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I. CYCLOPROPylimines—Convenient Intermediates for Alkaloid Synthesis
II. Isoxazoles—An Alternate Approach to Dextrin

by

J. Michael Fitzpatrick

A thesis submitted
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy

Thesis Director's signature:

Robert [Signature]

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October, 1973
ABSTRACT

by J. Michael Fitzpatrick

I. Cyclopropylimines—Convenient Intermediates for Alkaloid Synthesis

Functionally substituted cyclopropylimines \( \text{1} \) were rearranged to \( \Delta'^{-}\)-pyrrolines \( \text{2} \) suitable for elaboration into members of the Senecio \( \text{3} \) and Lycorine \( \text{4} \) families of alkaloids.

II. Isoxazoles—An Alternate Approach to Dextrolin

Oxime \( \text{5} \) was prepared as part of a program to utilize isoxazoles in the synthesis of Eschenmoser's vitamin \( \text{B}_{12} \) precursor, the semicorrin, Dextrolin \( \text{6} \).
DEDICATION

To those who have touched my life these four years
ACKNOWLEDGMENTS

The author wishes to express his gratitude to Professor R. V. Stevens, who conceived and guided this research, and for the financial support supplied by him. In addition, his patience and friendship during a most trying time in my life is greatly appreciated.

A special thanks goes to Professor A. I. Meyers, whose belief in me as an undergraduate enabled me to enter into this program.
When one considers the progress that has been made in synthesis during the last 100 years, one is aware of a steady and impressive advance, but no revolutionary change such as has occurred in Analysis. The number of synthetically useful reactions is still within the capacity of the human intellect to remember. The number of economically important reagents is still small. More importantly the yield in an Organic Chemical reaction is very rarely quantitative. To carry out an industrially significant synthesis with more than fifty steps is still quite exceptional. Indeed it is well accepted that the smaller the number of steps in an industrial synthesis the better it is. However there is a Master Synthesist—Nature—who knows how to carry out many thousand step syntheses with seemingly 100% yield in each step. It is clear, therefore, that, in comparison with what Nature accomplishes in quantitative yield under mild aqueous conditions, the synthetic power of Organic Chemistry represents a grossly underdeveloped Science. There is therefore, a strong incentive, both intellectually and economically, to devote large resources to Synthesis in Organic Chemistry. Certainly the chances of a socially significant return for the expenditure seem far greater than for certain, traditionally more expensive, branches of Science. 80

D. H. R. Barton
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PART I

Cyclopropylamines--

Convenient Intermediates for Alkaloid Synthesis
INTRODUCTION

Alkaloids, basic nitrogenous products mostly of plant origin, display a myriad of functionality and structural units. It is this complexity, along with their pharmacological importance, which has attracted the attention and tested the skills of the synthetic organic chemist. The following list, which is by no means exhaustive, gives the reader some insight into the multifarious structural types within several alkaloid families. Though the structures of these alkaloids appear diverse, pyrrolidine and piperidine rings of various substitution patterns and oxidation states appear as a recurring feature. It is for this reason that alkaloid synthesis has become largely an exercise in the synthesis of fused piperidines\(^1\) and pyrrolidines. This thesis describes the development of two general methods of alkaloid synthesis involving (1) a cyclopropylimine to \(\Delta^2\)-pyrroline rearrangement and (2) an annelation of endocyclic enamines to give fused polycyclic ring systems.
Pyridine Alkaloids

Myosmine

Apoferrosamine

Mesembrine Alkaloids

Mesembrine

Mesembrinine

Joubertiamine

Dihydrojoubertiamine

Dehydrojoubertiamine
Amaryllidaceae Alkaloids

Elwesine

Crinine

Narwedine

Caranine

R = -CH₂-

Pluviine

R = CH₃

Erythrina Alkaloids

Erysotine

Erythratine
Aspidosperma Alkaloids

Aspidospermine

Limaspermine

Vincadiformine

Deoxyaspidodispermine

Lycopodine & Senecio Alkaloids

Lycodine

Trachelanthamidine
Model Studies. The Pyridine Alkaloids

The fact that many alkaloids contain pyrrolidine rings heavily substituted on a single face suggested that an endocyclic enamine such as 2 would be ideally functionalized for further elaboration in that the \( \beta \)-carbon is susceptible to electrophilic attack with concomitant generation of an electrophilic center at the \( \alpha \)-position (\( 2 \rightarrow 3 \rightarrow 4 \)). The production of the properly disposed \( \Delta^2 \)-pyrrolines, it was felt, might best be carried out via a cyclopropyliminium rearrangement, \( 1 \) to \( 2 \).

Although the desired rearrangement had been reported in the literature\(^2\) to be a purely thermal one, it was determined\(^3\) that acid catalysis was necessary. Cloke's original procedure (Scheme 1) involved the formation of the hydrochloride salt of imine \( 5a \) in order to separate it from neutral material and then regeneration of the imine by passing ammonia through a chloroform solution of the salt. The ammonium chloride was filtered away and the solution concentrated and distilled to yield pure \( \Delta^2 \)-pyrroline \( 7 \). This rather laborious procedure was circumvented during the present studies by employing phenyllithium and destroying the resulting lithio salt \( 9 \) with \( \text{Na}_2\text{SO}_4 \cdot \text{10H}_2\text{O} \). Concentration of the ether solution and distillation yielded the reportedly thermally
Scheme 1

**5** as a pure liquid. Thermal studies to determine optimum conditions for rearrangement failed to produce clean reorganization to the desired pyrrole. Cloke had further reported that the
hydrochloride salt \( \text{6} \) also rearranges smoothly and this is completely reproducible. Indeed not only does salt \( \text{6} \) rearrange but also imine \( \text{5} \) mixed with catalytic amounts of \( \text{6} \) proceeds well. The finding that pyrroline formation could be catalyzed by ammonium chloride (the innocuous byproduct of Cloke’s purification procedure) removed the dichotomy between Cloke's findings and those presented here.

Following the now clearly defined conditions, the synthesis of the pyridine alkaloids myosmine and apoferrorosamine was undertaken. Cyclopropane carbonitrile was treated with \( 3\)-lithiopyridine \( ^{1} \) and the resulting lithic salt decomposed with \( \text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O} \). Ketimine \( \text{10} \) was distilled without incident. Admixture of \( \text{10} \) with a catalytic amount of its hydrochloride salt and heating at \( 100^\circ \) for 15 min resulted in smooth production of myosmine \( \text{11} \) in 68% yield. \(^3\)
In a similar fashion, ketimine 12 was prepared and converted to apoferrorosamine\textsuperscript{3} 13 in 75\% distilled yield.

The Mesembrine Alkaloids

Having in hand a method for generating a variety of $\Delta^2$-pyrrolines of general structure 2, it remained to test the ability of these endocyclic enamines to undergo the desired further elaboration ($2 \rightarrow 3 \rightarrow 4$) via electrophilic attack at the $\beta$-carbon and simultaneous creation of an electrophilic center at the $\alpha$-position. Pyrroline 17 was prepared by the sodium amide promoted bisalkylation of phenyl acetonitrile in ether to give cyclopropane carbonitrile 14. Selective hydride reduction followed by acidic workup yielded aldehyde 15 which was transformed to $N$-methylinine 16 by condensation with methylamine. Acid catalyzed thermal rearrangement of 16 produced endocyclic enamine 17 in high yield.\textsuperscript{8}
It was hoped that methyl vinyl ketone (MVK) would react via a Michael addition at the \( \beta \)-carbon of 2-pyrrolidine 17 and then counter with alkylation at the newly formed electrophilic center at the \( \alpha \)-position, an assumption not without precedent for exocyclic enamines with electrophilic olefins.\(^5\),\(^6\) Furthermore a series of equilibria encompassing dihydropyran formation or 1,2 addition to form cyclobutylmethyl ketone 19 were anticipated but are known to be thermally reversible.\(^7\) These thermodynamic considerations and earlier experiments in refluxing ethanol\(^9\) suggested the use of the higher boiling protic solvent ethylene glycol. Indeed admixture of pyrrolidine 17 and methyl vinyl
ketone in hot ethylene glycol gave in moderate yield the cis-fused perhydroindolone 21 as the exclusive product.\textsuperscript{8a,9} The cis stereochemistry was predicted by maximum overlap considerations\textsuperscript{9,11} for the \(\pi\) orbital systems in intermediate 20.

Although the annelation of exocyclic enamines with methyl vinyl ketone finds a prominent role in organic synthesis, its employment here with an endocyclic enamine is unique.\textsuperscript{*} It is interesting to note that if the \(\alpha\)-position of the endocyclic enamine is substituted in such a way that the immonium ion 22 can deprotonate and produce a new enamine 23, this nucleophilic center will then condense with the carbonyl.\textsuperscript{11,12}

\*Almost simultaneously with this report, two other communications appeared reporting similar results.\textsuperscript{1b,6}
With the conditions for the requisite annelation available through model studies, the synthesis of racemic mesembrine was performed in an analogous fashion.\(^9\)

While 3,4-dimethoxyphenyl acetonitrile failed to undergo cyclopropanation under the influence of sodium amide, the reaction proceeded, albeit in low yield, using n-butyllithium as the base. The difference in reactivity between phenylacetonitrile and the dimethoxyphenyl acetonitrile is due, no doubt, to the destabilization of the benzylic anion by the methoxyls and was compensated for by using the more covalent gegen ion lithium. The yields of this reaction are even further increased if the nonnucleophilic base lithium disopropyl amide in hexamethyldiphosphoramidie is employed.\(^{14}\) Cyclopropanecarbonitrile \(^{24}\) via selective hydride reduction yielded aldehyde \(^{25}\) which was converted to aldmine \(^{26}\) and thence to \(\Delta^2\)-pyrroline \(^{27}\). Methyl vinyl ketone annelation followed by column chromatography gave racemic mesembrine \(^{10}\) in 56% yield.\(^*\)

\(^*\)Since the emergence of this annelation procedure, several additional ones have appeared.\(^{15}\)
Mesembrine

Pyrroline 27 has also been annelated with methyl 8-chloro vinyl ketone to yield mesembrinine. 8c
The discovery and characterization of the seco-mesembrine alkaloids joubertamine, dihydrojoubertamine and dehydrojoubertamine presented yet another opportunity to test the generality of the cyclopropylimine rearrangement and methyl vinyl ketone annelation.

p-Methoxyphenyl acetonitrile underwent smooth cyclopropanation employing lithium amide in glyme as the base. Diisobutylaluminum hydride in benzene followed by aqueous acidic workup produced aldehyde 29 which was converted to N-methyl imine 30 by a benzene solution of methylamine with suspended magnesium sulfate at room temperature. Ammonium chloride catalyzed thermal rearrangement of imine 30 produced Δ²-pyrroline 31 in excellent yield. Admixture of the hydrochloride salt of 31 and methyl vinyl ketone in acetonitrile and warming produced exclusively the cis-fused perhydroindolone 32. The conversion of 32 to (±)-O-methyljoubertamine 34 resulted from formation of the methiodide salt 33 and base catalyzed Hoffman elimination. Treatment of 34 with hot aqueous hydrobromic acid produced (±)-joubertamine in 80% yield. The dihydro derivative 36 was produced in quantitative yield from 35 upon hydrogenation over palladium. 16
C_{8}H_{13}CN \xrightarrow{\text{DIBAL} ; \text{H}_{3}\text{O}^{+}} C_{8}H_{13}CHO \xrightarrow{\text{CH}_{3}\text{NH}_{2}} C_{8}H_{13}NCH_{3}

C_{8}H_{13}NCH_{3} \xrightarrow{\text{NH}_{3}\text{Cl}} \xrightarrow{\Delta} C_{8}H_{13}OCH_{3}

C_{8}H_{13}OCH_{3} \xrightarrow{\text{CH}_{3}\text{I} ; \text{HO}^{-}} C_{8}H_{13}OCH_{3}

C_{8}H_{13}OCH_{3} \xrightarrow{\text{MVK}} C_{8}H_{13}OCH_{3}

C_{8}H_{13}OCH_{3} \xrightarrow{\text{HBr}} OH

C_{8}H_{13}OCH_{3} \xrightarrow{\text{H}_{2} \text{Pd/C}} C_{8}H_{13}OCH_{3}

C_{8}H_{13}OCH_{3} \xrightarrow{\text{H}_{2} \text{Pd/C}} C_{8}H_{13}OCH_{3}
The Erythrina Alkaloids

Access to fused polycyclic systems through the annelation of endocyclic enamines is further demonstrated by the facile synthesis of the Erythrina alkaloid\textsuperscript{17} model (±)-15,16-dimethoxyerythrina-3-one 38. The requisite endocyclic enamine 37 was prepared by a modification of Wiesner's\textsuperscript{18} procedure and reacted smoothly with methyl vinyl ketone\textsuperscript{19} to yield amino ketone 38 which had previously been reported as a degradation product of erysostrine.

![Chemical structures](image)

Erysostrine

The Amaryllidaceae Alkaloids

The Amaryllidaceae alkaloids include as one major group members containing the 5,10b-ethanophenanthidine nucleus which is usually referred to as the crinine group after the parent alkaloid.\textsuperscript{20} The structural similarity between mesembrine and the crinine alkaloids implied that the already proven cyclopropyl imine rearrangement and
methyl vinyl ketone annelation of endocyclic enamines might prove to be, with only minor additions, amenable to utilization in this latter series. The strength of this conviction was borne out by the following reactions.

Pyrroline 32 was prepared by the usual sequence of cyclopropanation, selective hydride reduction, condensation and acid catalyzed thermal rearrangement. Acid catalyzed methyl vinyl ketone annelation produced perhydroindolone 40, which when treated with sodium borohydride
yielded a 3:1 mixture of epimeric alcohols which were separated by preparative thin layer chromatography. Debenzylation of the major isomer 41 and Pictet-Spengler cyclization completed the synthesis of (±)-3-epi-elinesine 21 42. Catalytic reduction of ketone 40 over platinum, debenzylolation and Pictet-Spengler closure produce racemic (±)-elinesine 22.

The Aspidosperma and Related Alkaloids

The generality of the methyl vinyl ketone annelation, which has been shown to proceed smoothly with 2-pyrrolines, was further enhanced by the successful annelation 23 of 2-piperidine 44, prepared by the outlined sequence. The resulting cis fused hydroquinolone had previously 24 been converted to hydrolulolidine 45 and ultimately to aspidospermine itself.

![Chemical Structures](image-url)
The implied generality of the annelation step was further corroborated by the synthesis of hydroquinolone which can be envisioned to play a role in the synthesis of limaspermine via hydrolulolidone.
The efficacy of the cyclopropylimine to \( \Delta^2 \)-pyrrole rearrangement and annelation of endocyclic enamines as general methods of alkaloid synthesis is reiterated by the fundamentally different approach to hydrolulolidone 45 depicted below.\(^{25}\) Cyclopropane carboxaldehyde \(^4\) and ketal-amine \(^4\) were condensed and the resulting imine rearranged to \( \Delta^2 \)-pyrrole 50. Treatment of 50 with anhydrous HCl in ether and aqueous, basic workup\(^{26}\) yielded keto ester 51 which was converted to amino-ketone 52 as outlined.
The work reviewed in this section, along with that presented in the Results and Discussion, supports the original contention that the acid catalyzed thermal rearrangement of cyclopropylimines to $\Delta^2$-pyrrolines and the methyl vinyl ketone (or some similar vinyl ketone) annelation of endocyclic enamines are completely general methods of alkaloid synthesis.
RESULTS AND DISCUSSION

The pyrrolizidine alkaloids have been isolated from many genera of the botanical families Compositae, Leguminosae and Boraginaceae. Senecio, the largest genus belonging to the Compositae family, provides the greatest number of species containing alkaloids with a hydroxylated pyrrolizidine moiety and for this reason the term "Senecio alkaloids" is retained to describe this family of alkaloids. These bases normally appear esterified by one or more carboxylic acids and a single pyrrolizidine base may appear as the central framework of a number of alkaloids differing only by the carboxylate portion of the molecule. Comprehensive reviews of the Senecio alkaloids have appeared\textsuperscript{27,28} and the chemistry, structure proofs and prior syntheses of these compounds are to be found there. This section will be devoted to the attempted synthesis of one or both of the enantiomeric necine bases (±)-trachelanthamidine \textsuperscript{2} or (±)-isoretonecanol \textsuperscript{3}. 

![Chemical structure of pyrrolizidine alkaloid]
It was reasoned that a practical approach to the pyrrolizidine ring system might be the initial formation of the A ring as a $\Delta^2$-pyrroline 2 and then acid catalyzed cyclization of the ketal amine to the indolizidinone 10. This latter step had ample precedent in the synthesis of perhydroquinolones $^{1,26}$ and perhydroindolones $^{25}$. The formulation of the properly substituted $\Delta^2$-pyrroline could best be accomplished via the acid catalyzed thermal rearrangement $^{16}$ of cyclopropyl-imine 8, whose synthesis was realized by the following scheme.

Ethyl cyanoacetate with sodium ethoxide as the base, under conditions of controlled pH, undergoes bisalkylation with ethylene dibromide to produce ethyl-1-cyanocyclopropane-1-carboxylate in 52% yield $^{30}$. Nitrile 4 was converted to aldehyde 6 employing Meyers' procedure $^{31}$. Thus 2-methyl-2,4-pentane diol was added to a mixture of nitrile and concentrated sulfuric acid at 0°C; workup yielded dihydro-1,3-oxazine 5 in 64% yield. Sodium borohydride reduction followed by steam distillation of an oxalic acid solution of the tetrahydrooxazine produced cyclopropane carboxaldehyde 6 in 55% overall yield from 5.
The ethylene ketal of bromoacetone was reacted with potassium phthalimide to generate the corresponding N-alkyl phthalimide which was cleaved under the influence of hydroxide to produce the desired ketal amine. Admixture of aldehyde and amine in benzene in the presence of anhydrous magnesium sulfate resulted in the formation of aldimine in 80% distilled yield. Ammonium chloride catalyzed thermal rearrangement produced 2-pyrroline in 75-82% chromatographed yield.
Having successfully synthesized the requisite pyrroline, the remainder of the scheme involved the aforementioned acid catalyzed cyclization of ketal amine 9, presumably via immonium salt 9a, to pyrrolizidine 10, lithium aluminum hydride reduction to pyrrolizidine 11, and exposure of ketone 12 to Wolff-Kishner reduction.

However, placement of 9 into an ether solution saturated with anhydrous HCl for up to 72 hr failed to produce a smooth conversion to pyrrolizidine 11. Small amounts of material containing a band at 1724 cm⁻¹ in the infrared, the frequency expected for saturated esters, were produced but the major product was starting pyrroline 9. This result was unsettling in light of the facility with which the perhydroindolone systems were formed. Pyrroline 9 was next treated with tosic acid in refluxing benzene for 12 hr. Basic workup yielded a mixture of products devoid of the characteristic infrared bands (1650, 1590 cm⁻¹) of the
8-acyl enamine \(^{33}\) chromophore and containing a band in the region 1725 cm\(^{-1}\). Attempts at chromatographic purification of this material met only with further resification.

In an attempt to reach a stage at which purification could be effected more easily, the crude reaction mixture from the benzene tosic acid treatment was reduced with lithium aluminum hydride in ether to produce a mixture which hopefully contained some alkanolamine \(^{11}\). The product was no less complicated than before but was subjected to hydrolysis conditions in hopes of securing amino ketone \(^{12}\). It is noteworthy that upon hydrolysis, the infrared spectrum of the resulting material contained carbonyl absorption at 1720 cm\(^{-1}\) instead of the region typical of five-ring ketones (1740-1750 cm\(^{-1}\)). In spite of this, the crude hydrolysis product was subjected to Wolff-Kishner reduction and then chromatographed on alumina. The resulting fractions were treated with picric acid in hopes of isolating a solid derivative of one of the hydroxymethyl pyrrolizidines. The picrates were oily mixtures which were not further characterized.

This annoying inability to successfully cyclize pyrroline \(^{2}\) to pyrrolizidine \(^{10}\) is now understandable in terms of the electronic requirements of the intermediates involved. Thus treatment of \(^{2}\) with acid produces immonium ion \(^{14}\). Prior to formation of enol ether \(^{25}\), protonated ketal \(^{15}\) must be formed. The close proximity of the two positive charges is a most unfavorable arrangement and apparently prevents generation of
the requisite enol ether. This same effect has been witnessed by Evans in the attempted enolization of aminoketone 16, which failed to incorporate deuterium even after prolonged heating with deuterated acids.

This problem may ultimately be resolved by synthesis of enol ether 17, a project currently in progress in these laboratories, which would circumvent any dipositive species.
The Amaryllidaceae Alkaloid Pluviine

Pluviine is a minor Amaryllidaceae alkaloid isolated from *Lycoris radiata* and from several garden varieties of *Narcissus pseudonarcissus* and *N. incomparabilis*. It is a member of the Lycorine group, all of which have the pyrrolo[d,e]phenanthridine nucleus. Although several reports of the synthesis of aromatic degradation products of the Lycorine alkaloids and of the pyrrolophenanthridine nucleus have appeared, there has not been a single successful total synthesis in this group. We were challenged by this finding and initiated the following study on the synthesis of pluviine.

Having successfully synthesized the pyrroloquinoline ring system via a cyclopropylimine rearrangement during the Aspidospermine studies, it was felt that a similar approach might be employed in the construction of the pyrrolophenanthridine nucleus.
Pluviine 3 is simply a stereoselective reduction step away from 

\[ \beta,\gamma \text{-unsaturated ketone} \ 4 \text{ which, it was envisioned, could best be prepared} \]

by an intramolecular aldol condensation involving keto-aldehyde 6 and subsequent deconjugation\(^{37}\) of the resulting enone 5. Keto-aldehyde 6 would arise from acid catalyzed cyclization\(^{25}\) of pyrroline 7 which would be generated from cyclopropyl imine 8 by acid catalyzed, thermal rearrangement.\(^{16}\) The initial task then was to synthesize the necessary components of aldimine 8, i.e. ketal-amine 14 and dialdehyde 15.

Thus veratraldehyde was condensed with nitroethane in the presence
of n-butylamine to yield nitroalkene 10 in essentially quantitative yield. The olefin is formulated as the trans-isomer based upon the coupling constants ($J = 1$ cps) of the vinyl proton and the vinyl methyl group. The crude reaction mixture was then reduced directly by an iron-HCl mixture and the product steam distilled to yield aryl acetone 11 contaminated by approximately 25% veratraldehyde. The aldehyde, which can be removed by spinning band distillation, arises from hydration of the nitroolefin and concomitant loss of nitroethane.

$$\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{CH}_2\text{O} & \quad \text{CH}_3\text{O} \\
\text{H}_3\text{O}^{+} & \quad \text{CH}_3\text{O} \\
\text{CHO} & \quad \text{C}_2\text{H}_5\text{NO}_2
\end{align*}$$

Ketone 11 when treated with N-hydroxymethyl phthalimide 40 under the influence of BF$_3$:Et$_2$O yielded phthalimide 12 in 80% yield. This reaction yields a single aromatic substitution product in spite of the fact that three possible sites of substitution are available. The actual position

$$\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{CH}_2\text{O} & \quad \text{CH}_2 \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{O}
\end{align*}$$

20
of alkylation is, no doubt, due to a steering effect arising from a six-
membered chelate \(^{20}\) involving the carbonyl oxygen, the phthalimido-
methyl carbenium ion and the site of substitution. This same mechanism
has been proposed for the high degree of specificity found in electrophilic
thallation reactions.\(^{41}\) The orientation was substantiated by degrada-
tion of the amine by potassium permanganate to yield \(^4,5\text{-dimethoxy-}
phthalic acid (\(\text{\textit{m}}\text{-hemipic acid}).

Ketal \(^{12}\) was produced in high yield upon azeotropic removal of
water from a mixture of ethylene glycol and tosic acid. Cleavage to
amine proceeded smoothly employing hot, alcoholic hydrazine hydrate or
aqueous methyamine.\(^{42}\)

The synthesis of the requisite \(1,1\text{-diformyl cyclopropane began}
with ethyl-1-cyanocyclopropane-1-carboxylate\(^30\) \(^{16}\) (cf. Senecio and
aspidospermine\(^25\) alkaloids). Ammonolysis\(^{43}\) using ammonium hydroxide
produced cyano amide \(^{17}\) in excellent yield. Dehydration of the amide
using phosphorous oxychloride\(^{44}\) produced \(1,1\text{-dicyano cyclopropane}\(^{18}\)
which underwent selective reduction and hydrolysis to the dialdehyde \(^{15}\).

An alternate procedure involved the bis-reduction of diethyl-\(1,1\text{-}
cyclopropane dicarboxylate with lithium aluminum hydride to diol \(^{19}\).
Collins\(^{45}\) oxidation produced the dialdehyde \(^{15}\).

With the two halves in hand the production of cyclopropylimine \(^8\)
and \(\Delta^2\text{-pyrroline}\(^7\) was undertaken. Ketal amine \(^{14}\) and dialdehyde \(^{15}\)
were mixed in the presence of suspended magnesium sulfate for 12 hr.
At this time infrared showed no N-H stretch and a strong band at 1650
\(\text{cm}^{-1}\) (aldimine). Attempts to characterize this material by chromatography
resulted in hydrolysis of the aldime and recovery of the benzylamine.
Furthermore prolonged standing at room temp, resulted in the weakening
of aldehyde absorption in the infrared. Nmr also showed a disproportionately small resonance due to aldehyde. The crude reaction product was treated with ammonium iodide in refluxing benzene for 18 hr. This produced increased resinification but the infrared did display bands at 1605 and 1645 cm\(^{-1}\), the region for the \(\beta\)-acyl enamine chromophore.\(^{33}\)

The problem at this stage may well arise from a competing cyclopropane carboxaldehyde rearrangement which would produce the dihydrofuran \(^{21}\). Although the problem was in its infancy, no further experiments were performed in this series due to changing priorities.

This alternate mode of rearrangement (viz. \(^{8}\) to \(^{21}\)) is not a serious drawback to the ultimate outcome of this project. If instead the aldime \(^{23}\) is prepared using the versatile aldehyde \(^{22}\) (cf. Senecio and aspidospermine \(^{25}\) alkaloids), acid catalyzed rearrangement, selective hydride reduction and hydrolysis would yield the key ketoaldehyde \(^{6}\). This route will hopefully be pursued at some future date.
PART II

Isoxazoles: An Alternate Approach to Dextrolin
INTRODUCTION

Since the isolation of crystalline vitamin $B_{12}$ by Folkers and coworkers and by Smith and Parker, thousands of publications concerning the vitamin have appeared. New impetus to the field has been added by Crowfoot-Hodgkins' X-ray structure determination and by attempts in several laboratories at the total synthesis, culminating in the successful completion of one such effort by Woodward, Eschenmoser, and their collaborators at Cambridge and Zurich.

The nomenclature of the vitamin $B_{12}$ group can be summarized as follows. The macro-ring is named corrin and compounds containing this ring system are called corrinoids. Except for one preliminary report of less than convincing nature, all the corrinoids investigated thus far contain cobalt as the central atom. When all of the carboxyl groups in 2 are acids, the compound is called cobyric acid 3 and is the parent compound in the series. If all the carboxyl groups in 2 are amidated except for position (f), the compound is known as cobyric acid 4. In cobinic acid 5, the carboxyl group at (f) is amidated with
D-(-)-1-aminopropan-2-ol while the others are free. In cobinamide 6, the f-carboxyl group is amidated with l-aminopropan-2-ol and all others are amidated with ammonia. Cobinamides 6 which are esterified with a
5,6-dimethylbenzimidazole ribonucleotide are called cobalamin \footnote{1}. Other ligands on the cobalt may be water or anions but the coenzyme forms which are biologically active contain neither. Instead the second coordination site is filled by the 5'-deoxyadenosyl residue. As usually isolated, the sixth coordination position of the Co(II) atom is filled by cyanide, an artifact of isolation; this derivative is called cyanocobalamin. In vivo it is the coenzyme form which exists but these are unstable (particularly to cyanide) and difficult to isolate.

The pedagogical aspects of a total synthesis of vitamin \textbf{B}_{12} are, within themselves, justification for such an undertaking but the tangential biomedical knowledge gained might well be an overshadowing bonus. Synthetically prepared analogues with antagonistic activity may be suitable for the treatment of leukemia or other malignant diseases, for enhanced activity against pernicious anemia or other dysfunctions of the blood system. Indeed some of the most powerful present day antibiotics are synthetic analogues of the naturally occurring forms.

With these goals in mind a fundamentally different approach, one which allows ample manipulation of structural features, to corrinoid synthesis is being developed employing isoxazoles as the basic synthon.
Vitamin B

\[ L = \text{CN} \quad \text{Cyanocobalamine} \]

\[ L = \text{Vitamin B} \quad \text{Coenzyme} \]
Model Studies

The concept of corrinoid synthesis must focus upon a general method of constructing the ring-bridging vinylogous amidine system 8. This may be seen as an aza-analogue of vinylogous amides 2, an attractive synthesis of which might entail reduction of a properly substituted isoxazole 11 with concomitant tautomerization of postulated intermediate 10.

\[ \begin{array}{cccc}
\text{(8)} & \Rightarrow & \text{(9)} & \Rightarrow \\
& & \text{(10)} & \\
& & & \text{(11)}
\end{array} \]

Of the methods of preparation of isoxazoles available, the cycloaddition of nitrile oxides 12 with terminal acetylenes to generate the requisite 3,5-disubstituted isoxazoles 11 appeared most attractive.
All of the nitrile oxides prepared in this study were generated *in situ* by one of the following three methods: (1) phosphorous oxychloride or phenyl isocyanate induced dehydration of primary nitro compounds; (2) lead tetraacetate dehydrogenation of syn-aldoximes (*anti*-aldoximes fail to yield nitrile oxides with this reagent); (3) and by reaction of either syn- or anti-aldoximes with N-bromosuccinimide or N-chlorosuccinimide in the presence of sodium methoxide or triethylamine. These methods have been the subject of an excellent, recent review by Gruneman.55

The initial experiments involved preparation of primary nitro ester 13, phenyl isocyanate dehydration to nitrile oxide 14 and cyclo-addition with phenyl acetylene to isoxazole 15. Two isomeric isoxazoles are possible from such a combination of dipole and dipolarophile, the depicted 3,5-disubstituted nucleus and/or the vicinally substituted 3,4 isoxazole, cf. 11. To this date none of the latter isomer has been detected in any of the cycloadditions performed within this program. This result is predictable based upon steric arguments. Isoxazole 15 was reduced to the isolable vinylogous amide 16 which underwent cyclo-dehydration to the desired lactam 17 upon heating in vacuo.54

Dilution studies in the infrared proved that 17 had the cisoid geometry necessary for further elaboration to a vinylogous amidine moiety.
With the postulated reduction and cyclodehydration steps proven to be viable methods of vinylogous amide preparation, the synthesis of a known semicorrin was undertaken. Thus acetylenic ketone 18 and nitro-diester 19 were subjected to cycloaddition conditions to yield isoxazole 20. Saponification and decarboxylation yielded isoxazole acid 21 which underwent hydrogenation and spontaneous cyclodehydration to lactam 23. Ammonia in methanol produced carbinolamine 24 which smoothly dehydrated 51 to semicorrin 25, identical in all aspects to Eschenmoser's compound. 51
A Synthetic Target—Dextrolin

In the successful synthesis of vitamin $\text{B}_{12}$ carried out by Woodward and Eschenmoser, the two halves of the corrinoid cobyric acid were joined via a triphenylphosphine mediated sulfide contraction (viz. $26 + 27 \rightarrow 28$) and thence on to $4$. The aspects of this complex series of
reactions will not be delved into here, since they are available elsewhere.\textsuperscript{50,51,56} Thiodextroin, or more appropriately its oxo precursor dextroin \textsuperscript{30}, possesses the semicorrinoid structure (of \textsuperscript{25}) produced by isoxazole reduction and cyclodehydration. And it is this compound which was chosen as our synthetic target.
A retrosynthetic analysis of the structural features of dextroin 30 reveals the following subtleties: the lactone fused to ring B may arise from a carbinolimine such as 31, which in turn is only a cyclodehydration away from diketone 32 (cf. 23 to 24). Intermediate 32 is itself derivable from cyclization of vinylogous amide 33 (cf. 22 to 23), an intermediate in the reduction of isoxazoles (cf. 21 to 22). The requisite 3,5-disubstituted isoxazole 34 can be envisaged to arise from the aforementioned cycloaddition of acetylene 36 and the nitrile oxide derivable from aldoxime 35. It is the synthesis of this latter compound which occupies the remainder of this thesis.
RESULTS AND DISCUSSION

In choosing an acceptable synthon for oxime 1, it was observed that aldehyde 2 was a substituted glutarate ester, the carboxylate groups being 1,5 to each other. One of the most general techniques for glutaric acid synthesis is the oxidative cleavage of the properly substituted cyclopentene by peroxides of transition metals 57 or by ozone. 58 The initial task then was the preparation of a substituted cyclopentene 3 in which "P" was some protecting group capable of surviving the oxidative conditions necessary for securing aldehyde 2.

One scheme for preparing such a compound involved thermally cracking dicyclopentadiene to give the monomer 4 which was reacted with a controlled amount of anhydrous halogen acid, MX, to give the allylic 59 halide 5. This highly unstable halide was then reacted with the dicyclohexyl enamine of isobutyraldehyde. Instead of the desired δ2-cyclopentene acetaldehyde 7, a nearly quantitative yield of dicyclopentadiene and isobutyraldehyde was obtained. This apparently occurred via dehydrohalogenation of 5 promoted by the basic enamine and subsequent dimerization of the labile diene.
It was envisaged that aldehyde 7 might be prepared in yet another fashion. If enol ether 8 could be prepared, there was ample precedent for a Claisen rearrangement to occur giving the desired carbonyl compound. Thus 3-hydroxycyclopentene 10 was obtained by the action of aqueous sodium bicarbonate on allylic halide 2. It was then hoped
that the dicyclopentenyl acetal 11 could be formed and converted to the
desired enol ether 8. Unfortunately the sole olefin product was once
again dicyclopentadiene.

In searching the literature for a viable alternative to the above
procedures, it was discovered that 2-cyclopentene-1-acetic acid 12 was a
commercially available compound. With this material in hand the plan
was to produce aldehyde 14 by selective hydride reduction using diisobutyl-
aluminum hydride, formation of the pyrrolidine enamine and sequential

\[
\begin{align*}
 & \text{HOC} & \text{HOC} & \text{OH} & \text{OH} \\
 & \text{CH}_2\text{N}_2 & \text{HCO} & \text{HN} & \\
 & \text{12} & \text{13} & \text{14} & \text{15} & \text{16}
\end{align*}
\]

bisalkylation with methyl iodide. The reduction step (viz. 13 to 14)
proceeded smoothly with 80% of the material being converted to aldehyde
14 and the remaining 20% being ester 13 and the alcohol derived from
overreduction of the aldehyde. The reactants were conveniently
separated by distillation and the enamine 15 was formed in 43% yield by
acid catalyzed condensation of aldehyde 14 and pyrrolidine. Several
attempts to alkylate the enamine yielded, upon basic workup, only the
unalkylated aldehyde. This result may be attributed to N-alkylation of
the pyrrolidine portion of the enamine and subsequent hydrolysis upon
workup to yield the aldehyde. This problem is a common one and is
usually circumvented by preparing hindered enamines (cf. dicyclohexyl-
enamine 6). This hypothesis was not tested, for at this time it was
realized that by employing the powerful, nonnucleophilic base lithium diisopropyl amide the α positions of both acids 65 and esters 66 could be alkylated. The decision was made to employ acid 12 rather than ester 13 due to the higher reported yields for the alkylation of acids and from our own experiences with ester 13. Accordingly 2-cyclopentene-1-acetic acid, when treated with two equivalents of lithium diisopropyl amide, smoothly monoalkylated to give monomethyl acid 17 as a mixture of diastereomers in 96% distilled yield. All efforts to dialkylate 17 by

adding a second aliquot of amide and methyl iodide met with disappointment. However if mono-acid 17 was worked up and then submitted to the action of two equivalents of amide and methyl iodide once again, the second methyl group could be added cleanly to yield dimethyl acid 18 in 94% yield. The puzzling reluctance of the gem alkylation to proceed in a
single reaction flask without an intermediate purification can be attributed to the decreased solubility of the dilithio salt (cf. 12) as the concentration of lithium iodide increases and the polarity of the solvent decreases due to added hexane (the solvent for n-butylithium).

Dimethyl acid 18 was esterified in quantitative yield using diizomethane and then treated with diisobutylaluminum hydride to effect selective reduction to aldehyde 21. However the yields of the aldehyde were approximately 40%, the remaining material being a 1:1 mixture of alcohol 20 and ester 19. Even lowering the temperature to -95°C did not significantly change the ratios. This result is particularly annoying in light of acceptable yields of aldehyde when the unsubstituted ester was reduced under identical conditions (cf. 13 to 14). Zakharkin 67 claims that the initial 1:1 adduct 23 formed by the action of diisobutylaluminum hydride decomposes spontaneously above -35°C. In the present case the ester in question may be viewed as a neopentyl ester and the complex corresponding to 23 can be assumed to be quite crowded, thereby decreasing its half-life. With the accelerated collapse of the 1:1 adduct and comcomitant exposure of aldehyde 21 to hydride the yield of alcohol 20 rises at the expense of that of aldehyde.

This problem of overreduction was obviated by reducing ester 19 to alcohol 20 quantitatively with lithium aluminum hydride and oxidizing the
primary alcohol to aldehyde in 94% yield using chromium trioxide-pyridine. This two step procedure, as can be seen, gives excellent yields. The aldehyde was then protected as its ethylene acetal 22.

Having in hand the desired protected aldehyde 22 (cf. 3), the first attempt at oxidation employed the phase transfer catalysis procedure of Starks. This method employs a quaternary ammonium salt, tricaprylylammonium chloride, to transport anions from the aqueous phase to the organic phase. In fact this material is capable of solubilizing potassium permanganate in benzene and thereby producing a powerful oxidant. The initial studies with cyclopentene and this reagent gave good yields of glutaric acid.

When olefin 22 was treated with a mixture of aqueous potassium permanganate, tricaprylylammonium chloride and benzene, instead of the desired diacid 25 being isolated, a complex mixture of products containing the diastereomeric lactol 26 was recovered. The fact that the ring-chain tautomerism between aldehyde-diacid 25 and lactol 26 favors the latter is well understood in terms of the Thorpe-Ingold "gem-dialkyl effect" but it was hoped that conditions of controlled pH would allow isolation of the diacid with the acetal protecting group still intact; this was not to be the case. All attempts to isolate this diacid met with failure. Finally the problem was partially circumvented by isolating the dipotassio salt 24 and treating it with methyl iodide in hexamethyl phosphoric triamide. This results in bisalkylation of the carboxylate anions to produce diester 27. This compound appeared to be only a hydrolysis step away from aldehyde 2. Unfortunately all attempts to hydrolyze 27 resulted in formation of lactol 26 (R = CH3).
The issue was further clouded by the finding that upon esterification of 24, the triester 28 was also present. The production of this compound, it was determined, arises from oxidation of the acetal by permanganate to ester 22, saponification and reesterification by methyl iodide. This sequence is supported by the finding that the diethyl acetal of acetaldehyde 30 is rapidly oxidized to ethyl acetate even in the absence of the trialkylammonium chloride catalyst. This eliminates the possibility that the acetal is first hydrolyzed to aldehyde by the slightly acidic ammonium salt. Acetals have been oxidized to esters under a variety of
acidic conditions, but as far as can be determined only two reports of such a transformation under neutral or basic conditions appear. One involves photochemical oxygenation to give a peroxy orthoester which undergoes reductive (Na$_2$S$_2$O$_4$) or hydrolytic (NaOH) workup to produce glycol ester. The other entails the attack of ozone on acetal and reorganization to ester. This report of the action of permanganate on acetals appears to be unique.

The difficulty arising from the production of triester was removed by cleaving the olefin with ozone rather than permanganate. As it has been pointed out above, ozone attacks cyclic acetals even at -78°C (viz. to 34). However, Deslongchamps has further noted that acyclic acetals are attacked only slowly at low temperature. Accordingly, dimethylacetal was prepared by admixture of aldehyde, trimethyl
orthoformate and tosic acid in methanol. By adding only an equivalent amount of ozone at -78°C, the olefin was selectively attacked. The resulting ozonide was then oxidized to disodic salt 36. Although the

problem of triester formation had been eliminated, all attempts at acid catalyzed regeneration of aldehyde 2 resulted in production of lactol 26. It was now obvious that the protecting group P (viz. 3) must not only be stable to oxidation, but also be able to be removed under neutral conditions. One such group, it was felt, would be a benzyl ether.
Thus alcohol 20 when treated with sodium hydride and benzyl chloride was converted to benzyl ether 38 in 94% yield. Ozonolysis of 38 at 
-78°C in methanol and hydrolysis of the ozonide with aqueous sodium hydroxide at room temperature yielded the sodium salts of the mixed aldehydo-acids 39. Addition of two equivalents of 30% hydrogen peroxide to the methanolic hydroxide solution and gentle warming for two hours, followed by esterification of the acidic material produced diester 40 along with approximately 15% lactone 41 and methyl benzoate. The latter
two products were derived from oxidation of the benzyl ether by alkaline hydrogen peroxide and subsequent lactonization of alcohol $\text{H}_2$ either at the diacid or diester stages.

The pure diester $\text{H}_0$ could be isolated by column chromatography on alumina. But on preparative scale the mixture was distilled through a short-path distillation head prior to the debenzylation step. This ensured that all traces of acid were removed, thereby preventing acid catalyzed cyclization to lactone $\text{H}_1$. Alcohol $\text{H}_2$ ($R = \text{CH}_3$) is so sensitive to acid that even minute amounts such as residual acetic acid in the tubing leading to the hydrogenation vessel have caused complete conversion to lactone. For this reason the apparatus is dismantled and washed with aqueous sodium bicarbonate before each debenzylation attempt.

If the above steps are employed, debenzylation proceeds in excellent yield, by hydrogenation at 50 psi with palladium on charcoal as catalyst to produce alcohol $\text{H}_2$. Collins oxidation of $\text{H}_2$ produced aldehyde 2 which was converted to aldoxime $\text{H}_1$, the original target compound. The crude oxime was then purified by column chromatography on silica gel.
Anxious to incorporate aldoxime 1 into a model compound possessing the salient features of ring C in Eschenmoser's dextrobin 45, isoxazole 43 was prepared by the addition of N-bromosuccinimide to aldoxime 1 at 0°C followed by slow addition of phenylacetylene and triethylamine. Lactam 44 was obtained by hydrogenation of isoxazole 43 over Raney nickel until the theoretical amount of hydrogen was taken up and then allowing the mixture to stir for 12 hours. Filtration of the catalyst and concentration of the methanol gave 44 as a paramagnetic nickel complex. This complex was destroyed by dissolving the solid in methanol, adjusting the pH to 8 with 15% sodium hydroxide and bubbling through hydrogen sulfide. The black nickel sulfide was filtered away and the methanol concentrated to yield lactam 44.

Model Studies in Acetylenic Ketone Synthesis

Simultaneous with the above-mentioned studies was a program whose goal was the synthesis of the acetylenic ketone 46, necessary for combination with aldoxime 1 in the preparation of dextrobin. One method for the
synthesis of such compounds involves the thermally induced fragmentation of α,β-epoxy-hydrazones \(^{73,74}\) (viz. 47 to 48). The two most commonly used hydrazones are derived from tosylhydrazide \(^{47a}\) or N-amino phenylaziridine \(^{47b}\). The similarity between 48 and ynone 46 is apparent and the synthetic plan revolved around the obtention of a suitably substituted epoxyketone (viz. 49) which would then be fragmented to ynone 46.

\[
\begin{align*}
47 & \xrightarrow{\Delta} 48 \\
R = & \text{H, alkyl} \\
R^2 = & \text{NSO}_2^{-p\text{-tolyl}} \\
R^3 = & \text{HSO}_2^{-p\text{-tolyl}} \\
R = & \text{Ph} \\
\end{align*}
\]

The partial synthesis of one such ketone 51 is outlined below. All of the reactions appearing in this scheme were performed by Dr. B. L. Harrison\(^ {75}\) and appear here for the sake of completeness.
Yet another enone, prepared as a model system for 46, is compound 52 whose synthesis was effected by Mr. R. E. Cherpeck. 76

![Chemical Reaction Diagram]

Compounds 50, 51 and 52 and their preparations are entered here because of the integral part they played in fragmentation studies carried out as part of this thesis work.

Prior to initiating efforts directed towards the synthesis of ynene 46, a brief study on the reproducibility and applicability of the fragmentation process to five-ring epoxyketones was undertaken. Thus 53 was combined with N-amino-phenylaziridine 73 in methylene chloride at 0°C. Glc indicates that formation of 54 is instantaneous even at 0°C. The oily hydrazone when heated to 150°C at 60 mm in a Kugelrohr cleanly fragments to ynene 55.
It was deemed desirable to test this fragmentation on epoxyketones with a greater degree of functionality and steric crowding and with 50, 51 and 52 now in hand the program began. Epoxyketone 51 when treated with N-amino phenylaziridine in methylene chloride at 0°C is rapidly and quantitatively converted to hydrazone 56. Heating of 56 in a Kugelrohr at 150°, 3 mm produces ynone 57 in 63% yield.
However when epoxyketone \textbf{52} was treated with the aminoaziridine acetate at 0° for up to 6 hr, no reaction occurred. Even at room temperature (29-30°C) there was no reaction, other than decomposition of the thermally labile aziridine. If the free aziridine either in methylene chloride or with no solvent at all was allowed to stand with epoxyketone \textbf{52} for up to 24 hr, no hydrazone \textbf{58} was produced. The reluctance of \textbf{52} to form hydrazone \textbf{58} is attributed to the steric crowding created in going from an \textit{sp}^2 to an \textit{sp}^3 center in intermediate \textbf{59} which would have severe eclipsing strain between adjacent substituents.\textsuperscript{77}
An alternative to forming the hydrazone of an epoxyketone is to form the epoxide of an α,β-unsaturated hydrazone.\textsuperscript{78,78} The initial attempt to perform this sequence involved enone \textbf{50}. Tosylhydrazide and enone \textbf{50} were reacted in refluxing methanol to yield hydrazone \textbf{60} in good yield. Treatment of \textbf{60} with m-chloroperbenzoic acid in methylene chloride at 27°C resulted in quantitative return to enone \textbf{50}. This is a known\textsuperscript{74,75} side reaction in the epoxidation of six-ring α,β-unsaturated hydrazones, but appears to be the exclusive reaction for five-membered rings. Indeed even at 0-5°C for four days none of the desired epoxy hydrazone is formed and 25 to 30% of the enone \textbf{50} is produced by admixture of \textbf{60} and m-chloroperbenzoic acid.
EXPERIMENTAL

Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. PMR spectra were recorded on a Varian A-56-60-A spectrometer in deuterchloroform with TMS as internal standard and sweep width 500 Hz. Mass spectra were obtained on a Consolidated Electrodynamics Corp. 21-110 high resolution spectrometer. Microanalyses were obtained from Ebleck Microanalytical Laboratory, Harbor City, California. Thin-layer chromatography employed Brinkman precoated silica-gel F-254 or aluminum oxide F-254, Type T plates. Melting points are uncorrected.

**Senecio**

\[ \text{CO}_2\text{Et} \quad \text{CN} \quad - \quad \text{Br} \quad \text{NaOEt/EtOH} \rightarrow \quad \text{CO}_2\text{Et} \quad \text{CN} \]

**Cyclopropanation:** Following the procedure of Mitchel \(^{43}\) 545 g (2.9 moles) of ethylene dibromide and 1.8 l. of absolute ethanol was added to a 5 l., 3 necked round bottomed flask equipped with a 250 ml addition funnel, mechanical stirrer and a Claisen adaptor fitted with a reflux condenser and 250 ml addition funnel. The mixture was refluxed and stirred under nitrogen while from separate funnels 270 g (2.39 moles) of ethyl cyanoacetate and a solution of 50 g of sodium in 700 ml of ethanol were added proportionately during four hours. The pH was monitored throughout the addition with p-Hydron pH paper moistened with water and remained between 7 and 9. (If the pH becomes greater than 9 the addition of ethoxide should be halted until the proper range is reached.)
A second equal portion of sodium in ethanol was added over a six hour period so that pH 9 was never exceeded. Reflux was continued for one hour after addition was complete. After stirring overnight at room temperature, the sodium bromide was filtered away from the strawberry colored solution and the ethanol was removed by rotary evaporation.

The residue was taken up in 800 ml of ether and washed with two 200 ml portions of water. The aqueous extracts were saturated with ammonium sulfate and the organic phase separated and combined with the ethereal layer. The combined organic layers were dried over MgSO₄, concentrated by rotary evaporation to give 157.4 g of ethyl 1-cyanocyclopropane-1-carboxylate, bp 112-114° at 26 mm. The product was found to contain <2% ethyl cyanoacetate by pmr but was usable as was in the preparation of dihydrooxazine. Pmr (CDCl₃) δ 1.33 (t, 3 H, J = 7); 1.58 (s, 4 H); 4.26 (q, 2 H, J = 7). Ir 2250, 1735 cm⁻¹.

Dihydrooxazine: Concentrated sulfuric acid (23 ml) was cooled to -5°C. Then cyclopropyl carbonitrile (15.9 g, 0.113 mole) was added dropwise with stirring at such a rate that the temperature was maintained between 0° and -5°C. Following nitrile addition, 2-methyl-2,4-pentane diol (14.7 g, 0.124 mole) was added at a rate such that the temperature was again maintained between 0° and -5°C. The viscous dark orange mixture was stirred for one additional hour at 0°C and then poured onto 150 g of
crushed ice. The aqueous mixture was extracted with three 75 ml portions of CHCl₃, made basic with 40% sodium hydroxide and extracted with ethyl ether (3 x 75 ml). The combined organic layers were dried over K₂CO₃, and concentrated to yield 22.1 g (86%) of a yellow oil which was distilled at 89-91°C, 0.48 mm. IR 1659, 1724 cm⁻¹; PMR (CCl₄) δ 4.07 (q, 2 H, J = 7) overlapping (m, 1 H); 1.83-0.83 (m, 18 H). Anal. Caled for C₁₃H₂₁NO₃: C, 65.25; H, 8.84. Found: C, 65.10; H, 8.95.

Reduction to tetrahydroxazine: Dihydroxazine (15.6 g, 0.068 mole), 50 ml of 95% ethanol and 50 ml of THF were added to a 400 ml beaker and the mixture cooled to -35 to -45°C by means of a dry-ice acetone bath. The pH was adjusted (p-Hydrion paper) to a range of 6-8 by means of 9N HCl.

A NaBH₄ (2.58 g, 0.068 mole) solution was prepared by dissolving the borohydride in the minimum amount of water necessary (~4 ml) and adding one drop of 40% NaOH.

The NaBH₄ was added dropwise with stirring to the beaker containing the dihydroxazine, ethanol and THF, care being taken to maintain the temperature between -35 and -45°C throughout the addition. The pH was maintained between 6 and 8 by the addition of 9N HCl. After the addition was complete, the mixture was stirred at -35 to -45°C for one hour and then poured into 150 ml of water and made basic by the addition
of a sufficient amount of 40% NaOH to cause separation of the layers. The aqueous layer was extracted with three 75 ml of ether. The combined organic layers were extracted with four 60 ml portions of saturated NaCl solution and dried over K$_2$CO$_3$. Concentration by rotary evaporation yielded 15.5 g (99%) of a colorless oil, bp 78-79° (0.2 mm). Anal. Calcd for C$_{13}$H$_{23}$NO$_3$: C, 64.70; H, 9.61. Found: C, 64.57; H, 9.63. Pmr (CDCl$_3$) δ 0.8-1.6 envelope (19 H); 2.1 (s, broad, 1 H); 3.75 (m, 1 H); 4.15 (q, 2 H, J = 7); ir (film) 1720 cm$^{-1}$.

Aldehyde formation: Oxalic acid dihydrate (24.5 g, 0.195 mole), water (75 ml) and tetrahydrooxazine (8 g, 0.039 mole) were placed into a 500 ml three-necked round bottomed flask fitted with a Greiner-Friedrich condenser and steam inlet tube. The mixture was heated to a boil and the live steam was bubbled through the system.

The milky distillate was collected until admixture of a few drops with 2,4-DNP produced no precipitate. The distillate was extracted with three 50 ml portions of ether and the combined organic layers were dried over Na$_2$SO$_4$. Filtration and concentration by fractional distillation yielded 3.06 g (56%), bp 101-102° (40 mm), 2,4-DNP, mp 136.5-37° (95% EtOH); pmr (CCl$_4$) δ 1.33 (t, 3 H), 1.55 (s, 4 H), 4.25 (q, 2 H, J = 7), and 10.13 (s, 1 H); ir 1715 cm$^{-1}$. Anal. Calcd for C$_7$H$_{10}$O$_3$: C, 59.14; H, 7.09. Found: C, 58.96; H, 7.15.
Cyclopropylimine formation: Cyclopropane carboxaldehyde (4.50 g, 0.032 mole), ketal amine (4.45 g, 0.038 mole), MgSO₄ (4.45 g, 0.038 mole) and benzene (100 ml) were combined in a 250 ml round bottomed flask fitted with a nitrogen bubbler and stirring bar. The heterogeneous solution was stirred at room temperature for 72 hr. Filtration of the solvent and concentration by rotary evaporation yielded 6.14 g (80%) cyclopropylimine, bp 96-98° (0.40 mm); pmr (CDCl₃) δ 1.25 (t, 3 H, J = 7 cps); 1.33 (s, 3 H); 1.51 (s, 4 H), 3.49 (d, 2 H, J = 1.5); 3.97 (s, 4 H); 4.20 (q, 2 H, J = 7); 8.72 (t, 1 H, J = 1.5); ir 1665, 1725 cm⁻¹. Anal. Calcd for C₇H₁₂N₂O₄: C, 59.73; H, 7.9%. Found: C, 59.90; H, 8.00.

Cyclopropylimine rearrangement: Cyclopropylimine (3.80 g, 0.0158 mole) and NH₄Cl (0.85 g, 0.0158 mole) were placed into a sealed tube and heated at 165° C for two hours. The product was removed with ether and eluted on silica gel with ether to yield 2.79 g (74%) (distillation
causes decomposition), bp 115° (0.07 mm). Fmr (CDCl₃) δ 1.23 (t, 3 H, J = 7); 1.30 (s, 3 H), 2.75 (m, 2 H); 3.16 (s, 2 H); 3.7 (m, 2 H); 3.97 (s, 4 H); 4.13 (q, 2 H, J = 7); 7.05 (t, 1 H, J = 1); ir (neat) 1600, 1675 cm⁻¹.

A solution of vinylogous amide (500 mg, 2.08 moles) in anhydrous ether was saturated with HCl (g) and left stirring at room temperature for 12 hr. CH₂Cl₂ (100 ml) and NaHCO₃ (3 g) were added to a stirred solution. The CH₂Cl₂ was washed with aqueous NaHCO₃ and dried over Na₂SO₄. Tlc and nmr showed no reaction.

Pluviine

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3,4-Dimethoxyphenyl acetone⁴⁹ ¹¹: A mixture of verstraldehyde (49.8 g, 0.30 mole), nitroethane (27 g, 0.33 mole), n-butylamine (6 ml) and toluene (60 ml) were refluxed in a 250 ml flask fitted with nitrogen, Dean-Stark trap and condenser until the production of water ceased.
Nitroolefin may be isolated by concentration and recrystallization from CCl$_4$, mp 96-96.5°; pmr (CDCl$_3$) δ 2.55 (d, 3 H, J = 1); 6.05 (s, 2 H), 6.96 (m, 3 H); 8.02 (s, 1 H). Ir 3150, 1600, 1650 cm$^{-1}$.

However, the toluene solution containing nitroolefin, water (150 ml), iron (60 g, 100 mesh powder), and FeCl$_2$ (1.2 g) was added to a one liter three-necked, round-bottomed flask fitted with a condenser, cone driven stirrer and addition funnel. With vigorous stirring the solution was heated to about 75° and concentrated HCl (110 ml) was added over a 45 min period. The mixture was refluxed for an additional 0.5 hr. A steam distillation was attempted to isolate the ketone but the amount of ketone per unit volume of distillate was quite small. Therefore the mixture was cooled and extracted with three 100 ml portions of toluene. The combined organic layers were concentrated under rotary evaporation yielding 46 g (81%) of a viscous dark brown oil. This material was filtered through a short silica gel column with ether as the eluent to yield 38.5 g (61%) of a fluid amber oil. Spinning band distillation yielded 32 g of pale yellow oil, bp 96-98° (0.01 mm), 2,4-DNP 150-50.5.

Pmr (CDCl$_3$) δ 2.12 (s, 3 H); 3.61 (s, 2 H); 3.83 (s, 6 H); 6.75 (m, 3 H); ir (neat) 1710 cm$^{-1}$; m/e 194.

\[
\text{CH}_3\text{O} \rightarrow \text{HOCH}_2\text{N}
\]

N-Hydroxymethylphthalimide: The procedure of Winstead and Heine$^{40}$ was followed to give 23 g (96%) white crystals, pmr (CDCl$_3$) δ 3.50 (t, 1 H,
J = 8), 5.4 (d, 2 H, J = 8); 7.95 (m, 4 H).

Phthalimidomethylation (12): Arylacetonitrile (1.0 g, 5.16 mmole), N-hydroxymethylphthalimide (0.91 g, 5.16 mmole), 47% boron trifluoride etherate (4.66 g, 4.04 ml, 20.3 mmole) and CCl₄ (20 ml) were combined and heated to 45°C for 5 hr. The black mixture was diluted with 100 ml of CH₂Cl₂, washed with two 40 ml portions of saturated NaHCO₃, two 40 ml portions of water and the organic layer dried over MgSO₄. Concentration yielded 1.9 g (104%) of a yellow low melting solid (mp < 80°). Recrystallization from CH₃OH yielded 900 mg (80% based on recovered ketone, 300 mg), mp 154-54.5°; m/z/e 353; pnmr (CDCl₃) δ 2.30 (s, 3 H); 3.92 (s, 3 H); 3.95 (s, 3 H); 4.20 (s, 2 H); 4.33 (s, 2 H); 6.78 (s, 1 H); 7.30 (s, 1 H); 7.90 (m, 4 H); ir (CHCl₃) 1775 (w), 1715 cm⁻¹ (s).

Ketal formation (13): Arylketone (100 mg, 0.28 mmole), ethylene glycol (9 mg, 1.4 mmole), tosic acid (10 mg, 0.06 mmole) and benzene (15 ml)
were placed into a 50 ml round-bottomed flask fitted with a Dean-Stark trap filled with Linde 4Å molecular sieve. The solution was refluxed for 36 hr, cooled, washed with two 15 ml portions of 8% NaHCO₃ and one 15 ml portion of water and dried over K₂CO₃. The material was concentrated to yield 120 mg (102%). Preparative layer chromatography (Al₂O₃, ether) or recrystallization from chloroform-methanol yielded 85 mg (75%) white powder, mp 211-12°; pmr (CDCl₃) δ 1.46 (s, 3 H); 3.37 (s, 2 H); 4.75 (m, 4 H); 3.95 (s, 6 H); 5.05 (s, 2 H); 6.97 (s, 1 H); 7.23 (s, 1 H); 7.75 (m, 4 H); ir 1715 cm⁻¹.

In the final stages of this work a small amount of material [mp 211-12°; pmr (CDCl₃) δ 2.28 (s, 3 H); 3.93 (s, 6 H); 4.48 (s, 2 H); 4.70 (s, 2 H); 4.76 (s, 2 H); 7.30 (s, 1 H); 7.75 (m, 8 H)] was isolated by crystallization from methanol-chloroform which has been assigned structure A. This material apparently arises from bis-phthalimidomethylation of the aryl acetone.
Cleavage to amine (14): Phthalimide (570 mg, 1.43 mmols), 85% hydrazine-hydrate (140 mg, 4.36 mmols) and absolute ethanol (10 ml) were refluxed for 2 hr. The solution was concentrated by rotary evaporation, the residue suspended in ether and washed with four 5 ml portions of 40% NaOH. The organic layer was dried over K₂CO₃, concentrated and chromatographed on activity III Al₂O₃ (95:5 CHCl₃:CH₃OH) to yield 300 mg, 78% of benzylamine, oil; pmr (CCl₃) δ 1.33 (s, 3 H); 1.45 (s (broad), 2 H); 2.95 (s, 2 H); 3.75 (m, 12 H); 6.87 (s, 1 H); 7.0 (s, 1 H); IR (neat) 3400 cm⁻¹; m⁺/e 269.

1-Cyanocyclopropane carboxamide: Following the procedure of Mitch⁴ cyclopropyl ester (11.2 g, 0.08 mole) and concentrated NH₄OH (35 ml) were stirred overnight at room temperature. The heterogeneous mixture was chilled, filtered and the white precipitate was washed with ice water. Yield 7.76 g (88%), mp 162-63° (H₂O, sublimed 125°C at 1.5 mm);
$^1$H NMR (CD$_3$CN) $\delta$ 1.50 (s, 4 H); 2.2 (s, broad 2 H); ir 3540, 3435, 2400, 1710, 1600 cm$^{-1}$.

1,1-Dicyanocyclopropane: Following the procedure of Surrey, cyanoamide (11 g, 0.10 mole), NaCl (6.7 g) and ethylene chloride (33 ml) were stirred for 0.25 hr at room temperature. Then phosphorous oxychloride (5.36 ml, 0.059 mole) was added and the mixture was refluxed for six hours. The mixture was cooled and filtered; the solid was washed with more ethylene chloride. The solvent was distilled from the combined filtrates and the dicyanocyclopropane was distilled to yield 7.2 g (80%), bp 102°C (23 mm); ir 2260 cm$^{-1}$; $^1$H NMR (CCl$_4$) $\delta$ 1.76.

1,1-Diformylcyclopropane: Dicyanocyclopropane (1.0 g, 10.9 mmoles) and dry (LAH) benzene (30 ml) were added to a flame dried, three-necked, round-bottomed 100 ml flask and cooled to 0°C. DIBAL-H (2.48 g, 17.2 mmoles) in benzene (20 ml) was added dropwise with stirring keeping the temperature near 0°C. The solution was stirred for 2 hr and then 25 ml
of 10% H$_2$SO$_4$ was added dropwise over 10 min and the solution stirred at 0°C for 0.5 hr. The phases were separated and the aqueous layer extracted three times with ether; the combined organic layers were dried over Na$_2$SO$_4$.

After prolonged rotary evaporation 300 mg (30%) of a liquid which contained 35% dicyanocyclopropane and 65% 1,1-diformylcyclopropane was obtained; ir 1720 cm$^{-1}$; pmr (CDCl$_3$) δ 1.80 (s, 4 H); 9.0 (s, 2 H).

**Dextroplin**

Gem dimethylation: Diisopropylamine (222 g, 2.2 mmoles) distilled from CaH$_2$ and THF (750 ml) were placed into a three liter, three-necked, round-bottomed flask fitted with thermometer, mechanical stirrer and nitrogen bubbler. The solution was cooled to -5°C and n-butyllithium (942 ml, 2.2 moles, hexane, 2.34 M) was added dropwise at such a rate that the temperature was kept below 5°C. After addition was complete, stirring was continued for 0.5 hr at 0°C and then the solution was allowed to warm to room temperature and then stirred for 0.5 hr. The solution was cooled to 0°C and 2-cyclopentene-1-acetic acid (freshly distilled) was added slowly at less than 5°C. The solution was allowed to stir for 0.25 hr at 0°C after addition and then warmed to room temperature and stirred for one hour. The solution was cooled to 0°C again and
methyl iodide (213 g, 1.5 moles) was added at less than 5°C to the heterogeneous solution. The mixture was stirred at 0° for one hour, then allowed to stir at ambient temperature for six hours.

The viscous material was poured into 1.5 l. of water, the layers separated and the aqueous layer extracted with ether (3 x 250 ml). The combined organic layers were washed with water (200 ml) and the saturated NaCl (3 x 100 ml), then dried over Na₂SO₄. Filtration, concentration and distillation yielded 135.8 g (97%) of a pale yellow oil, bp 134-36° (20 mm). This material is a mixture of diastereomers of mono-alkylated acid along with small amounts of non- and dialkylated acid.

Alternatively the acid may be dried by dissolving it in benzene and azeotropically removing the water. The crude acid may then be used in the next step.

The procedure followed for addition of the second methyl group is identical to that above. The quantities were THF (750 ml), diisopropylamine (222 g, 2.2 moles), n-butyllithium (942 ml, 2.2 moles) 2.34 M in hexane, diastereomeric acids (133.1 g, 0.95 mole) and methyl iodide (142 g, 1.0 mole). After all of the above reagents were added, the solution was stirred for 0.5 hr at 0°C and then at ambient temperature for one hour. The solution was cooled to 0°C and additional n-butyl-lithium (214 ml, 0.5 mole) was added slowly. Then methyl iodide (142 g, 1 mole) was added and the solution stirred at ambient temperature for 6 hr. Workup is as before. Distillation yielded 135 g (92.5%), bp 110-12° (1.6 mm); pmr (CDCl₃) δ 1.13 (s, 3 H), 1.18 (s, 3 H), 1.40-2.50 (m, 4 H), 2.85-3.28 (m, 1 H), 5.50-5.93 (m, 2 H), 12.15 (s, 1 H); mp 25-27°; ir 1695 cm⁻¹. Anal. Calcd for C₉H₁₄O₂: C, 70.10; H, 9.15. Found: C, 69.59; H, 9.16.
Ester 19: Ether (400 ml) and 50% KOH (240 ml) were placed into a diazo-
methane generator, and to this nitrosonmethyl urea (164 g, 1.6 moles) was
added in portions (10-12 g) such that a continuous flow of ethereal
diazomethane distilled into a receiver containing chilled ether (300 ml)
and dimethyl acetic acid (131 g, 0.845 mole). Attached to this receiving flask
was a second receiver containing ether (300 ml) through which the
effluent gases from the first bubbled prior to exhausting into the hood.
Distillation was continued until the yellow color persisted in the flask
containing acid. The reaction was allowed to stir for an additional
30 min at 0° and then enough acetic acid was added to discharge the
yellow color. The ether solution was washed with 8% NaHCO₃ (2 x 30 ml)
and dried over Na₂SO₄. Distillation yielded 137.6 g (98%), bp 54-56°
(2.5 mm). Pmr (CDCl₃) δ 1.10 (s, 3 H); 1.15 (s, 3 H); 1.90 (m, 4 H);
3.05 (m, 1 H); 3.67 (s, 3 H); 5.70 (m, 2 H); ir (neat) 1730, 1365,
1385 cm⁻¹.
Reduction to alcohol 20: Lithium aluminum hydride (0.7 g, 18.5 mmole) and ether (25 ml) were mixed in a flask fitted with addition funnel, condenser, drying tube and magnetic stirring bar. To this was added dropwise, with stirring, cyclopentenyl ester (5 g, 30 mmole) at such a rate that brisk reflux was maintained. After one hour at ambient temperature water (0.7 ml) was cautiously added, followed by 15% NaOH (0.7 ml) and then water (2.1 ml) again. The solution was stirred for 0.5 hr and the granular precipitate was filtered away and washed with ether. The ether was dried over Na$_2$SO$_4$ and concentrated to yield 4.2 g (100%) of the alcohol, bp 92-94° (15 mm); pmr (CDCl$_3$) δ 0.85 (s, 6 H); 1.4-2.9 (m, 7 H); 3.39 (s, 2 H); 5.77 (m, 2 H); ir (neat) 3380, 3065, 1370, 1380 cm$^{-1}$.

Oxidation to aldehyde 21: Following the procedure of Ratcliffe and Rodehorst$^{45}$ anhydrous CrO$_3$ (13.8 g, 0.138 mole) was added to a
mechanically stirred solution of dry (4A sieve) CH₂Cl₂ (325 ml) and dry pyridine (21.8 g, 0.276 mole) (4A mole sieve) which had been cooled to 0°C. The solution was stirred at room temperature for 15 min and then dimethyl alcohol (2.83 g, 0.02 mole) was added all at once. The solution was stirred for 30 min at ambient temperature and then poured through 30 g of activity III alumina which had been placed in a sintered glass filter funnel. (A small piece of filter paper on top of the Al₂O₃ prevents rutting by the solvent.) The Al₂O₃ was washed with EtOAc and the combined organic layers were washed with sufficient 5% HCl to remove the pyridine (200 ml) and dried over MgSO₄.

Concentration of the organic layers yielded 2.54 g (98%) of aldehyde, pure by nmr and vpc.  Pmr (CDCl₃) δ 1.03 (s, 6 H); 1.4-2.4 (m, 4 H); 2.90 (m, 1 H); 3.75 (m, 2 H); 9.50 (s, 1 H); ir (neat) 3060, 2700, 1730 cm⁻¹. 2,4-DNP (yellow), mp 160-61°C (95% ethanol). Anal.
Calcd for C₁₅H₁₆N₄O₄:  C, 56.60; H, 5.70.  Found:  C, 56.47; H, 5.89.

Formation of acetal 35: Dimethyl aldehyde (2 g, 14.5 mmoles), trimethyl orthoformate (15.4 g, 0.145 mole), methanol (1.85 g, 58 mmoles) and tosic acid (125 mg, 0.73 mmole) were heated to reflux for 8 hr. At that time the solution was diluted with ether (50 ml) and washed with 8% NaHCO₃. The organic layer was dried over K₂CO₃, concentrated by rotary evaporation and distilled to yield 2.54 g (95%) of the dimethyl
acetal, bp 86-88° (10 mm); pmr (CDCl₃) δ 0.80 (s, 3 H); 0.834 (s, 3 H); 1.75 (m, 2 H); 2.22 (m, 2 H), 2.82 (m, 1 H); 3.50 (s, 6 H); 3.92 (s, 1 H); 5.72 (m, 2 H); ir (neat) 3060, 1390, 1360 cm⁻¹.

Permanganate oxidation: Following Stark's procedure,⁶⁷ the cyclopentenyl compound (8.5 g, 0.05 mole) was added dropwise to a mixture of water (50 ml), KMnO₄ (31.2 g, 0.20 mole), benzene (25 ml) and tricaprylylmethyl ammonium chloride⁶⁹ (1.25 g, 0.0025 mole) at such a rate that the exo-thermic reaction remained between 40-45°C. (Caution: There is an induction period of several minutes at the start of this reaction.) After addition was complete, the solution was stirred for 1.5 hr at ambient temperature. The reaction is worked up by adding alternately 9N HCl and NaHSO₃ until all of the brown, insoluble MnO₂ is converted to the white, soluble MnSO₄ (more H₂O may be needed). The solution is made slightly basic, the layers separated and the aqueous layer extracted with ether, made acidic (9N HCl) and extracted with ether (3 x 75 ml) again. The combined organic extracts were dried over Na₂SO₄ and concentrated to yield 8.2 g of a complex mixture of acidic products. Ir 1780 cm⁻¹.
Benzyl ether 20: Sodium hydride (9.6 g, 0.40 mole as a 50% oil dispersion), which had been washed several times with dry benzene, was suspended in dry THF (400 ml). The alcohol (28 g, 0.20 mole) was added rapidly through an addition funnel and then benzyl chloride (38 g, 0.30 mole) was added. The mixture was refluxed for 12 hr. The tan solution was cautiously added to water (500 ml), the layers separated and the aqueous layer extracted with ether (3 x 100 ml). The combined organic layers were washed with water (50 ml), then saturated NaCl (3 x 100 ml) and dried over K₂CO₃. Concentration and distillation of the residue yielded 44.2 g (96%) of a colorless liquid, bp 84-86°C (0.04 mm); pmr (CDCl₃) δ 0.86 (s, 3 H); 0.89 (s, 3 H); 1.72 (m, 2 H); 2.22 (m, 2 H); 2.78 (m, 1 H); 3.18 (s, 2 H); 4.47 (s, 2 H); 5.69 (m, 2 H); 7.30 (s, 5 H).

Ozonolysis: Olefin (8.6 g, 37 mmole) was dissolved in CH₃OH (200 ml) and placed into a gas washing bottle. The theoretical amount of ozone (Welsbach T-23 ozonator) as determined by the Na₂S₂O₃ titration of the
iodine produced in a 2% KI solution per unit time was bubbled through the solution at -78°C. The equation used to calculate the ozone flow rate was $\text{H}_2\text{O} + 2\text{S}_2\text{O}_3^- + \text{O}_3 + \text{S}_4\text{O}_6 + 20\text{H}^- + \text{O}_2$.

When the theoretical amount of ozone had passed, the reaction was stopped, the system purged with nitrogen and the cold solution poured into a solution containing NaOH (4.43 g, 111 mmoles) and water (75 ml) and stirred for two hours at room temperature.

The methanol was removed by rotary evaporation and the basic aqueous layer extracted with ether (3 x 25 ml). These extracts contained 1.7 g (7.2 mmoles) unreacted olefin. (It is best not to add excess ozone.)

The aqueous layer was mixed with 30% hydrogen peroxide (4.2 g, 37 mmoles) and warmed to -45°C and stirred for two hours. (Overheating causes overoxidation.) Palladium (10%) on charcoal was added and the solution stirred until fizzing stopped. The solution was saturated with Na$_2$SO$_4$, acidified and extracted with ether (3 x 100 ml) to yield 8.3 g (95%) of a complex mixture of products. Analysis is done on the esterified material.

Esterification: An ethereal solution of diacid (2.94 g, 0.01 mole) was treated with sufficient diazomethane in ether to maintain a yellow color upon swirling. The excess CH$_2$N$_2$ was destroyed by glacial acetic acid,
the solution extracted with 8% NaHCO₃, dried over K₂CO₃ and concentrated to yield diester and lactone.

Column chromatography (Al₂O₃ III, 50 g per g of ester, 7:3 ether to hexane) yielded methyl benzoate, benzyl ether then lactone.

Benzyl ether: $\nu$mr (CDCl₃) δ 0.98 (s, 3 H); 1.0 (s, 3 H); 1.6-2.6 (m, 5 H); 3.20 (m (AB), 2 H); 3.64 (s, 3 H); 3.59 (s, 3 H); 4.46 (s, 2 H); 7.30 (s, 5 H); $\nu$H 1735 cm⁻¹; m/e 322.

Lactone: $\nu$mr (CDCl₃) δ 1.0 (s, 3 H); 1.15 (s, 3 H); 1.5-2.80 (m, 5 H); 3.53 (s, 3 H); 3.87 (s, 2 H); $\nu$H 1780, 1735 cm⁻¹; m/e 200.

Debenzylation: Prior to using the Parr apparatus it was dismantled and the reaction flask, stopper and hydrogen inlet tube were washed with dilute NaHCO₃, tap water and then 95% ethanol. The benzyl ether must be either distilled or chromatographed before using.

Benzyl ether (322 mg, 0.01 mole), absolute ethanol (15 ml) and 10% palladium on charcoal (100 mg) were placed into a Parr hydrogenation apparatus under a hydrogen atmosphere (50 psi) and shaken for 12 hr. The Pd/C was filtered away and washed with ethanol. Concentration of the solution was effected on the rotary evaporator without heating to yield 230 mg (98%) of the alcohol. $\nu$mr (CDCl₃) δ 0.917 (s, 3 H); 0.95 (s, 3 H); 1.6 to 2.6 (m, 5 H); 3.37 (s, 2 H); 3.71 (s, 6 H); $\nu$(neat) 3500, 1735 cm⁻¹.
**Aldehyde formation:** The procedure is identical to that for alcohol 21 (p 80). The amounts of reagents used were: alcohol (266 mg, 1.15 mmoles), \( \text{CrO}_3 \) (690 mg, 6.90 mmoles), pyridine (1.09 g, 13.80 mmoles), methylene chloride (20 ml). Filtration through \( \text{Al}_2\text{O}_3 \), acid wash and concentration yielded 243 mg (92%) of the aldehyde. Pmr (CDCl\(_3\)) \( \delta \) 1.06 (s, 3 H); 1.13 (s, 3 H); 1.6-2.8 (m, 5 H); 3.68 (5, 6 H); 9.27 (s, 3 H); ir 1740 cm\(^{-1}\).

**Oxime formation:** Aldehyde (400 mg, 1.74 mmoles), hydroxylamine hydrochloride (180 mg, 2.62 mmoles) and pyridine (7 ml) were combined and stirred for six hours at room temperature. The solution was diluted with ether (15 ml), washed with 6N HCl (2 x 5 ml), water (5 ml) and dried over MgSO\(_4\). Concentration yielded oxime (557 mg, 87%). Pmr (CDCl\(_3\)) \( \delta \) 1.16 (s, 6 H); 1.7-2.7 (m, 5 H); 3.67 (s, 3 H); 3.72 (s, 3 H); 7.41 (s, 1 H); 8.43 (s, broad, 1 H); ir 1735 cm\(^{-1}\); m/z 245.
Isoxazole formation: Aldoxime (480 mg, 1.96 mmoles) and dry (4 Å sieve) dimethylformamide (DMF) (4 ml) were cooled to 0°C under nitrogen. N-bromosuccinimide (524 mg, 2.94 mmoles) in DMF (3.5 ml) was added dropwise by syringe, maintaining the temperature between 0-5°C. The solution was stirred for one hour at this temperature and then a solution of triethylamine (297 mg, 2.94 mmoles) and phenylacetylene (1.0 g, 9.8 mmoles) was added dropwise, again at 0-5°C. The mixture was allowed to stir at ambient temperature for 12 hours, then poured into water (20 ml), extracted with ether (3 x 20 ml), dried over \( \text{CaCl}_2 \) and concentrated to yield 557 mg (87%) of crude isoxazole. The material was purified by column chromatography (silica, 9:1 hexane:ether) to yield 350 mg (54%).

\( \text{Fmr (CDCl}_3 \} 8 \) 1.42 (s, 3 H); 1.48 (s, 3 H); 1.8-2.5 (m, 4 H); 2.8 (m, 1 H); 3.60 (s, 3 H); 3.67 (s, 3 H); 6.50 (s, 1 H); 7.50 (m, 5 H); ir (CCl\(_4\)) 1735, 1615, 1595, 1570 cm\(^{-1}\).
Hydrogenation of isoxazole 44: Raney nickel (1.5 g Roche type 28 #731) was washed with methanol until the wash liquid remained clear. The Ni(R) was suspended in methanol (10 mL) and allowed to stir 18 hr in a hydrogen atmosphere. The isoxazole (140 mg) in methanol (5 mL) was added to the Ni(R) and stirred until the theoretical amount of hydrogen had been taken up. The formula used for calculating theoretical hydrogen is:

\[
V_{H_2} = \frac{(62.3)(T^0K)(\text{no. moles } H_2 \text{ needed})(\text{mmoles compound})}{(P_{\text{atm}} - P_{\text{MeOH}})}
\]

\[P_{\text{atm}} = \text{atmospheric pressure in mm Hg}\]

\[P_{\text{MeOH}} = \text{vapor pressure methanol at } ^0\text{K}\]

The reaction mixture was filtered through Celite (Caution: Ni(R) is pyrophoric; keep under CH$_3$OH) and concentrated to yield 130 mg. Inspection by pmr indicated the vinylogous amide had not cyclized to lactam. Pmr (CDCl$_3$) δ 1.33 (s, 6 H); 3.67 (s, 3 H); 3.75 (s, 3 H); 5.92 (s, 1 H) inter alia.

The oil was dissolved in methanol (10 mL) and poured onto Ni(R) (1.5 g) which had been washed with several portions of methanol. The mixture was allowed to stir for 14 hours at room temperature. The
solution had turned green by this time and a check of the pH indicated that it was 5. Filtration and concentration yielded 150 mg of solid yellow material, insoluble in EtOAc, CHCl₃ and ether. An attempt to take the nmr in methanol d₄ produced a spectrum with no resonance.

The paramagnetic nickel complex was dissolved in methanol and made basic (pH = 9) with 15% NaOH. Hydrogen sulfide was bubbled through the solution for 0.5 hour. The solution was filtered and concentrated to yield 63 mg (47%) of the lactam. Purified by preparative layer chromatography (silica 7:3 CHCl₃:EtOAc, R f = 0.7); pmr (CDCl₃) δ 1.21 (s, 3 H); 1.38 (s, 3 H); 1.7-2.8 (m, 5 H); 3.66 (s, 3 H); 6.14 (s, 1 H); 7.4 (m, 3 H); 7.95 (m, 2 H).

![Diagram](image)

**Hydrazone 56:** Epoxyketone (570 mg, 2.89 mmoles) and N-amino phenylaziridinium acetate (617 mg, 3.18 mmoles) prepared according to Eschenmoser's procedure, were combined in methylene chloride (15 ml) at 0°C and stirred for one hour. The solution was extracted with 8% NaHCO₃ (3 x 10 ml) and the organic layer dried over MgSO₄ and concentrated to yield 900 mg (102%) of the diastereomeric mixture of hydrazones.
Fragmentation: Hydrazone (500 mg, 1.61 mmole) was placed into a Kugelrohr and heated at 150°C, 1.5 mm. The ynone (181 mg, 62%) collected as a nearly pure compound in the first bulb out of the oven.
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