nitrogen gas was kept flowing over this stirred (mechanical) solution. Potassium metal (0.50 g, 0.01 mol) was added slowly and the mixture was stirred until all the metal had dissolved. After stirring for 25 hr and with the aid of a warm water bath, most of the metal had dissolved. Bromoacetaldehyde diethylacetel (2.80 g, 0.01 mol) was added slowly and dropwise. A brown solution
resulted which was stirred for an additional 5 hr. The cooled dark mixture was separated by filtration and the filtrate was concentrated under reduced pressure yielding an orange oil which solidified upon standing. Recrystallization from ethanol yielded 1.90 g (48%) of a white solid, mp 137-138°. All spectral and analytical data were identical with starting material (13).

**Attempted Alkylation with Bromoacetaldehyde Diethylacetal of the Potassium Salt of the (+)-** trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidine (13) **at Elevated Temperature.** The (+)-** trans-** oxazolidine (13, 3.20 g, 0.01 mol) was dissolved in 100 ml of freshly distilled toluene and a catalytic amount of ferric chloride was added. A constant stream of nitrogen gas was kept flowing over this stirred (magnetically) mixture. Potassium metal (0.40 g, 0.01 mol) was added slowly and the mixture was stirred and heated to reflux until all the metal had dissolved. The mixture was cooled after 5 hr and bromoacetaldehyde diethylacetal (1.40 g, 0.01 mol) was added slowly. The mixture was heated to reflux again for an additional 3 hr. The cooled mixture was separated by filtration and the filtrate was concentrated under reduced pressure yielding a tan solid. Recrystallization from ethanol yielded 1.00 g (31%) of a white solid, mp 138-139.5°, whose spectral data were identical with starting material (13).

**(+)-** trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (16). In this preparation a modification of the method of M. S. Newman and A. Kutner24 was followed. A solution of the (+)-** threeo-** aminoalcohol (9, 6.00 g, 0.02 mol) in 80 ml of diethyl carbonate and 10 ml of toluene was placed in a 250 ml round-bottom flask equipped with a magnetic stirrer and a distilling column. After distilling the toluene to insure
dryness, sodium methoxide (0.50 g, 0.09 mol) was added. The mixture was stirred and heated for 75 min. A clear liquid distilled between 75-80° when a white solid began to appear. The temperature then rose quickly to 102°. Distillation was stopped when the temperature rose to 120°. The mixture was separated by filtration yielding a tan solid and a yellow filtrate. Recrystallization from methanol yielded 1.7 g of a tan solid which was also recrystallized. A total of 5.7 g (87%) of the racemic oxazolidinone (16) was obtained. The infrared spectrum showed the amide proton at 3350 cm⁻¹ and two carbonyl absorptions at 1780 cm⁻¹ (sh), and 1740 cm⁻¹ (s). There was no evidence of hydroxyl absorption. The ultraviolet spectrum in methanol gave the following curve: 

$$\lambda_{\text{max}} = 287 \text{ nm} \ (\epsilon 7,300), \ 238 \ (\epsilon 7,700).$$

**Anal.** Calcd for C₁₇H₁₃NO₆: C, 62.38; H, 4.00; N, 4.28. Found: C, 61.93; H, 3.94; N, 4.16.

(+)-trans-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (16a). The (+)-enantiomer was prepared in the above manner, mp 198.5-199.5°, $[\alpha]_D^{25} +195° \ (c 0.49, \text{methanol})$

starting with the (+)-threo-aminoalcohol (9a), $[\alpha]_D^{25} +192°$.

The cd spectrum (Figure 4) in methanol (c 0.10 was 

$[\theta]_{230-310} 0°, \ [\theta]_{294} +18,300°, \ [\theta]_{292} +18,400°, \ [\theta]_{270-260} 0°, \ [\theta]_{243} +31,500°, \ [\theta]_{241} +30,900°, \ [\theta]_{225} +12,700°, \ [\theta]_{215} +13,800°$. Spectral data were identical with the racemate (16).

Preparation of (+)-trans-3-Ethoxycarbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone (17). In this preparation a modification of the procedure of C. S. Marvel and W. W. Moyer, Jr. 19 was followed. The trans- (+)-oxazolidinone (16, 1.8 g, 0.006 mol) and 0.080 g of a 56.2% emulsion of sodium hydride (0.018 mol) in mineral oil was heated to reflux in toluene (dried over sodium metal) for 10 hr. An inert atmosphere (N₂) was
maintained over the magnetically stirred mixture. Ethyl bromoacetate (2.4 g, 0.014 mol) in toluene was added drop-wise and the mixture was heated to reflux for 4 hr. The cooled mixture was separated by filtration and the filtrate was concentrated under reduced pressure yielding a yellow oil. The oil was purified by stirring in hot petroleum ether and then freezing this mixture in a Dry Ice-acetone bath five times. Each time fresh petroleum ether was employed. After drying 2 g (80%) of an orange solid, mp 51-52°, was obtained.

The infrared spectrum showed two distinct carbonyl absorptions at 1780 cm⁻¹ and 1740 cm⁻¹ for the oxazolidinone ring carbonyl and another carbonyl absorption at 1720 cm⁻¹ (sh). There was no amide proton absorption at 3350 cm⁻¹. The nmr spectrum showed aromatic protons at 3.2 τ (m, 6H), methylenedioxy protons at 3.9 τ (s, 4H) and the benzylic protons as an AB quartet centered at 5.0 τ (J_{AB} = 8 Hz, 2H). The ethoxy group appeared at 8.7 τ (J = 7 Hz, 3H) and 5.8 τ (J = 7 Hz, 2H). The geminal methylene protons α to the amine appeared as an AB quartet at 5.5 τ (J_{AB} = 18 Hz, 1H) and 6.5 τ (J_{AB} = 18 Hz, 1H). The ultraviolet spectrum in methanol gave the following curve: \( \lambda_{\text{max}} \) 287 nm (ε 85,000), 237 (ε 87,000).

Anal. Calcd for C_{21}H_{19}NO₈: C, 61.01; H, 4.63; N, 3.39. Found: C, 61.10; H, 4.76; N, 3.18.

**Attempted Cyclization of (†)-trans-3-Ethoxycarbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone (17) at Elevated Temperature.** In this preparation a modification of the procedure of T. Kametani and K. Fukumoto was employed. To the (†)-trans-3-ethoxycarbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone (17, 1.00 g, 0.003 mol) was added 45 ml of warm polyphosphoric acid. The resul-
tant dark solution was stirred (magnetically) and heated to 100° for 5 hr. The dark solution was poured onto crushed ice and stirred. The aqueous layer was extracted with chloroform and dried over magnesium sulfate. The chloroform was removed under reduced pressure yielding an oily tar. The infrared spectrum revealed no carbonyl absorption and no evidence of aromatic absorption.

**Attempted Cyclization of (+)-trans-3-Ethoxycarbonylmethylene-bis(4,5-methylenedioxyphenyl)oxazolidinone (17) at Cold Temperature.** A modification of the procedure of Kamatani and Fukumoto was employed. The (+)-trans-3-ethoxycarbonylmethylene oxazolidinone (17, 1.00 g, 0.003 mol) was added to 45 ml of ice-cold (5°) polyphosphoric acid. The resultant solution turned green. At the end of the prescribed reaction period a dark solution resulted which was poured onto crushed ice and stirred. The aqueous orange solution was extracted with chloroform and the organic layer was dried over magnesium sulfate. Removal of the chloroform layer under reduced pressure resulted in an orange oil: $\lambda_{max}$ 315 nm (ε 18,600), 285 (ε 43,000), 261 (ε 28,000), 233-234 (ε 63,000). The nmr spectrum showed an AB quartet for the benzylic protons at 5.2 τ ($J_{AB} = 6$ Hz, 2H) and another quartet for the geminal protons of the methylene group α to the amine at 6.3 τ ($J_{AB} = 17$ Hz, 2H). The methylene dioxy protons appeared at 4.0 τ (s, 4H) and the aromatic protons at 3.3 τ (m, 5H). Too little material remained for further experimentation.
B. Attempts to Prepare the Erythro-1,2-Diarylethanol Amine

2-Benzamido-1,2-bis(3, 4-methylenedioxyphenyl)-ethanol (29). A modification of the procedure of M. L. Durand\textsuperscript{14} was employed. To the (+)-threo-aminoalcohol (9, 2.00 g, 0.006 mol) in benzene was added 3.0 ml of benzoyl chloride solution. This mixture was heated to reflux with magnetic stirring for 0.5 hr. The hot mixture was separated by filtration and the filtrate was extracted with 30 ml portions of 2% sodium carbonate, 2% hydrogen chloride and water. The benzene solution was left overnight. Separation by filtration yielded 1.6 g (65%) of a white solid, mp 157-159°, (lit.\textsuperscript{14} mp 158-159°).

The infrared spectrum showed an amide proton absorption at 3350 cm\textsuperscript{-1} and the amide carbonyl at 1650 cm\textsuperscript{-1}. The nmr spectrum showed amide proton at 5.4 \(\tau\) (d, \(J = 6\) Hz, 1H), which disappeared after addition of \(\text{D}_2\text{O}\), and the benzylic protons as an AB quartet at 4.9 \(\tau\) (\(J_{\text{AB}} = 9\) Hz, 1H) and 5.2 \(\tau\) (\(J_{\text{AB}} = 9.0\) Hz, 1H).

**Anal.** Calcd for C\textsubscript{23}H\textsubscript{19}NO\textsubscript{6}: C, 67.97; H, 4.71; N, 3.44. Found: C, 68.06; H, 4.63; N, 3.22.

Treatment of N-Benzoyl-(+)-threo-Aminoalcohol (29) with Hydrochloric Acid in Chloroform. The N-benzoyl-(+)-threo-aminoalcohol (29, 2.00 g, 0.006 mol) was stirred for 5 hr at room temperature in 75 ml of chloroform containing a large molar excess of anhydrous hydrogen chloride. The resulting amine hydrochloride (32), 1.00 g (50%), melted at 214-215° (lit.\textsuperscript{14} 214-215°), showed an infrared carbonyl absorption band at 1720 cm\textsuperscript{-1}, and the lack of any proton or amidocarbonyl absorption indicating that a migration of the benzoyl group from nitrogen to oxygen had taken place.
Oxidation of N-Benzoyl-(+)-threo-Aminoalcohol (29).

In this preparation a modification of the procedure of S. H. Pines, S. Karady, M. A. Kozlowski and M. Sletzinger\textsuperscript{31} was employed. To an ice cold, stirred solution of the N-benzoyl-(+)-threo-aminoalcohol (29, 1.00 g, 0.003 mol) in purified acetone (stored over molecular sieves) was added dropwise 3.0 ml of Jones reagent (0.024 mol equivalent). After completion of the addition, the solution was allowed to stir for one hour while warming to room temperature. Upon removal of most of the acetone under reduced pressure, the residue was dissolved in ether. Extraction with water, saturated sodium bicarbonate, and again water yielded a clear ether solution which was dried over magnesium sulfate. The ether was removed under reduced pressure yielding a yellow oil which solidified. Recrystallization from ether gave 1.00 g (85%) of the ketone 30 as a yellowish solid, mp 142-143°.

The infrared spectrum showed the amide carbonyl absorption at 1650 cm\textsuperscript{-1} and the aromatic carbonyl absorption at 1685 cm\textsuperscript{-1}.

**Anal. Calcd for C\textsubscript{23}H\textsubscript{17}NO\textsubscript{6}: C, 68.47; H, 4.24; N, 3.47. Found: C, 68.00; H, 4.26; N, 3.20.**

Reduction of α-Benzamido-(+)-deoxypiperoin (30). In this preparation a modification of the procedure of S. H. Pines, S. Karedy, M. A. Kozlowski, and M. Sletzinger\textsuperscript{31} was employed. To an ice cold stirred solution of the benzamido-(+)-deoxypiperoin (30, 0.30 g, 0.001 mol) in dioxane was added slowly and dropwise 10% aqueous sodium borohydride (3 ml). The resultant mixture was stirred for 1 hr. Dilute hydrochloric acid (5%) was added to cease the reaction. Upon addition of the acid, a clear solution resulted which was concentrated under reduced pressure. The resultant yellow oil solidified upon standing. Analysis by thin layer
chromatography revealed that two products were formed. This mixture was separated by dry column chromatography on silica gel H and elution with chloroform-acetone (20:1). The more mobile fraction was concentrated yielding 350 mg (85%), of the *erythro* benzamido alcohol (31), mp 200.5-202° (lit.14 mp 201-202°).

**Attempted Hydrolysis of the N-Benzoyl-(+)-threo-aminoalcohol (29) with Acid.** A modification of the procedure of Pines, Karady, Kozlowski, and Sletzinger was employed. The N-benzoyl-(+)-threo-aminoalcohol (29, 1.00 g, 0.003 mol) was put into 50 ml of methanol containing concentrated hydrochloric acid (5 ml). The mixture was stirred (magnetically) and heated to reflux for 3 hr. The cooled, acidic solution was concentrated under reduced pressure yielding 0.50 g (50%) of a solid, mp 214-215°, indication of the benzoate ester (32) of the threo-aminoalcohol.

The infrared spectrum showed a carbonyl absorption band at 1720 cm⁻¹ and loss of both the amide proton band and amide carbonyl band.

Upon treatment of this compound in ether with sodium bicarbonate, the N-benzoyl-(+)-threo-aminoalcohol (29) was obtained, identical in spectral data with the amidoalcohol 29 prepared from 9.

**Attempted Hydrolysis of the N-Benzoyl-(+)-erythro-aminoalcohol (31) with Acid.** A modification of the procedure of Pines, Karady, Kozlowski and Sletzinger was employed. The N-benzoyl-(+)-erythro-aminoalcohol (31, 1.00 g, 0.003 mol) was reacted in the above manner. Upon completion of reaction 0.75 g (75%) of a solid, mp 214-215° was obtained. The spectral data were consistent with the O-benzoyl-(+)-threo-aminoalcohol (32) structure.
**Attempted Hydrolysis of the N-Benzoyl-(+)-threo-aminoalcohol (29) with Base.** The N-benzoyl-(+)-threo-aminoalcohol (29, 0.50 g, 0.001 mol) was put into 40 ml of methanol and 2N sodium hydroxide (2 ml) was added. The mixture was refluxed for 1 hr and an aliquot was tested with acid to check the progress of the reaction. The basicity of solution was increased from 2N to 10N slowly. With 10N sodium hydroxide the solution was heated to reflux for 3 hr. The cooled, basic solution was treated with dilute hydrochloric acid yielding 0.30 g (60%) of a white solid, mp 158-159°. The infrared spectrum of the solid showed the amide proton absorption band at 3350 cm\(^{-1}\) and the amide carbonyl absorption band at 1650 cm\(^{-1}\) which is identical with starting material (29).

**Preparation of Piperoin (27).** A modification of the method of G. G. Lyle and M. L. Durand\(^{30}\) was employed. A solution of ethanol (210 ml), water (167 ml), piperonal (7, 159 g, 1.06 mol) and sodium cyanide (17 g) was heated to reflux for 5 hr. After cooling overnight, the yellow solid was removed by filtration and dried, yielding 125 g (80%) of material, which after recrystallization melted at 117-119° (lit.\(^{30}\) 114.5-118.5°).

**Preparation of Piperoin Oxime (28).** In this preparation, a modification of the method of Shriner, Fuson, and Curtin\(^{39}\) was employed. To a mixture of piperoin (27, 10.0 g, 0.030 mol) in 10% sodium hydroxide (100 ml) was added alcohol in an effort to increase the solubility of piperoin. To this stirred mixture was added a solution of hydroxylamine hydrochloride (25 g) in water (150 ml). The cloudy yellow mixture was stirred for 5 min. After removal by filtration of all insoluble materials, the cloudy solution was heated for 15
min on a steam bath. The clear hot solution was cooled in an ice-water bath. The cooled solution clouded and was concentrated over a period of five days with occasional scratching by a glass rod. The yellow solid was recrystal- lized from benzene yielding 5 g (53%) of product melting at 138-139° (lit.\textsuperscript{14} 138.5-139°). The infrared spectrum showed a band at 3250 cm\textsuperscript{-1} (OH) and a shoulder at 1625 cm\textsuperscript{-1} (C=N) but indicated the lack of any carbonyl function. All attempts at catalytic hydrogenation of the oxime gave mix- tures of isomers which failed to be separated in satisfac- tory quantity as was also reported previously by Durand\textsuperscript{14} and Mancini.\textsuperscript{16}
Figure 5. Infrared spectrum of (+)-\textit{trans}-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (16) as a potassium bromide pellet.
Figure 6. Infrared spectrum of (+)-trans-N-Ethoxymethylene-4,5-Bis(3,4-methylenedioxyphenyl)oxazolidinone (17) as a potassium bromide pellet.
Figure 7. Infrared spectrum of N-Benzoyl-(+)-threo-1,2-Bis(3,4-methylenedioxyphenyl)-ethanol (29) as a potassium bromide pellet.
Figure 8. Infrared spectrum of $\alpha$-Benzamido-(+) -deoxypiperin (30) as a potassium bromide pellet.
Figure 9. Infrared spectrum of N-Benzoyl-(+)-erythro-1,2-Bis(3,4-methylenedioxyphenyl)-ethanol (31) as a potassium bromide pellet.
Figure 10. NMR spectrum of (+)-trans-N-Ethoxycarbonylmethylene-4,5-bis(3,4-methylenedioxyphenyl)oxazolidinone (17) in deuteriochloroform.
Figure 11. NMR spectrum of 2,3-Dihydro-\textit{(+)-trans-}oxazolo-4(1H)-isoquinolone (18) in deuteriochloroform.
Figure 12. NMR spectrum of N-Benzoyl-(+)-three-1,2-bis(3,4-methylenedioxyphenyl)ethanol (29) in dimethyl sulfoxide d$_6$. 
Figure 13. NMR spectrum of α-Benzamido-(+)-deoxypiperoin (30) in deuteriochloroform.
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