

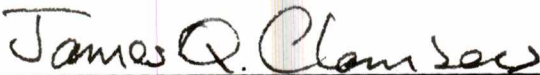
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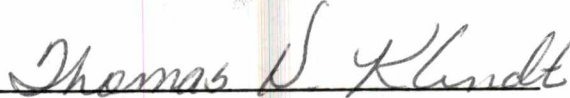
I am submitting herewith a dissertation written by Paul Randall Williams, Jr. entitled "Pyrrolizidine Synthesis via N-Chloroamine Rearrangements." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.


Fred M. Schell, Major Professor

We have read this dissertation
and recommend its acceptance:







Accepted for the Council:


Vice Chancellor
Graduate Studies and Research

PYRROLIZIDINE SYNTHESIS VIA N-CHLOROAMINE REARRANGEMENTS

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Paul Randall Williams, Jr.

August 1982

3063278

DEDICATION

The author dedicates this work to his wife, Jan, for her love, patience and support during the tenure of this work.

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ABSTRACT

A model system was investigated for its potential applicability toward pyrrolizidine diol synthesis via silver ion induced rearrangement of appropriately substituted N-chloroazabicyclo[4.2.0]octanes. The results clearly show that this synthetic route is possible.

Attendant to this work was the demonstration that stereospecific modification of a single bicyclic ketoester into a series of diols of differing stereochemistries could be accomplished in high yield. Analogous treatment of compounds with the appropriate regiochemical and stereochemical relationships should provide the naturally occurring necine bases upon rearrangement. That systems of this type are available synthetically was also demonstrated.

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LIST OF SYMBOLS

bs	Broad singlet
cm ⁻¹	Reciprocal centimeters (wave number)
cmr	Carbon-13 nuclear magnetic resonance
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
ir	Infrared
m	Multiplet
pmr	Proton nuclear magnetic resonance
ppm	Parts per million from tetramethylsilane
q	Quartet
R	Alkyl, aryl, etc.
s	Singlet
t	Triplet
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Tetramethylsilane
δ	Parts per million from tetramethylsilane

CHAPTER I

HISTORICAL SURVEY

A. Introduction

Since the beginnings of drug-related research, synthetic organic chemists have been challenged with the considerable task of devising synthetic routes toward compounds of biological significance and interest. The recent surge in the synthetic effort directed toward antitumor and antibiotic agents is evidence of this fact.

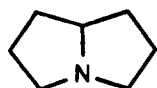
Many classes of compounds find importance in treatment of disease. Whereas one compound might effect desirable results, any small change in chemical structure destroys its applicability, and in some cases induces toxicity.

Frequently such biologically active compounds are discovered among natural sources, being isolated typically from trees and other plants. Unfortunately, obtaining sufficient quantities of these materials is sometimes precluded by relative abundance in the source, or, in some cases, rarity of the source itself. It then becomes important to exploit available, and develop new, synthetic methods to provide efficient routes to clinically practical amounts of material.

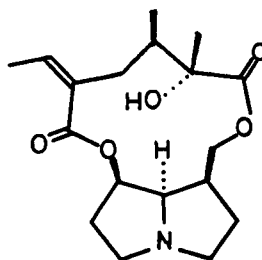
The pyrrolizidine alkaloids^{1,2} are one such class of compounds which induce varied physiological response in animals. Isolated from members of the Senecio (family Compositae),

Crotalaria (family Leguminosae) genera, these alkaloids enjoy a broad distribution in nature, are frequently structurally complex and number in the hundreds with isolation and characterization of new members continuing steadily. The parent alkaloids are characterized compositionally as possessing one nitrogen, approximately 18 carbons, and varying in hydrogen and oxygen content. As expected, all of the alkaloids in this series contain the pyrrolizidine ring system (1). Representative compounds platyphylline (2) and indicine-N-oxide (3) (vide infra) depict the stereochemical subtleties common to the Senecio alkaloids.

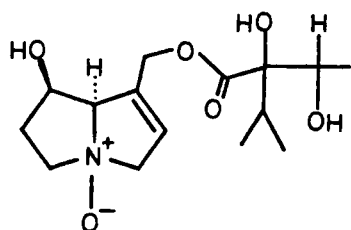
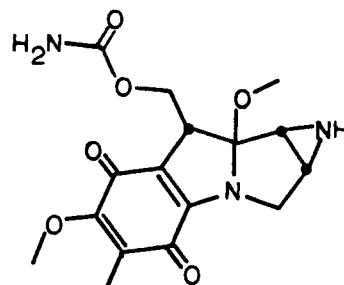
More recently, pyrrolizidines have been isolated from insects and other microorganisms, though they are not as common. For example, the potent antibiotic and antitumor agent mitomycin A³ (4), isolated from the bacterium Streptomyces caespitosus is also shown below and vividly portrays the structural complexity found in many pyrrolizidine natural products.



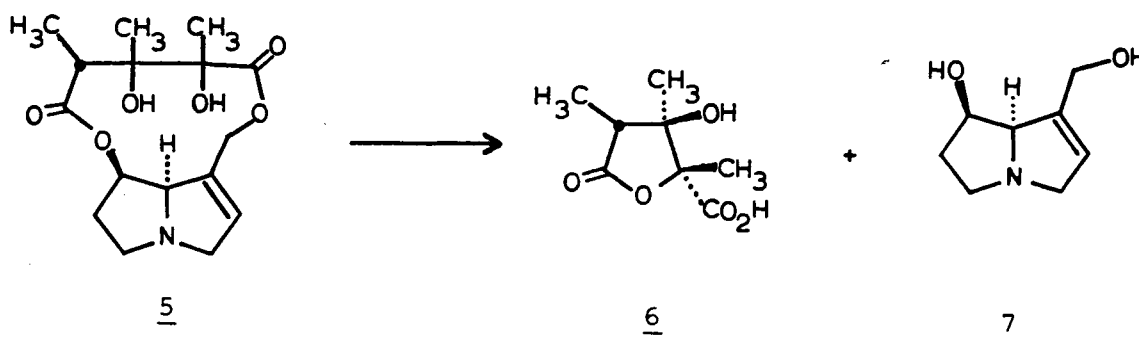
1



2

34

Alkaline hydrolysis of the C_{18} materials produces a C_{10} acidic fragment (necic acids) and a C_8 basic fragment (necine bases). For example, monocrotaline (5) provides monocrotalic acid (6) (after lactonization) and retronecine (7) upon hydrolysis.⁴



Of the two moieties, the necine bases have received the most attention due to their broad range of biological activity and their intriguing structure.

Comprehensive documentation of the physiological properties of the pyrrolizidine alkaloids is beyond the scope of this chapter. However, a brief examination will provide insight into their toxicology and potential beneficial uses.

Periodic reviews^{1,2,5,6,7} appear in the literature which delineate the biochemical consequences of pyrrolizidine exposure. At present, it is not unreasonable to conclude that most of the alkaloids are toxic to both human beings and animals. There are exceptions, to be discussed below, but generally they produce damage to liver, kidney and lung tissue.

It is known that pyrrolizidines are aromatized to their pyrrole derivatives in biological systems.⁵ Presumably it is these metabolites which are responsible for tissue destruction. Thus, exposure of animal (in vivo) and human (in vitro) tissue to pyrrole derivatives of pyrrolizidines (e.g. retronecine pyrrole⁸) promoted lesions of the lung and liver.^{6,9} However, not all of the alkaloids are toxic even though they form pyrroles.¹⁰ Rosmarinine¹¹ is not hepatotoxic, but has been shown to be metabolized to rosmarinine pyrrole. It has also been suggested that the ease with which the ester function is hydrolyzed might also be a factor in determining toxicity. Rosmarinine has an unactivated ester which is not easily cleaved, thereby reducing its toxicity.¹¹ Thus, it is not entirely clear the mode of action by which pyrrolizidines as a class are poisonous.

Other, more specific relationships include the following. Lasiocarpine,⁸ retorsine, isatidine, riddeline,¹² trichodesmine, incanine,¹³ senkirkine, hydroxysenkirkine¹⁴ and heliotrine¹⁵ produce necrosis of liver cells in humans and rats.

Unspecified liver damage is caused by the diastereomers intermediate and lycopsane¹⁶ (to cattle in the U.S.), retorsine¹⁹ (to humans, mice and rats), monocrotaline¹⁷ (to rats), and extracts of Senecio jacobea,¹⁸ the latter of which is accompanied by megakaryocytosis in rats. Retorsine, isatidine, riddeline and monocrotaline also cause lung edema.¹²

Some pyrrolizidines are also carcinogenic. Renal tumors result when kidney tissue is exposed to lasiocarpine⁸ and extracts from Heliotropium supinum.¹⁶ Retronecine¹⁹ (7, p 3) produces hepatocellular carcinomas in addition to myelogenous leukemias and tumors of the central nervous system. Hydroxysenkirkinine and extracts from Heliotropium ramoissimum also produce tumors of the central nervous system in rats.¹⁹

Some nonexperimental evidence also illustrates pyrrolizidine toxicity. In several countries, cattle, sheep and horses continue to be poisoned by Senecio plants.²⁰ Contamination of flour in the U.S.S.R. by Trichodesma incanum²¹ (trichodesmine and incanine) prompted Soviet researchers to develop analytical procedures to detect small quantities of pyrrolizidines.²² The proposed bioassay technique involves using guppies which are very sensitive to pyrrolizidines: 0.001% is lethal within a few hours. In India, 28 people died from a fatal hepatic veno-occlusive disease thought to result from consumption of cereals mixed with seeds of a Crotalaria species.²³ Bread made from the seeds of Heliotropium

plants caused liver damage to 1/4 of 7200 inhabitants of affected villages in Afghanistan.²⁴

The pyrrolizidines exhibit some potentially valuable biological effects as well. Crotalaburnine²⁵ produces significant anti-inflammatory activity toward several experimental edemas. Some quaternary pyrrolizidines, prepared by reacting the alkaloids with dihalogenated alkanes, possess neuromuscular blocking activity in addition to potent hypotensive activity as demonstrated by tests in rats.²⁶ The quaternary alkaloid indicine N-oxide (3, p 3)²⁷ shows some very promising anti-tumor activity. The nonhepatotoxic alkaloid platyphylline (2, p 2) is currently in use in the U.S.S.R. for treatment of hypertension and internal ulcers.¹

It is clear from the data presented in the preceding paragraph that continuing research into the pyrrolizidines is both justified and necessary. Because the demand for innovative and new pharmacologically useful compounds continues to increase, developmental synthetic chemistry must respond in kind. A historical survey of methods of pyrrolizidine preparation and natural product synthesis is therefore warranted.

Early efforts, as might be expected, were directed toward isolation and characterization of the Senecio alkaloids. Not long after their initial documentation in the literature, papers began to appear demonstrating the many approaches available to the pyrrolizidine skeleton. Furthermore, as researchers began

to establish their diversity and structural complexity, the synthetic approaches to them become more sophisticated in design and execution. The reciprocity served both well.

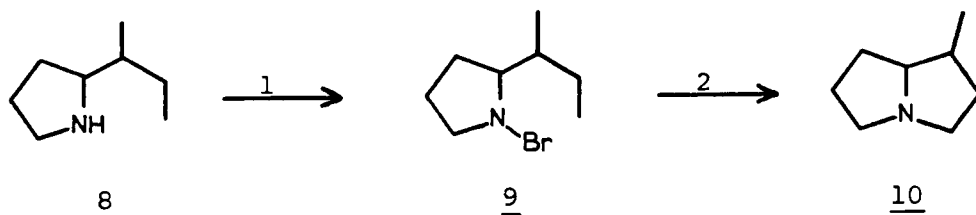
B. Pyrrolizidine Skeleton Synthesis

At present, there exist several general methods of pyrrolizidine synthesis. Although a chronological account of these would be historically instructive, for simplicity the methods will be categorized and discussed as follows: (1) cyclization of alkyl substituted N-halopyrrolidines; (2) cyclization of trihalides, aminoalkylhalides and intramolecular cyclodehydration; (3) intramolecular acylation of amino acids; (4) reductive cyclization of nitropimelates and related compounds; (5) Dieckmann condensations; (6) Houben-Hoesch cyclizations; (7) transannular reactions; (8) Wittig reactions; (9) 1,3-dipolar additions; (10) miscellaneous reactions. Many of the early methods are of little importance now, with the advent of more efficient means by which functionalized pyrrolizidines can be obtained and later converted into natural products.

1. Cyclization of Alkyl Substituted N-halopyrrolidines

The first synthesis of 1-methylpyrrolizidine (10) was reported in 1937 by Menshikoff.²⁸ Acid catalyzed cyclization of the N-bromopyrrolidine (9), prepared by bromination of the parent amine 8, provided 1-methylpyrrolizidine (10), but in poor yield (Scheme 1).

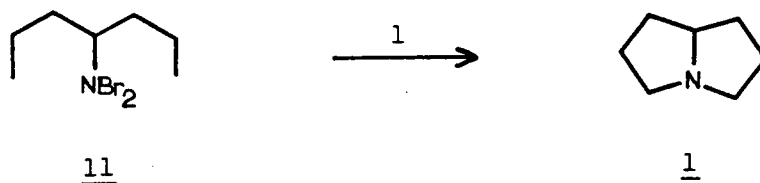
Scheme 1



Reagents: 1) Br_2 ; 2) H_2SO_4 .

Sorm and Brandejs²⁹ increased the cyclization yield to pyrrolizidine 1 (p 2) by using a photochemical modification of the same reaction ten years later. (Scheme 2).

Scheme 2



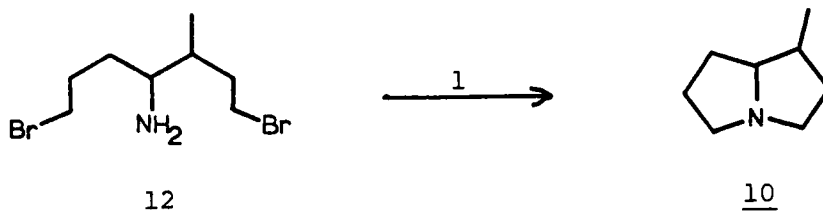
Reagents: 1) H_2SO_4 , hv.

2. Cyclization of Aminoalkylhalides, Trihalides and Intramolecular Cyclodehydration.

Prelog and Heimbach³⁰ found that intramolecular nucleophilic displacement of the amino dibromide 12 under basic conditions gave 1-methylpyrrolizidine (10) in moderate yield.

(Scheme 3).

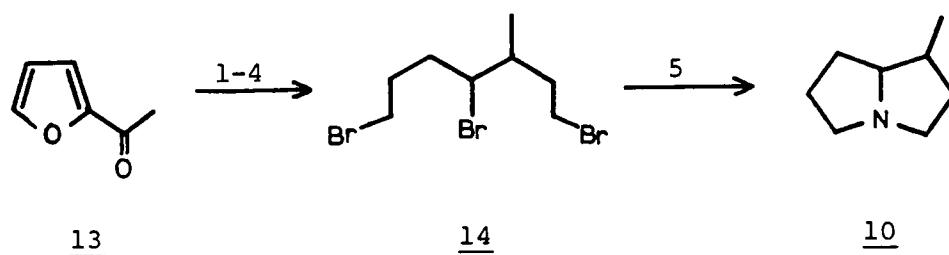
Scheme 3



Reagents: 1) dilute aqueous NaOH.

Compound 10 is also available from the tribromide 14, prepared from the acetyl furan 13, in the presence of methanolic ammonia³¹ (Scheme 4).

Scheme 4

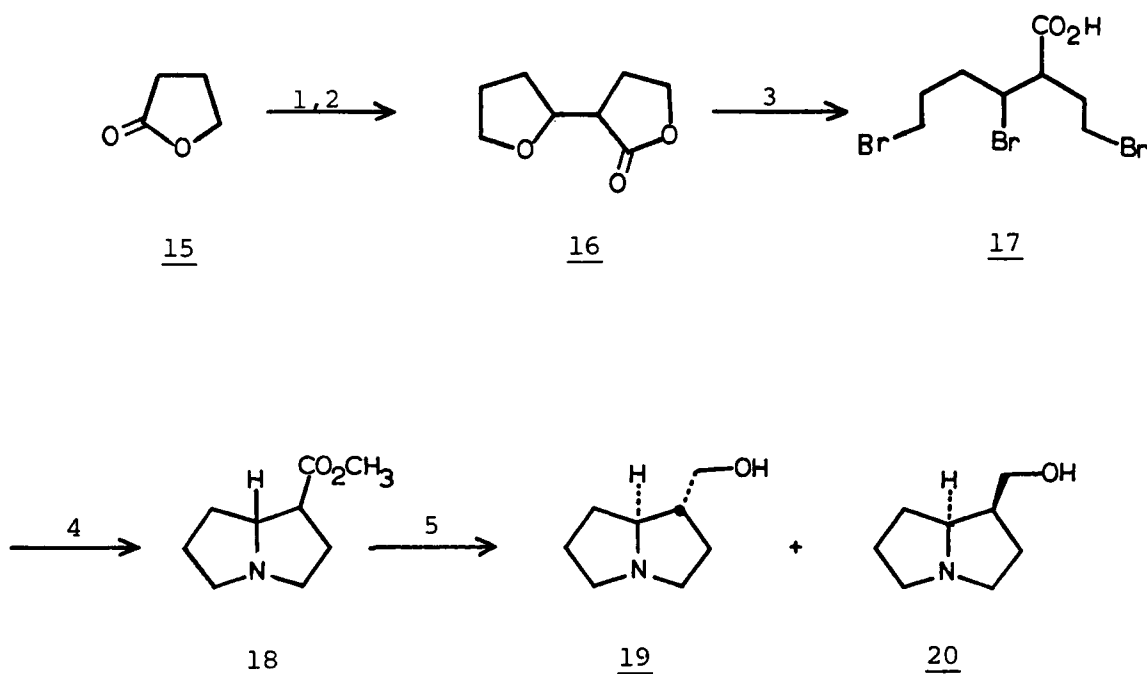


Reagents: 1) Zn, BrCH₂CO₂Et; 2) -H₂O; 3) H₂, Pt; 4) HBr;
 5) NH₃, CH₃OH.

Kochetkov, *et al.*,³² extended the use of this reaction in their synthesis of a mixture of the natural products trachelanthi-midine (19) and isoretronecanol (20). (Scheme 5). Thus, γ -butyrol-lactone (15) was self-condensed under basic conditions, then catalyt-ically hydrogenated to provide 16. Ring-opening was accomplished

with hydrobromic acid to afford the tribromocarboxylic acid 17. Intramolecular cyclization was effected with methanolic ammonia, and the product was isolated as its methyl ester 18. Reduction with lithium aluminum hydride provides 19 and 20, with the former dominating the mixture.

Scheme 5

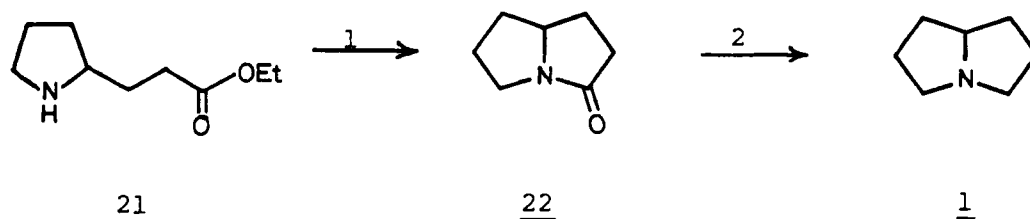


Reagents: 1) CH_3ONa ; 2) H_2 , Ra-Ni ; 3) HBr ; 4) NH_3 , CH_3OH ;
5) LiAlH_4 .

3. Intramolecular Acylation of Amino Acids.

This method of pyrrolizidine synthesis, outlined in Scheme 6,³³ was also extended to the synthesis of trachelanthi-
midine (19) and isoretronecanol (20) by Mandell and Branchard³⁴
(Scheme 7).

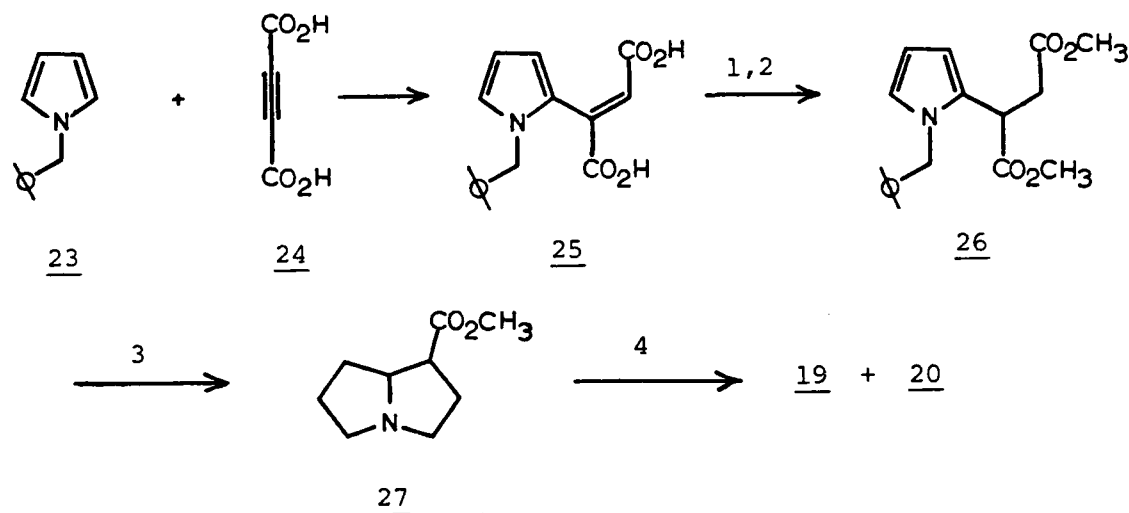
Scheme 6



Reagents: 1) heat; 2) e^- reduction.

The N-benzylpyrrole 23 when treated with the acetylenic diacid 24 provided the 1:1 adduct 25. Catalytic hydrogenation followed by esterification of the carboxylates gave the N-benzyl diester 26. Hydrogenation over palladium on carbon in methanolic hydrochloric acid reduced the pyrrole, debenzylated the nitrogen and cyclized the intermediate to 27. Lithium aluminum hydride reduction of the ketoester 27 provided a 9:1 mixture of 19:20 (p 10).

Scheme 7

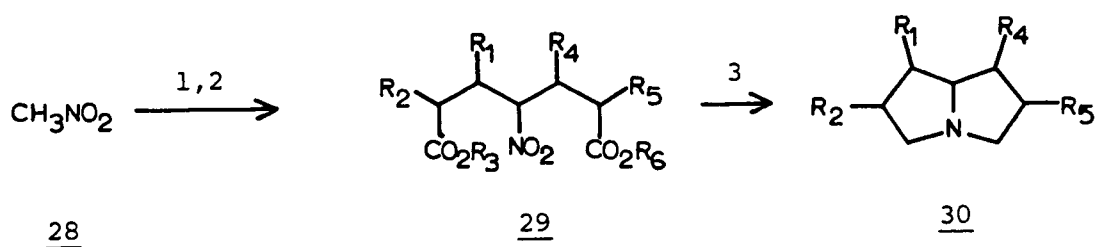


Reagents: 1) H_2 , Pd-C; 2) CH_3OH , HCl; 3) H_2 , Pd-C, CH_3OH , HCl;
4) $LiAlH_4$.

4. Reductive Cyclization.

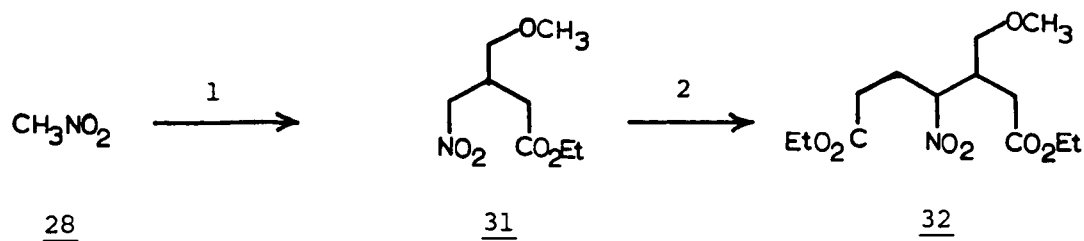
Leonard, et al.³⁵ demonstrated that aliphatic nitro diesters such as 29, prepared by successive Michael additions to nitromethane 28, produced polysubstituted alkyl pyrrolizidines (30) when catalytically hydrogenated (Scheme 8). Jezo and Kalac³⁶ extended this work by using suitably functionalized Michael acceptors in their synthesis of isoretronecanol (19, p 10) and trachelanthimidine (20, p 10) (Scheme 9).

Scheme 8

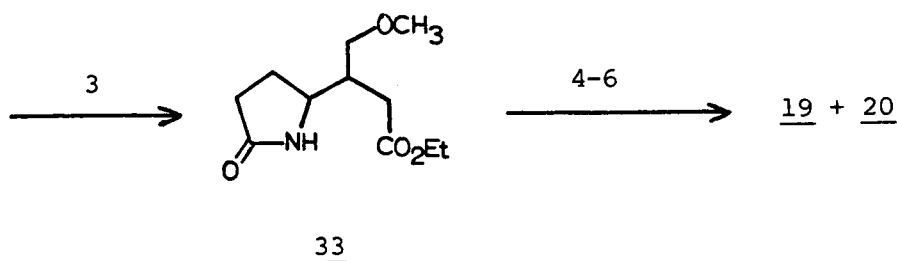


Reagents: 1) $\text{R}_1\text{CH}=\text{CR}_2\text{COOR}_3$; 2) $\text{R}_4\text{CH}=\text{CR}_5\text{COOR}_6$; 3) H_2 , Pt.

Scheme 9



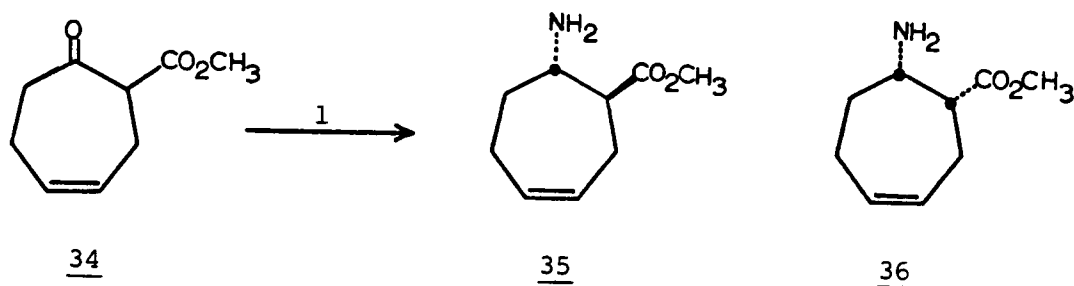
Scheme 9 (cont.)



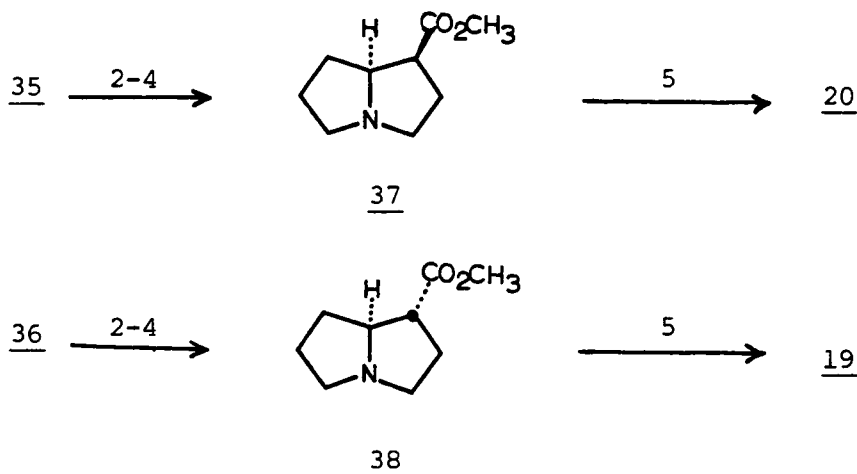
Reagents: 1) $\text{CH}_3\text{OCH}_2\text{CH}=\text{CHCO}_2\text{Et}$; 2) $\text{CH}_2=\text{CHCO}_2\text{Et}$; 3) H_2 , Ra-Ni;
4) LiAlH_4 ; 5) HBr ; 6) NaOH .

In a more recent example, Borch and Ho³⁷ also used reductive cyclization to produce 19 and 20 (p 10) but from different precursors than those used above. Sodium cyanoborohydride reduction of ketoester 34 in the presence of ammonium nitrate provided the diastereomeric amino esters 35 and 36. Oxidation of the double bond, followed by reductive cyclization with sodium cyanoborohydride, gave the isomeric methyl-1-pyrrolizidine carboxylates 37 and 38. Chromatographic separation of the esters, followed by lithium aluminum hydride reduction of each, gave the corresponding natural products. (Scheme 10).

Scheme 10



Scheme 10 (cont.)

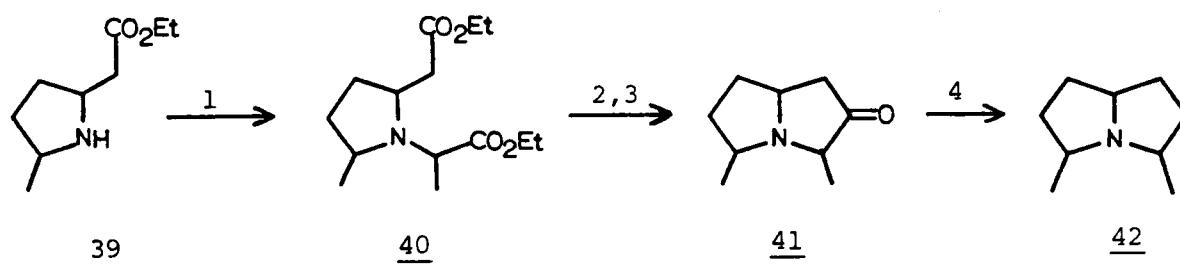


Reagents: 1) NaBH_3CN , NH_4NO_3 ; 2) OsO_4 , IO_4^- ; 3) NaBH_3CN ;
4) chromatography; 5) LiAlH_4 .

5. Dieckmann Condensations

This preparation of pyrrolizidine derivatives was first introduced in the literature in 1936 by Clemo and Metcalfe.³⁸ Their approach involved N-alkylation of a pyrrolidine ester followed by condensation, decarboxylation and reduction to generate 3,5-dimethylpyrrolizidine (42). (Scheme 11). The importance of this method is evidenced by the fact that it provided the means by which the first stereospecific total synthesis of isoretronecanol (20, p 10),³⁹ platynecine⁴⁰ and retronecine⁴¹ (7, p 3) were completed. The syntheses of the latter two natural products will be discussed later in this chapter.

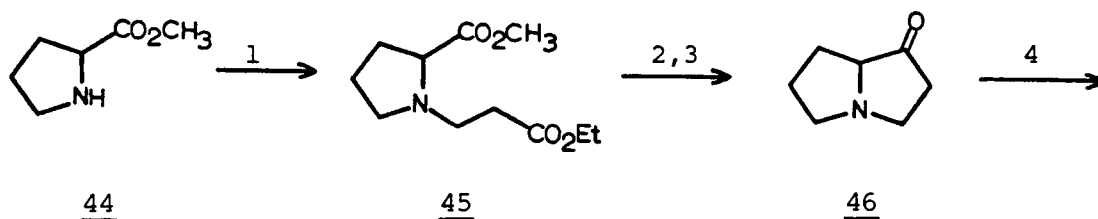
Scheme 11



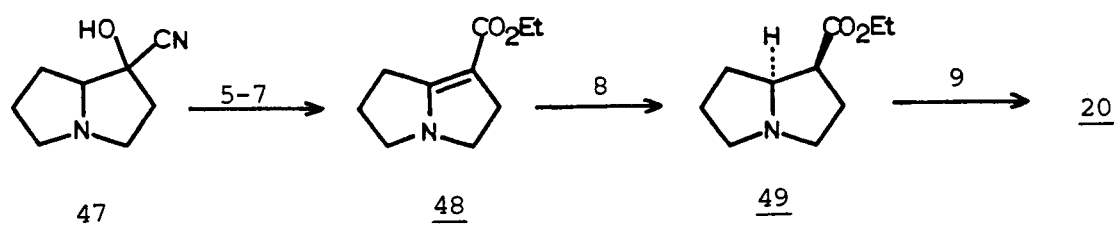
Reagents: 1) $\text{BrCH}(\text{CH}_3)\text{CO}_2\text{Et}$; 2) OH^- ; 3) heat; 4) N_2H_4 .

In 1960, Kochetkov and Likhoshesterov³⁹ found that Michael addition of methyl acrylate (43) to the methyl ester of proline (44) followed by condensation and decarboxylation provided the 1-oxo-pyrrolizidine 46. Formation of the cyanohydrin 48 followed by acid hydrolysis, esterification and dehydration gave the unsaturated ester 49. Catalytic reduction of the double bond proceeded from the α -face, securing the proper stereochemical relationship between C_1 and C_8 . Lithium aluminum hydride reduction of the saturated ester 37 produced isoretronecanol (20, p 10). (Scheme 12).

Scheme 12



Scheme 12 (cont.)



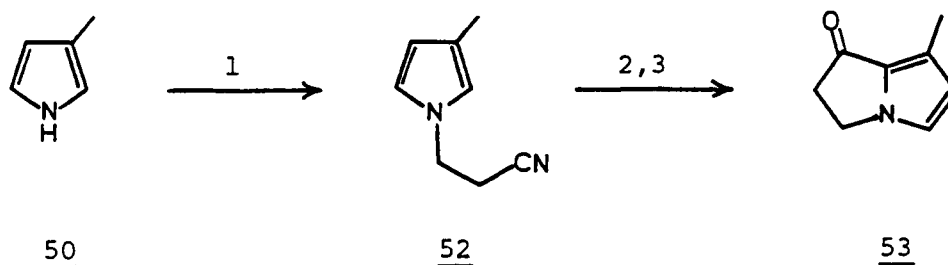
Reagents: 1) $\text{CH}_2=\text{CHCOOCH}_3$, 43; 2) OH^- ; 3) heat; 4) $\text{CH}_3\text{C}(\text{OH})(\text{CN})\text{CH}_3$, 47; 5) H^+ ; 6) esterification 7) $-\text{H}_2\text{O}$; 8) H_2 , Pt; 9) LiAlH_4 .

Dieckmann condensations were also used as the crucial cyclization reaction in two other syntheses of isoretronecanol 20 (p 10), both reported in 1961.^{42,43}

6. Houben-Hoesch Cyclizations

Meinwald and Meinwald⁴⁴ have reported a novel method of generating functionalized unsaturated pyrrolizidines (Scheme 13). The material necessary for cyclization, cyano pyrrole 52, was produced by Michael addition of acrylonitrile (51) to methyl pyrrole 50. Intramolecular electrophilic substitution by the nitrile is accomplished under acidic conditions and generates the dihydropyrrolizidine 53 after hydrolysis of the imminium ion intermediate.

Scheme 13

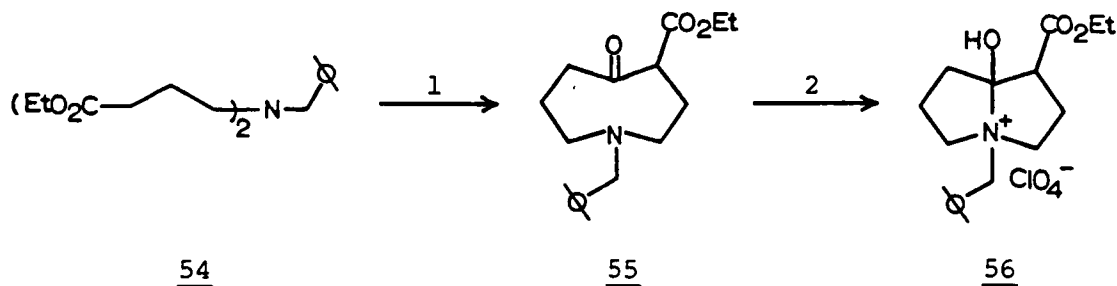


Reagents: 1) $\text{CH}_2=\text{CHCN}$, 51; 2) HCl ; 3) NaO_2CCH_3 .

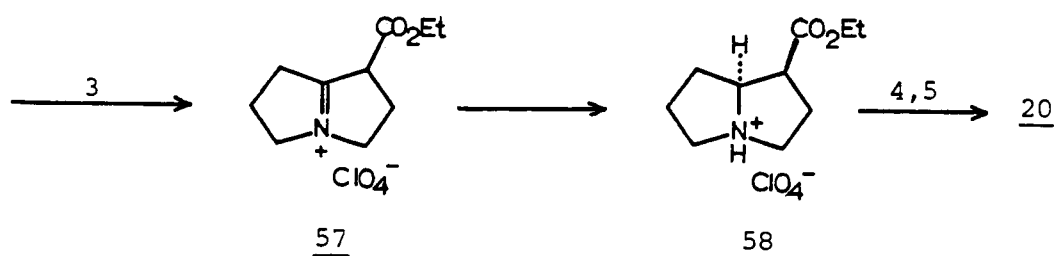
7. Transannular Reactions

In 1969, Leonard and Sato⁴⁵ synthesized isoretronecanol 20 (p 10) by the following route. High dilution Dieckmann condensation of the N-benzyl diester 54 provided the azacyclooctanone 55 which when treated with perchloric acid cyclized to the perchlorate salt 56. Catalytic hydrogenation gave the debenzlated salt 58 presumably through the imminium ion 57. The corresponding free base gave isoretronecanol (20, p 10) upon reduction with lithium aluminum hydride with an isomeric purity of 98% (Scheme 14).

Scheme 14



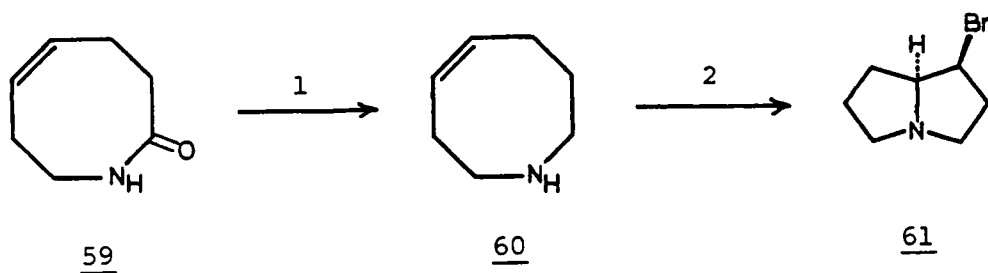
Scheme 14 (cont.)



Reagents: 1) OH^- ; 2) HClO_4 ; 3) H_2 , Pd-C; 4) OH^- ; 5) LiAlH_4 .

As a general entry into functionalized pyrrolizidines, Wilson and Sawicki⁴⁶ developed a simple two-step procedure from the unsaturated lactam 59. Reduction to the corresponding secondary amine 60, followed by bromination of the alkene, promoted ring collapse through nucleophilic displacement of bromide by nitrogen (Scheme 15). The cyclization reaction is stereospecific and high yielding; extension to syntheses of natural products appears feasible provided properly functionalized lactams can be made.

Scheme 15

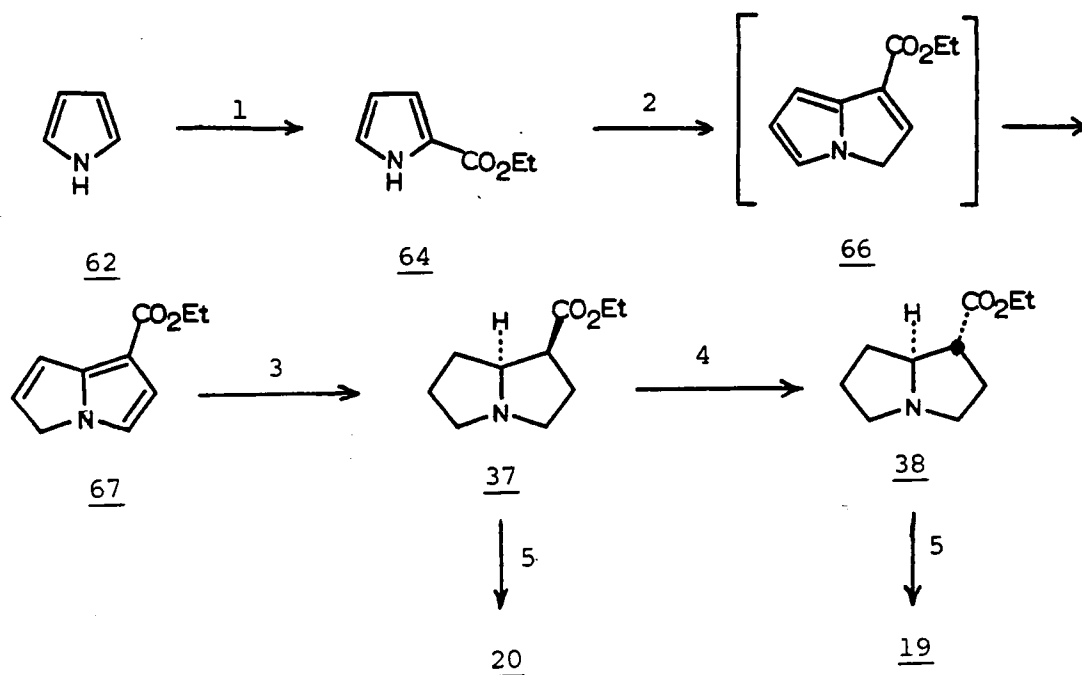


Reagents: 1) LiAlH_4 ; 2) Br_2 .

8. Wittig Reactions

Brandange and Lundin⁴⁷ synthesized isoretronecanol 20 (p 10) and trachelanthimidine 19 (p 10) by constructing the unsaturated pyrrolizidine ring system 66 via a Wittig reaction (Scheme 16). Pyrrole 62 and ethylchlorooxylate (63) gave the glyoxylate ester 64 which when treated with Wittig reagent 65 under basic conditions afforded 67. Complete catalytic hydrogenation gave the ester 37 which was converted into the corresponding natural product by reduction with lithium aluminum hydride. Epimerization of 37 to 38, then reduction, provided the isomeric natural material (Scheme 16).

Scheme 16

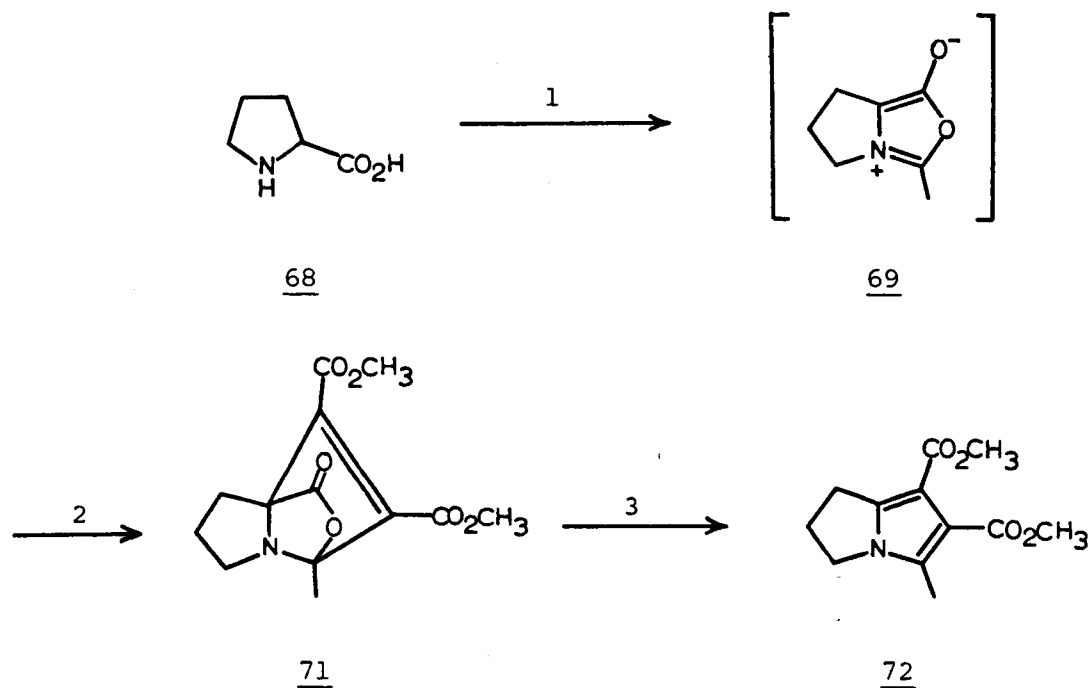


Reagents: 1) ClCOCO_2Et , 63; 2) $\text{CH}_2=\text{CHPh}_3\text{Br}$, 65, NaH; 3) H_2 , Rh/ Al_2O_3 ; 4) NaOEt; 5) LiAlH_4 .

9. 1,3-Dipolar Additions

In 1970, Huisgen and co-workers⁴⁸ developed a highly efficient means to generate functionalized pyrrolizidine intermediates. In a one-pot reaction sequence, L-proline (68) is acylated with acetic anhydride, yielding an intermediate which dehydrates to form the oxazolium oxide 69. This unstable intermediate is trapped with dimethylacetylenedicarboxylate (70) giving the tricyclic lactone 71. Loss of carbon dioxide then gives the unsaturated pyrrolizidine diester 72 in 76% yield from 71 (Scheme 17).

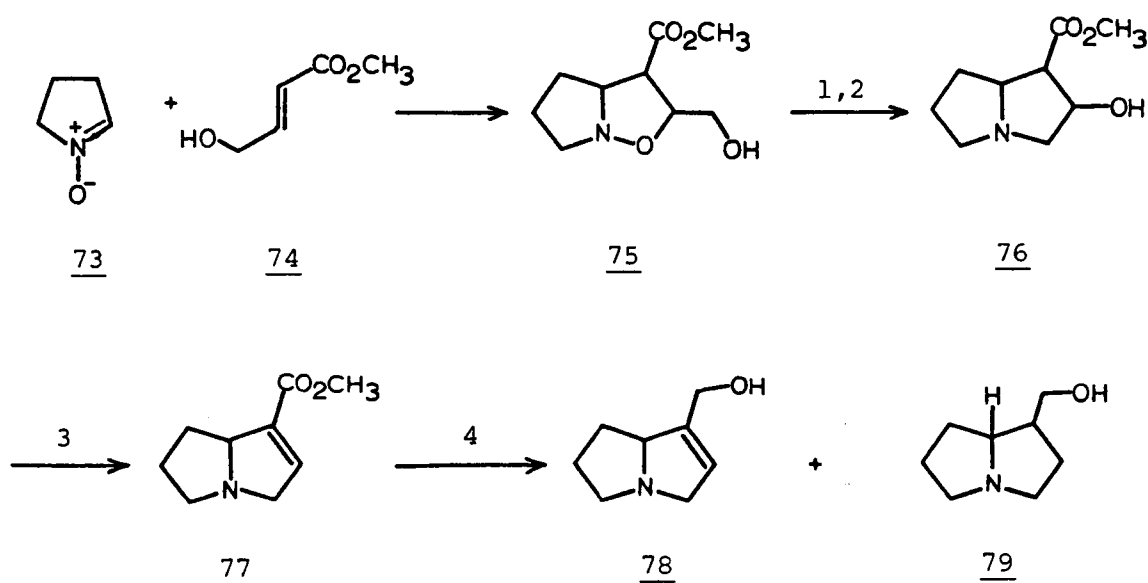
Scheme 17



Reagents: 1) Ac_2O ; 2) $\text{CH}_3\text{O}_2\text{CC CCO}_2\text{CH}_3$, 70; 3) heat.

Extending the work of Huisgen, Tufariello and Tette⁴⁹ were able to synthesize supindine (78), in addition to isoretro-necanol 20 (p 10) and trachelanthindine 19 (p 10). Regioselective addition of the unsaturated hydroxy ester 74 to Δ^1 -pyrroline-N-oxide (73) produced the isoxazolidine 75 in high yield. Hydrogenolysis of the methanesulfonate derivative of 75 produced the disubstituted pyrrolizidine ring system 76 in 95% yield. The dehydration and reduction steps were not as efficient, and a mixture consisting of supindine (78), and the 1-hydroxymethylpyrrolizidines 79 mentioned above was obtained.

Scheme 18

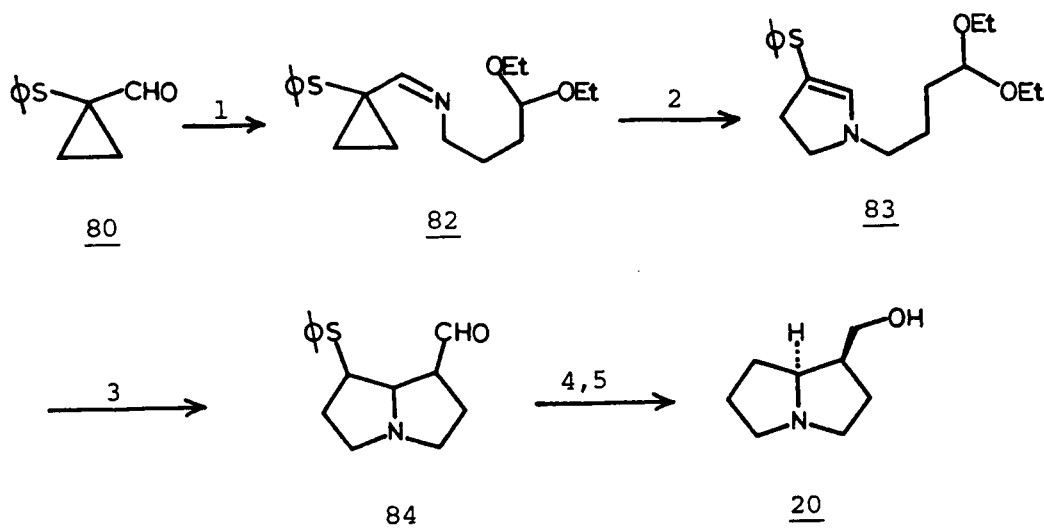


Reagents: 1) $\text{CH}_3\text{SO}_2\text{Cl}$; 2) H_2 , Pd-C; 3) $-\text{H}_2\text{O}$; 4) LiAlH_4 , AlCl_3 .

10. Miscellaneous Reactions

Stevens, et al.⁵⁰ have synthesized isoretronecanol 20 (p 10) by cyclopropyl imine rearrangement. The disubstituted cyclopropane 80 was condensed with acetal amine 81 to provide Schiff base 82. Rearrangement by refluxing a xylene solution of 82 and ammonium chloride gave the unsaturated pyrrolidine 83. Acetal release with acid cyclized this material to the disubstituted pyrrolizidine 84. Reduction, followed by desulfurization with Raney-Nickel, provided isoretronecanol (20), p 10).

Scheme 19

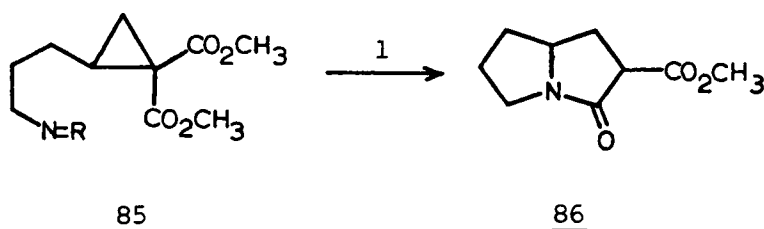


Reagents: 1) $\text{H}_2\text{N}(\text{CH}_2)_3\text{CH}(\text{OEt})_2$, 81; 2) NH_4Cl , xylene; 3) H^+
 4) LiAlH_4 ; 5) Ra-Ni.

Danishefsky and Dynak⁵¹ have also contributed to this field by demonstrating that activated imidocyclopropanes can be

induced to provide pyrrolizidine derivatives. (Scheme 20). Thus, cyclopropyl imido diester 85 (R=phthalimido), when treated with hydrazine, gives the disubstituted pyrrolizidine 86. This work was extended⁵² by Danishefsky and co-workers toward the total stereospecific synthesis of other pyrrolizidine natural products to be discussed later in this chapter.

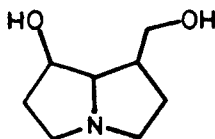
Scheme 20



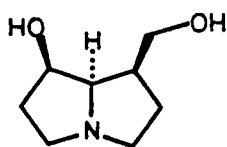
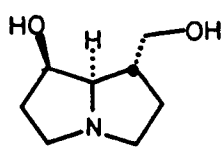
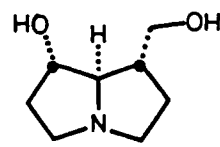
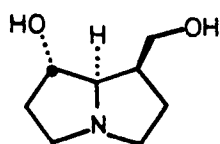
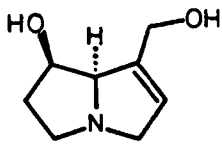
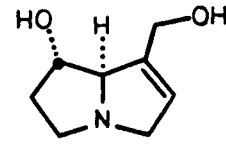
Reagent: 1) N₂H₄.

C. Pyrrolizidine Natural Product Syntheses

Recent synthetic efforts have been focused upon solving some of the more complex problems associated with pyrrolizidine synthesis, in addition to refining known methods. For example, the pyrrolizidine diols of general structure 87 are deceptively simple

87

synthetic targets from a stereochemical standpoint, but are generally unavailable by most of the methods just presented. To date, no investigator in this field has published total syntheses of the entire series from a common intermediate, perhaps an indication of their complexity. For this reason, a review of the total syntheses of: (1) platynecine (88), (2) turneforcidine (89); (3) hastanecine (90) and dihydroxyheliotridane (91); and (4) retronecine (7, p 3) and heliotridene (92) is warranted.

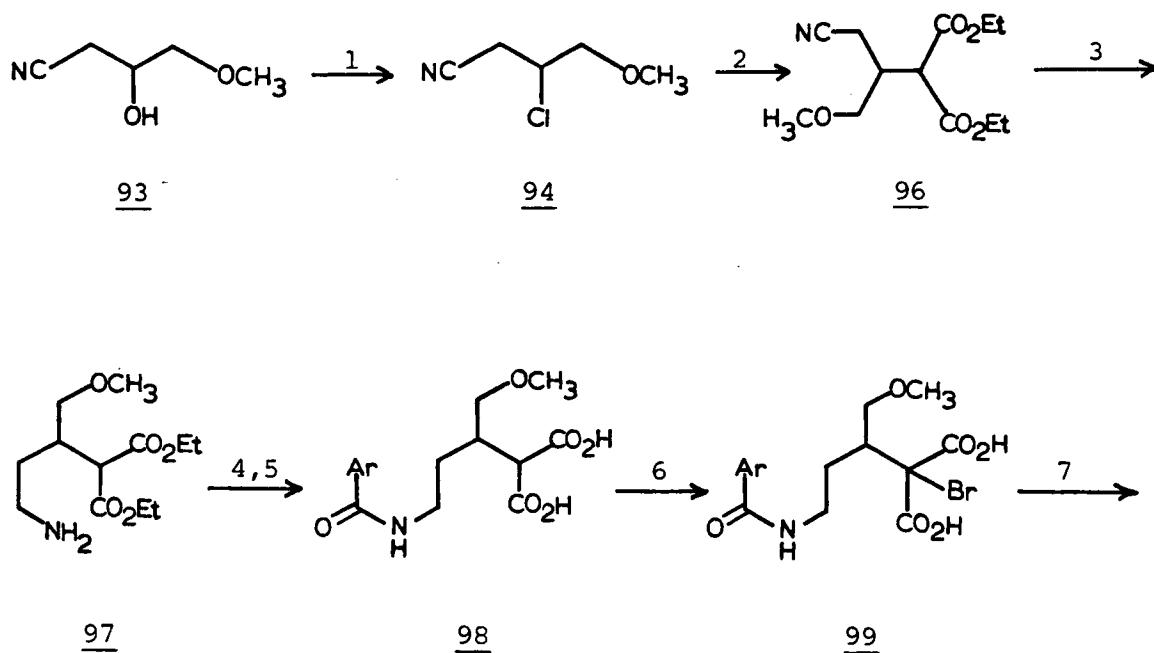
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1. Platynecine

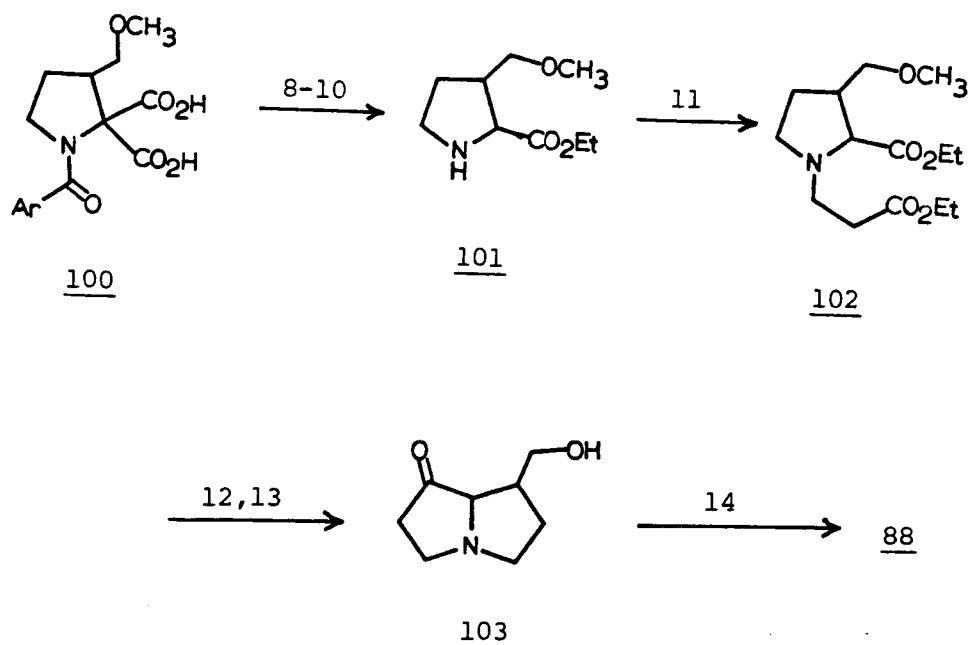
The first total synthesis of platynecine (88) was reported in 1960 by Jezo, *et al.*⁴⁰ and is outlined in Scheme 21. Interestingly, the stereochemistry of the natural product was unknown at the time. Chlorination of hydroxynitrile 93 to 94 followed by nucleophilic displacement of chloride ion with the anion of malonic acid diethyl ester (95) provided the diester

nitrile 96. Catalytic hydrogenation of the nitrile to the amine 97 then hydrolysis of the esters and condensation with 3,5-dinitrobenzoylchloride ($=\text{COAr}$) produced the amido diacid 98. Bromination in acetic acid to 99 followed by nucleophilic displacement of bromide ion by nitrogen gave the cyclic amide 100. Acidic hydrolysis, decarboxylation and esterification generated the pyrrolidine ester 101. Michael addition of ethyl acrylate to provide 102, Dieckmann condensation with potassium metal and acid hydrolysis of the resulting ketoester provided the pyrrolizidine ketone 103. Finally, reduction with hydrogen over platinum gave platynecine (88, p 24).

Scheme 21



Scheme 21 (cont.)

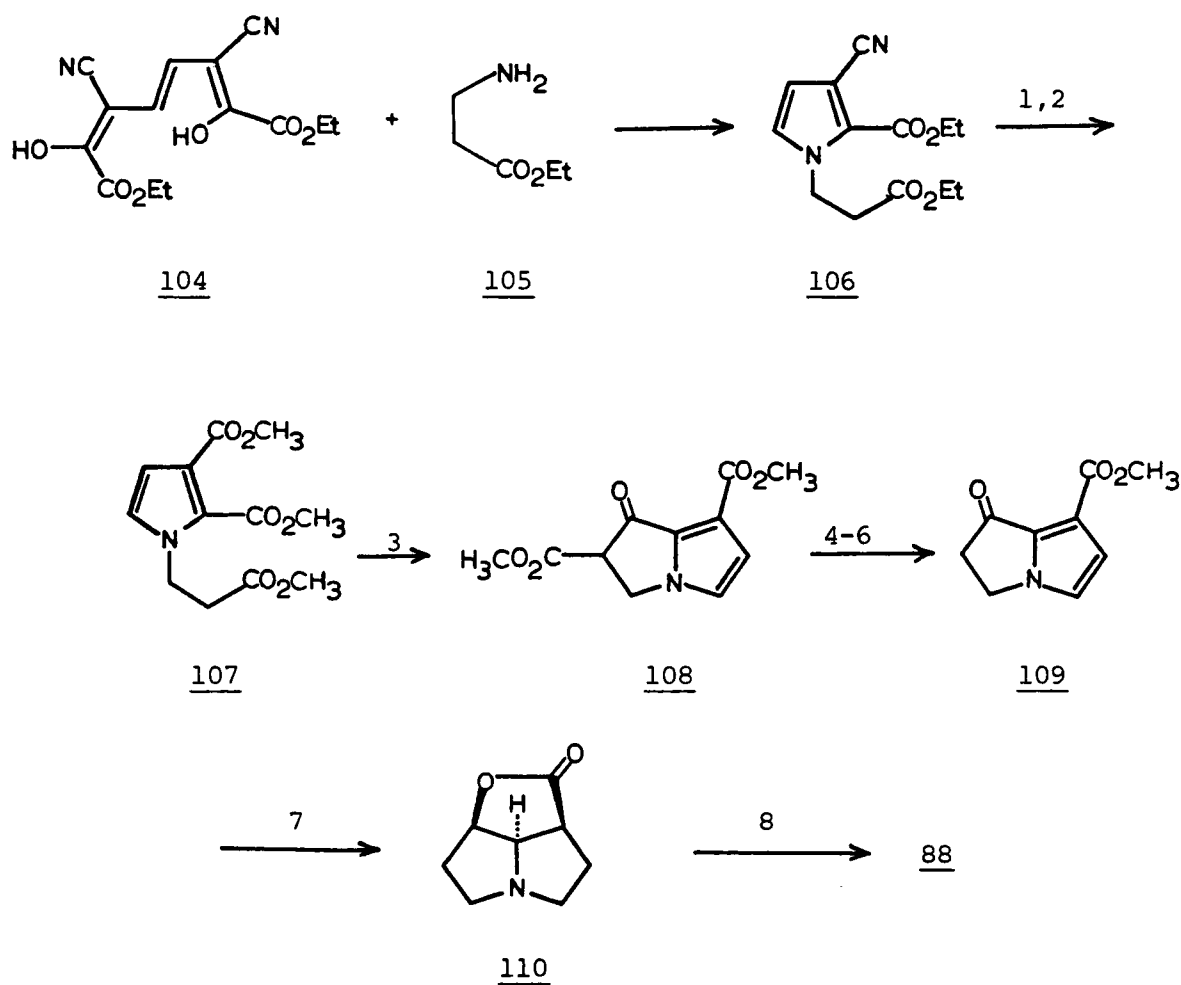


Reagents: 1) SO_2Cl_2 ; 2) $\text{EtO}_2\text{CCH}_2\text{CO}_2\text{Et}$, 95; 3) H_2 , Pt; 4) ^-OH ;
 5) 3,5-di NO_2 ArCOCl; 6) Br_2 , AcOH; 7) cyclization;
 8) HCl; 9) heat; 10) esterification; 11) $\text{CH}_2=\text{CHCO}_2\text{Et}$;
 12) K; 13) H^+ ; 14) H_2 , Pt.

Viscontini and Buzek⁵³ also recognized the utility of the Dieckmann condensation in their preparation of platynecine (88, p 24). Reaction of the enolized diketo diester 104 with ethyl 2-aminopropanoate (105) gave the diester cyano pyrrole 106. Hydrolysis of the nitrile followed by esterification with diazo-methane provided the triester 107. Dieckmann condensation with sodium methoxide cyclized 107 into 108. Acid hydrolysis of the

esters followed by decarboxylation and reesterification generated the keto ester 109. Reduction with three moles of hydrogen over platinum in acetic acid gave the lactone 110 in 40% yield. Reduction with lithium aluminum hydride gave platynecine (88, p 24) in 60% yield.

Scheme 22



Reagents: 1) OH^- ; 2) CH_2N_2 ; 3) NaOCH_3 ; 4) H^+ ; 5) heat;

6) CH_2N_2 ; 7) H_2 , Pt, AcOH; 8) LiAlH_4 .

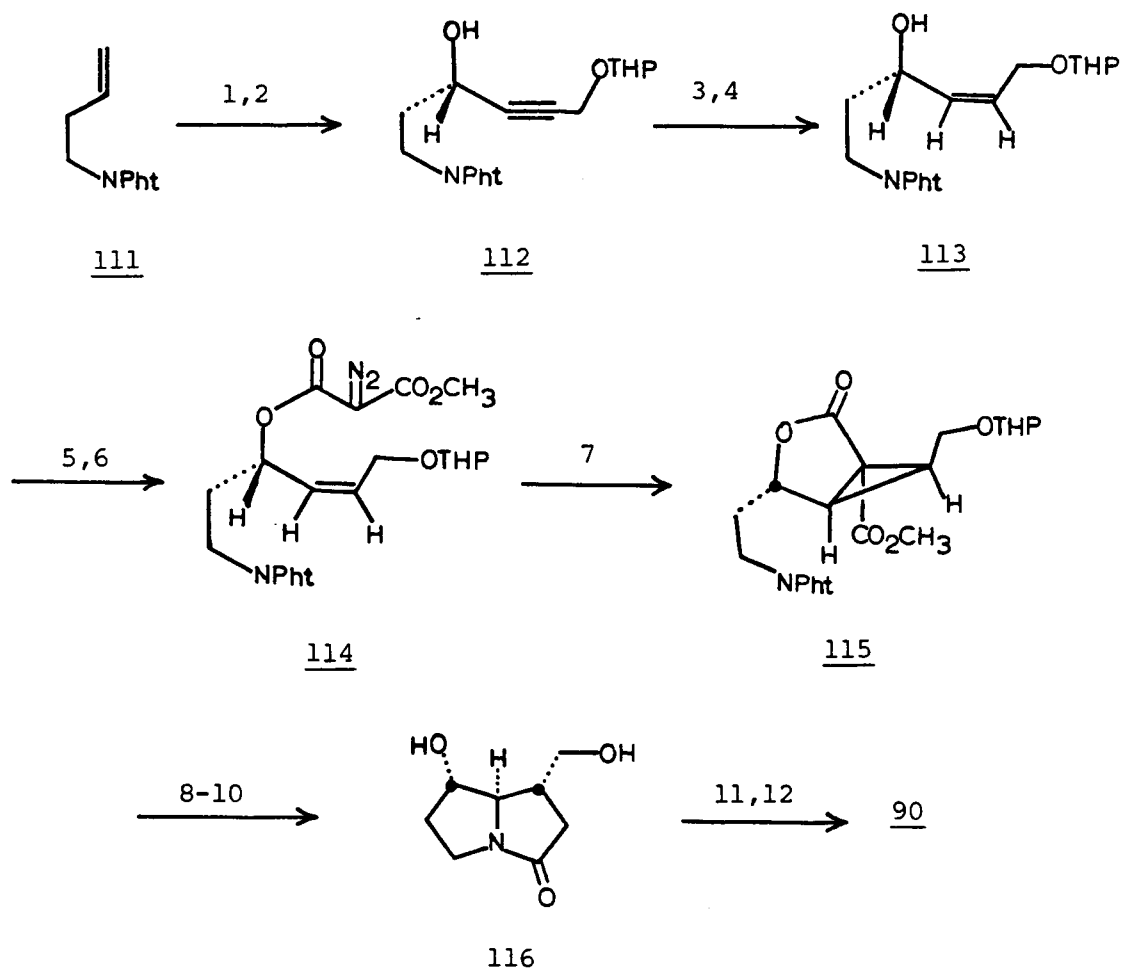
2. Turneforcidine.

To date, no total synthesis of turneforcidine (89, p 24) has been reported in the literature.

3. Hastanecine and Dihydroxyheliotridane.

Danishefsky and co-workers⁵⁴ have successfully extended their method of necine base synthesis via activated cyclopropanes (vide supra) to include the C₁ epimers hastanecine (90, p 24) and dihydroxyheliotridane (91, p 24) (Scheme 23). Ozonolysis of the phthalimide alkene 111 (Pht=phthalimido) to the corresponding aldehyde followed by coupling to the magnesium salt of propargyl alcohol tetrahydropyranyl ether provided the hydroxy alkyne 112. Semihydrogenation, followed by silica gel chromatography afforded the pure Z isomer 113. Acylation with carbomethoxyacetyl chloride then diazotization gave the Z diazo ester 114. Cyclopropanation with copper bronze at 110° gave a single cyclopropane, formulated as 115 only by its conversion into hastanecine (90, p 24). Formation of the pyrrolizidine skeleton was accomplished by the following series of steps, without isolation of intermediates: hydrazine; 10% aqueous hydrochloric acid; and sodium methoxide to provide 116. Reacetylation of the hydroxy groups with acetic anhydride in pyridine followed by reduction with lithium aluminum hydride gave d,l-hastanecine (90, p 24). Notably, no platynecine (88, p 24) was formed, thereby indicating that the only operative mechanism was inversion of configuration in the ring opening step.

Scheme 23

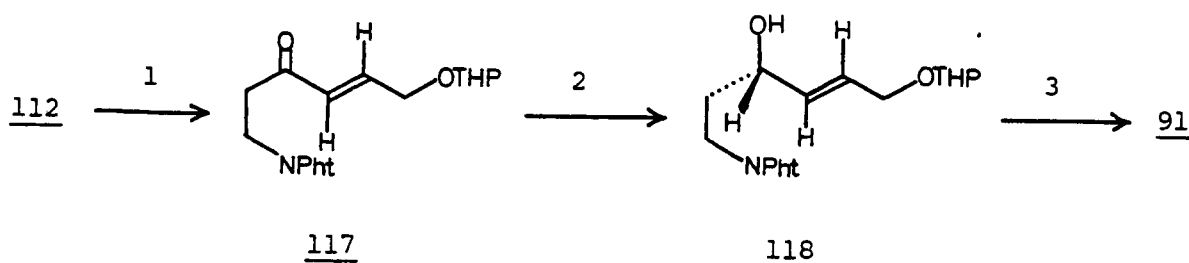


Reagents: 1) O_3 , -78° ; 2) $MgCCCH_2OTHP$; 3) H_2 , $Pd/BaSO_4$, quinoline, CH_3OH ; 4) silica gel; 5) $ClCOCH_2CO_2CH_3$; 6) tosyl azide; 7) copper bronze, 110° ; 8) $3 N_2H_4$, CH_3OH , reflux; 9) 10% aqueous HCl , reflux; 10) $NaOCH_3$, CH_3OH ; 11) pyridine, Ac_2O ; 12) $LiAlH_4$.

In an analogous fashion, Danishefsky⁵⁴ synthesized dihydroxyheliotridane (**91**) (p 24) from the E alcohol **118** prepared

from 112 in the following manner. (Scheme 24). Corey oxidation⁵⁵ of 112 afforded the E enone 117 in high yield. Reduction with sodium borohydride produced the necessary E alcohol 118 which was converted into dihydroxyheliotridane (91, p 24) by an identical reaction sequence as that used in the production of 90 (p 24).

Scheme 24



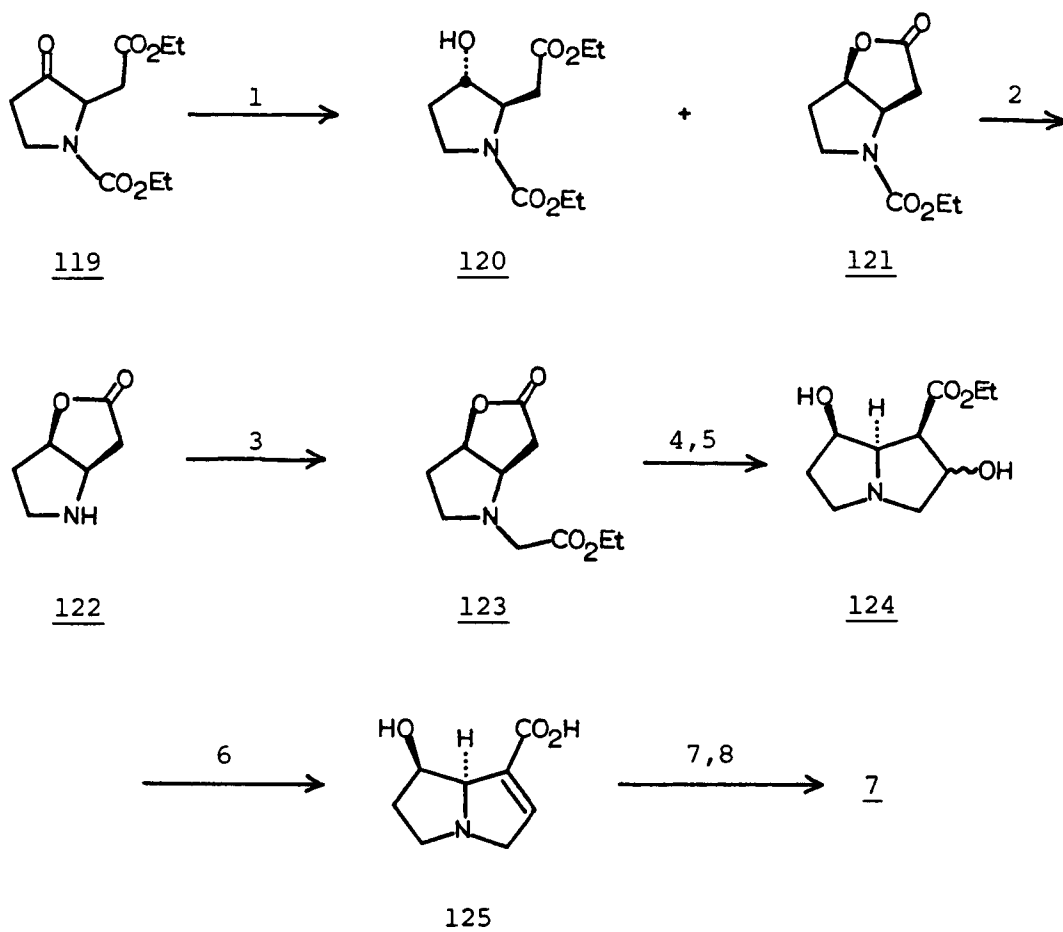
Reagents: 1) pyridinium chlorochromate; 2) NaBH₄; 3) steps (5)-(8) Scheme 23.

4. Retronecine and Heliotridine

The first total synthesis of retronecine (7, p 3) was reported in 1962 by Geissman and Waiss.⁴¹ (Scheme 25). The available keto diester 119 was reduced with sodium borohydride to a mixture containing alcohol ester 120 and lactone 121. Separation of the mixture, followed by hydrolysis of the urethane in 121 with barium hydroxide gave amino lactone 122. Alkylation with ethyl bromoacetate produced the ester lactone 123. Treatment of 123 with potassium ethoxide followed by catalytic hydrogenation of the ketone gave 124. Dehydration, accompanied by ester hydrolysis,

was effected with barium hydroxide to give 125. Reesterification, then lithium aluminum hydride reduction afforded retronecine (7, p 3).

Scheme 25

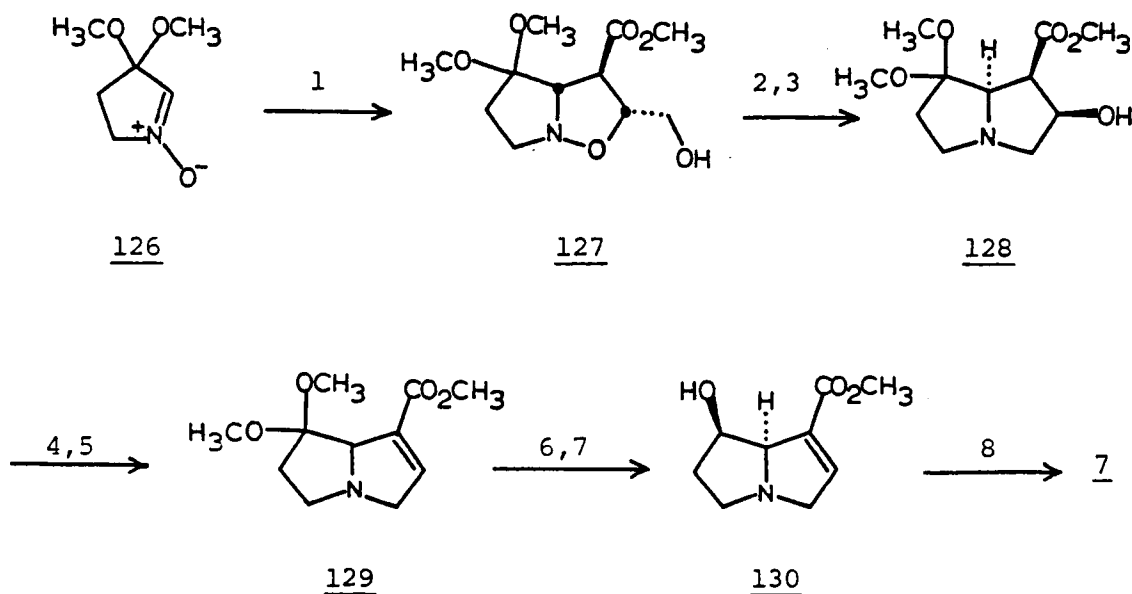


Reagents: 1) NaBH_4 ; 2) $\text{Ba}(\text{OH})_2$; 3) $\text{BrCH}_2\text{CO}_2\text{Et}$; 4) KOCH_2CH_3 ;
5) H_2 , Pt, HOAc; 6) $\text{Ba}(\text{OH})_2$; 7) EtOH, HCl; 8) LiAlH_4 .

Three independent syntheses of retronecine (7, p 3) appeared in the literature in 1980. Each demonstrated the utility of different types of reactive intermediates.

Tufariello and Lee⁵⁶ chose the functionalized nitron 126 as the focal point in their synthesis of 7 (p 3) (Scheme 26). The 1,3-dipolar cycloaddition of 126 to methyl δ -hydroxycrotonate was not sensitive to the expected inhibiting steric factors and isoxazolidine 127 was produced in high yield. Mesylation of the primary alcohol, followed by hydrogenolysis of the nitrogen-oxygen bond allowed the newly formed secondary amine to displace mesylate and form pyrrolizidine 128. The hydroxy group was mesylated and subjected to elimination to produce the unsaturated ester 129.

Scheme 26



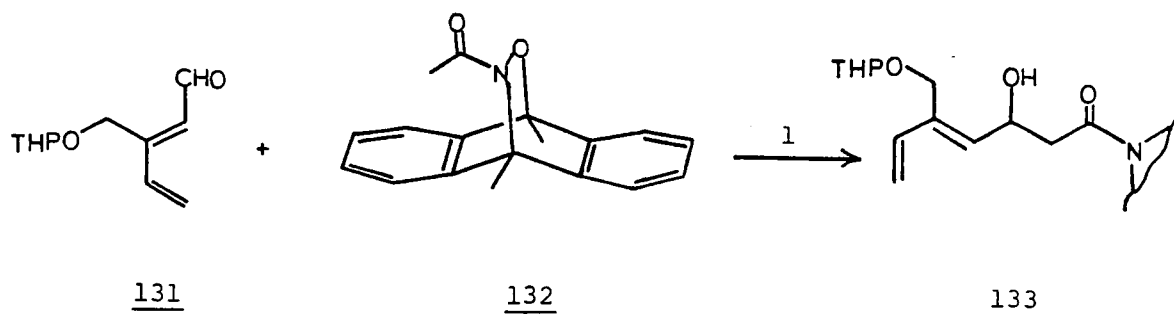
Reagents: 1) $\text{trans-HOCH}_2\text{CH=CHCO}_2\text{CH}_3$; 2) $\text{CH}_3\text{SO}_2\text{Cl}$, Et_3N ;
 3) H_2 , Pd-C, CH_3OH ; 4) $\text{CH}_3\text{SO}_2\text{Cl}$, Et_3N ; 5) Et_3N ;
 6) 37% HCl , DME; 7) NaBH_4 , CH_3OH ; 8) AlH_3 .

Liberation of the ketal with acid, followed by reduction of the ketone with sodium borohydride afforded the alcohol ester 130.

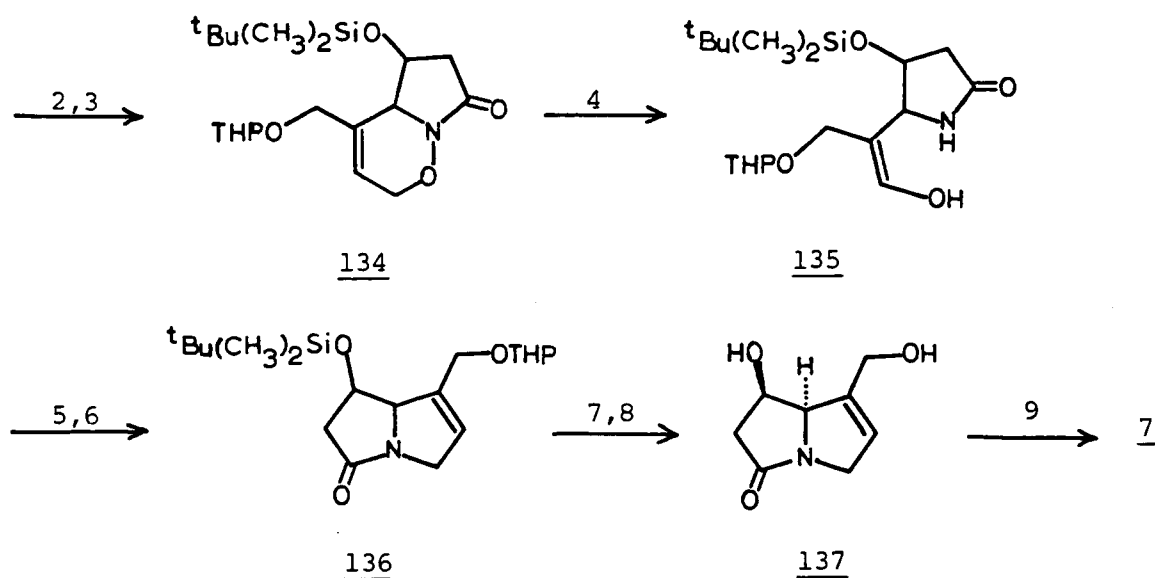
Alane reduction of 130 gave retronecine (7, p 3).

Retronecine (7, p 3) was also produced by an intramolecular dienophile transfer reaction (Scheme 27) published by Keck and Nickell.⁵⁷ Aldehyde 131 was added to the lithium enolate of isoxazole 132 which gave 133 cleanly. Protection of the secondary alcohol as its tert-butyldimethylsilyl ether, followed by thermolysis at 80°, induced the intramolecular cycloaddition to occur and 134 was produced in high yield. Reduction of the nitrogen-oxygen bond with sodium amalgam afforded hydroxy lactam 135. Mesylation of the hydroxy function, followed by treatment with strong base provided a mixture of C₇ epimers (136) which were separated by chromatography. Removal of the tetrahydropyranyl and tert-butyldimethylsilyl protecting groups was accomplished with appropriate reagents to afford, for retronecine (7, p 3) stereochemistry, dihydroxy lactam 137. Reduction with lithium aluminum hydride produced retronecine (7, p 3).

Scheme 27



Scheme 27 (cont.)



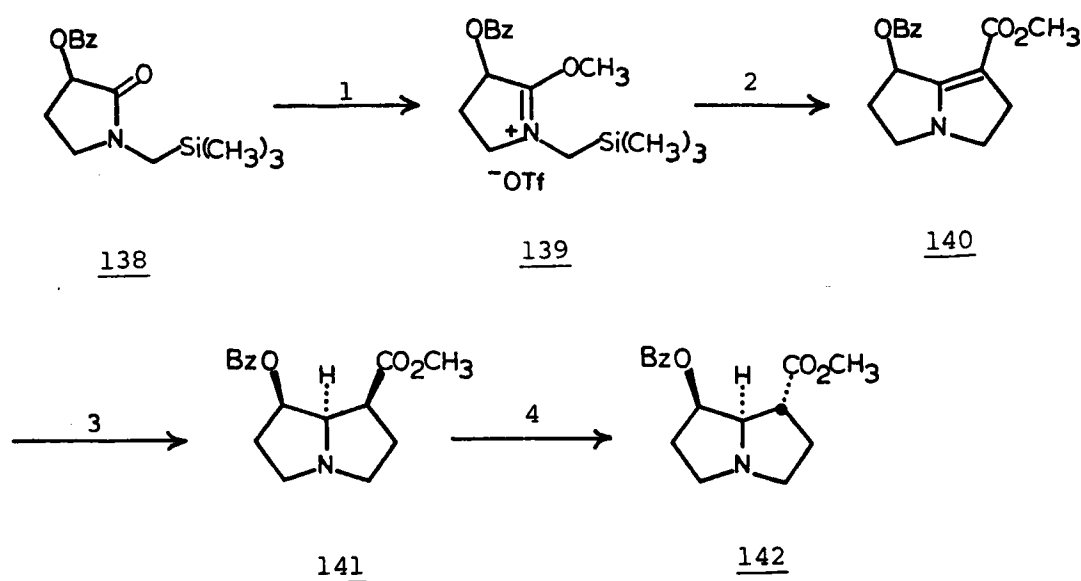
Reagents: 1) 1.1 LDA, HMPA, THF, -78° ; 2) tert- $\text{Bu}(\text{CH}_3)_2\text{SiCl}$,
 3) OH , 80° ; 4) 6% Na-Hg, 4 Na_2HPO_4 ; 5) $\text{CH}_3\text{SO}_2\text{Cl}$,
 Et_3N ; 6) LDA, THF; 7) pyridinium-p-toluenesulfonate,
 CH_3OH ; 8) $(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_4\text{NF}$, THF; 9) LiAlH_4 .

The alternative isomer of **136** was converted into helio-
 tridene (**92**, p 24) in an analogous fashion.⁵⁷ Of particular signi-
 ficance in this work are the differentially protected alcohols at
 the lactam stage **136**. The authors suggest that this would allow,
 or be conducive to, preparation of higher molecular weight analogs
 possessing the antitumor properties suggested earlier.

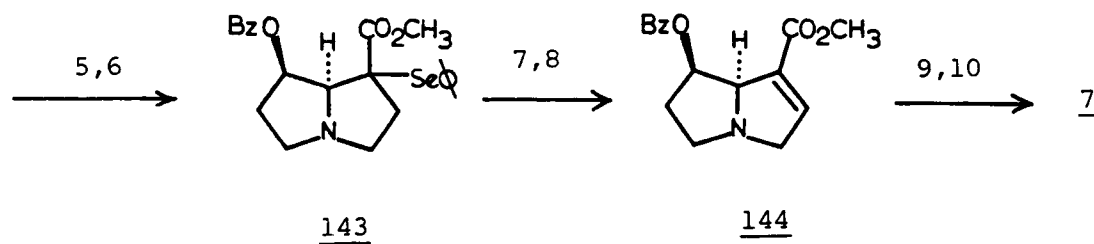
Vedejs and Martinez⁵⁸ have also successfully completed
 the synthesis of retronecine (**7**, p 3) by imidate methylide cyclo-

addition. (Scheme 28). Their route begins with oxygen alkylation of lactam 138, available by two different approaches, to provide the imminium salt 139. The crude salt was allowed to react with methyl acrylate in the presence of cesium fluoride which effected the desired cycloaddition in moderate yield giving 140. Catalytic hydrogenation directs the stereochemistry in the desired fashion to 141, which slowly epimerizes to the crystalline ester 142. Generation of the enolate, which is allowed to react with diphenyl diselenide gives the selenide 143. Oxidation of the selenium, followed by elimination provides the unsaturated ester 144. Dibal reduction of the ester, followed by a dissolving metal reduction to remove the benzyl ether, gave retronecine (7, p 3), in approximately 20% overall yield from 138.

Scheme 28



Scheme 28 (cont.)



Reagents: 1) $\text{CH}_3\text{OSO}_2\text{CF}_3$; 2) DME, $\text{CH}_2=\text{CHCO}_2\text{CH}_3$, CsF; 3) H_2 , Pd-C, EtOAc; 4) 20° , 48h; 5) LDA; 6) Ph_2Se , -35° ; 7) MCPBA; 8) CCl_4 ; 9) DIBAL; 10) Li, NH_3 .

CHAPTER II

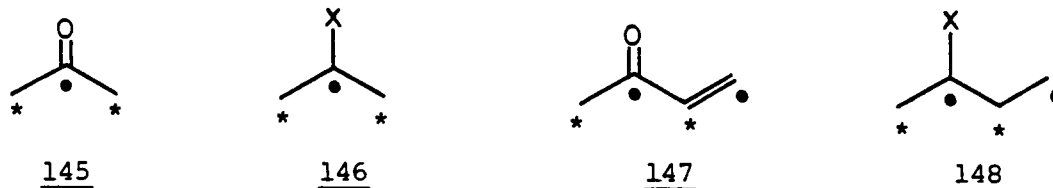
RESULTS AND DISCUSSION

The synthetic approaches to the saturated pyrrolizidine diols reviewed in the previous chapter, though manifold in scope, generally fall short in their treatment of the stereochemical problems posed by these molecules. Typically the strategies focus upon generation of two epimers in the series, but fail to address the problem of manufacturing, stereospecifically, the contiguous, three-carbon asymmetric array for each of the possible isomers. Successfully accomplishing such a task is without doubt difficult, but not beyond the reach of synthetic organic chemistry as it now stands.

The research described in this chapter will address this problem, and is discussed in full at the appropriate time. As a matter of introduction, however, it becomes necessary to theoretically examine the pyrrolizidine diol system, and then describe a novel entry into this class of alkaloids.

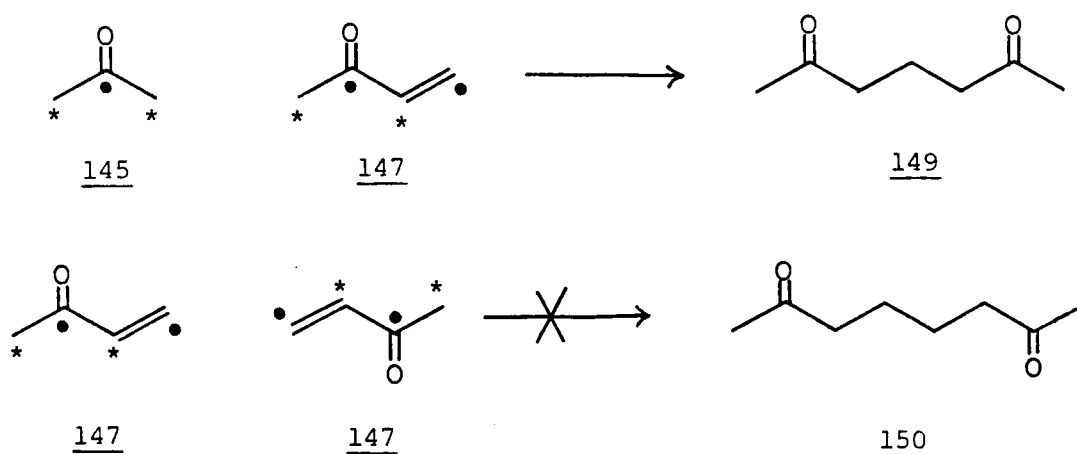
Evans and Seebach,⁵⁹ independently and simultaneously, arrived at a qualitative method of evaluating the difficulty one might encounter when devising ground state syntheses of any molecule. Based on the outcome of standard condensation chemistry (e.g., Aldol, Mannich, Michael reactions, etc.) the method concludes that even-numbered separations (2, 4, 6 carbons, etc.) between heteroatoms are difficult to synthesize, where odd-numbered separations (1, 3, 5 carbons, etc.) are relatively easy to construct.

This analysis states that any heterosubstituted carbon can be considered a carbonyl; the only difference being the oxidation state of the carbon in singly-bonded cases. Therefore, these heterosubstituted carbons will possess the potential reactivity of carbonyl carbons. Similarly, carbons once removed from this center will react in a manner analogous to carbonyl α -carbons. By extension to α,β -unsaturated carbonyl systems, this reactivity parallel can be viewed as proceeding down a chain of carbon atoms. This is illustrated below (145-148), where dots and asterisks are used to denote sites of differing reactivities.



Evaluation of the merits of this concept is best done with the aid of some classical condensation chemistry. Thus, 2,6-heptanedione (149, a 1,5-dicarbonyl, odd) is available in principle from the Michael addition of the enolate of acetone (145) and methyl vinyl ketone (147). Of particular significance is the fact that the new

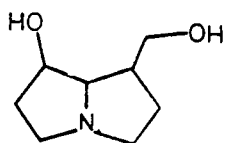
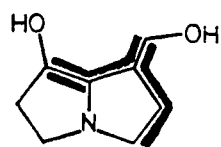
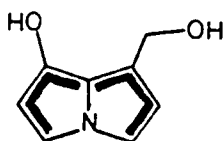
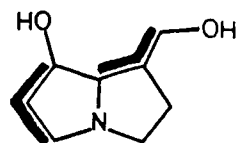
carbon-carbon bond is formed by reaction of carbons of dissimilar reactivity ($\bullet$ and $*$). This "special" reactivity cannot be used, however, to produce 2,7-octanedione (150 a 1,6-dicarbonyl, even) from two moles of methyl vinyl ketone (147) because the terminal carbons possess similar reactivity ($\bullet$ and $*$).



Thus, obtention of the latter molecule requires the use of some form of reactivity umpolung,⁵⁹ or starting materials which contain the even-numbered separation.

Using this method of analysis for the pyrrolizidine diols reveals their inherent difficulty of synthesis. Assuming that the heteroatoms in 87 are simply reduced carbonyl groups, it is clearly seen that the separations are, for the most part, even numbered (bold lines in 87a and 87b). Odd-numbered separations are shown in 87c. This precludes establishing all heteroatom separations entirely by odd routes, and coupled with the intriguing stereochemical issue,

presents saturated pyrrolizidine diol synthesis as a considerable challenge.

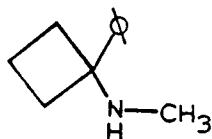
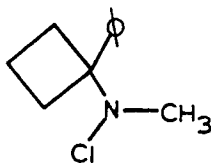
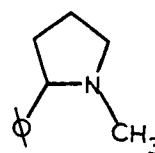
8787a87b87c

In addition to the necine bases, many of the known alkaloids possess a tertiary bridgehead nitrogen in the form of an amine or an amide. Through the years, synthetic organic chemistry has benefitted as a result of this due to development of methods centered upon their manufacture. No less elegant than any of the prior methods is the use of silver ion induced rearrangement of secondary N-chloroamines. The work described in this chapter investigates the use of this reaction to generate the pyrrolizidine ring skeleton from appropriate starting materials.

Introduced to the chemical literature nearly twenty years ago, the mechanism of N-chloroamine rearrangement still remains in question. Gassman and Edwards have been the principal exponents of

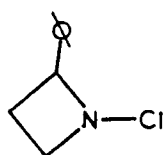
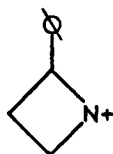
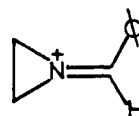
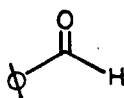
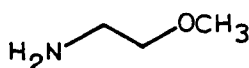
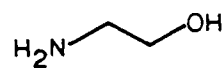
the mechanism issue, publishing papers which defend and oppose the nitrenium ion pathway, respectively. However, other investigators have seized the opportunity to exploit a relatively new organic reaction from a developmental standpoint. Most importantly, all of the papers published have served to illustrate the versatility which N-haloamine rearrangement enjoys. The following examples will be demonstrative.

Chlorination of the aminocyclobutane 151 followed by reaction of the N-chloroamine 152 with methanolic silver trifluoroacetate provides the pyrrolidine 153 after neutralization with sodium methoxide and reduction of the postulated immonium ion intermediate with sodium borohydride.⁶⁰ This ring-expanded product was produced in 36% yield and 24% of the parent amine was recovered from the reaction mixture.

151152153

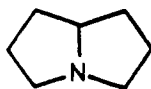
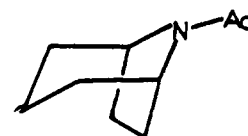
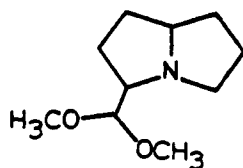
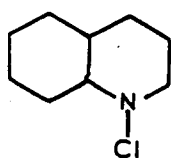
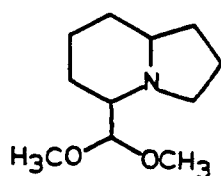
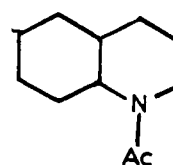
In the same communication,⁶⁰ Gassman also demonstrated that N-chloroamines could undergo silver ion induced ring contraction. Thus, N-chloro-2-phenylazetidine (154) was treated with methanolic silver trifluoroacetate to provide, upon hydrolysis, neutralization and benzoyl chloride addition, 67% of benzaldehyde (157), 39% of the benzamide of 158, and 36% of the benzoate-benzamide of 159. The

extensive fragmentation must involve aziridinium salt 156 which upon hydrolysis provides benzaldehyde (157); the protonated aziridine or 156 would be expected to ring-open under the reaction conditions employed thereby providing the other two products.

154155156157158159

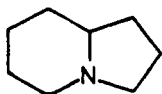
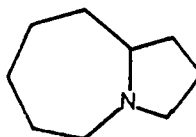
Schell, *et al.*⁶¹ have also reported ring contractions with N-chloroamines 160, 162 and 165 by treatment with refluxing silver nitrate followed by reduction with acidic sodium cyanoborohydride. Thus, N-chloronortropane (160) provided 35% of pyrrolizidine (1) and 45% of nortropane, isolated as its acetamide (161). Similar treatment of N-chlorogranatanine (162) afforded the pyrrolizidine acetal 163 in 25% yield, and 46% of granatanine, as its acetamide (164). Finally, N-chloro-trans-decahydroquinoline (165) also provided an acetal (166, 13%) and the acetamide of the parent amine (167, 40%). The formation

of acetals 163 and 166 is best explained by β -chloroenamine rearrangement after generation of the immonium ion intermediate.^{61, 62}

1601161162163164165166167

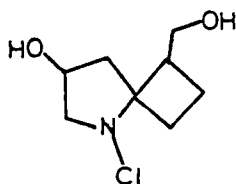
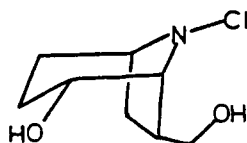
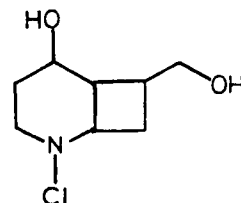
It is apparent from these examples that, although ring expansions and contractions are possible, they are frequently unpredictable and subject to further reaction prior to hydride reduction.

In an effort to reduce the likelihood of these side reactions, Schell and Ganguly⁶² speculated that forced precipitation of immonium salts from the reaction mixture might preclude undesirable oxidations and enhance the overall yield of rearrangement products. Further, by employing non-hydroxylic solvents, or solvents which are poor hydrogen atom donors, a reduction in the amount of hydrogen abstraction products (parent amines) would be possible. The study concluded that, by using silver tetrafluoroborate in anhydrous benzene, products arising from these competitive abstraction and oxidation reactions could be eliminated. Additionally, they showed that immonium ion intermediates can be isolated and characterized, demonstrating that rearrangement products can be handled effectively in the laboratory, an accomplishment heretofore left undone. Thus, N-chlorogranatanine (162, p 43) provided δ -coniceine (168) in 92% yield after reduction with sodium borohydride. Equally impressive yields were obtained of 1-azabicyclo[5.3.0]decane (169) from 165 (p 43) and pyrrolizidine (1, p 2) from 160 (p 43).

168169

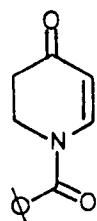
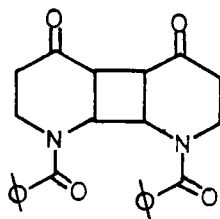
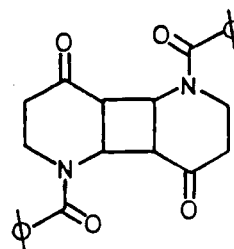
With this new, high-yielding synthetic method available, it was concluded that pyrrolizidine alkaloid synthesis would demonstrate

its applicability in a novel fashion. Analysis of the azabicyclo[3.3.0]nonane system suggests that three bicyclic starting materials could provide necine bases upon rearrangement and reduction. These are illustrated below (170, 171 and 172). Important to the decision of which bicyclic system to target was the ease of preparation of the stereochemically fixed N-chloroamine. Systems 170 and 171 were ruled out quickly due to the difficulty one might encounter in preparation of a series of stereoisomers of naturally derived configuration. Perhaps more important than this was control of bond-migration in 170 and 171, even though nortropine is known to be converted into pyrrolizidine. Introduction of the oxygen functions to these systems might allow the N-chloroamine to undergo reactions other than rearrangement. Although this is certainly a possibility with 172, it has the advantage of being the most readily available. Hence, it was decided that the azabicyclo[4.2.0]nonane 172 would be the best target upon which the necessary stereochemical modifications could be performed.

170171172

On the basis of Corey's⁶³ arguments, in addition to some of Wiesner's⁶⁴ results, formulation of an azabicyclo[4.2.0]octane system might be realized by [2+2] photoaddition of methyl acrylate to

the dihydropyridine 173.⁶⁵ Indeed, irradiation of a methanol solution of 173 and a 20% excess of methyl acrylate for four hours through Pyrex produced three products, and some starting imide was recovered. The minor product (2-4%), a dimer of 173, could not be characterized as the head-to-head (174) or head-to-tail (175) structural isomer by any routine analytical procedure. Unfortunately, attempted deuteration of the acidic hydrogens proved too vigorous (sodium methoxide in deuteriomethanol) and full characterization was not pursued further. However, on the basis of results to be presented in the next paragraph valid arguments in favor of 175 could be made. Presumably, incomplete consumption of the starting material is due to the inhibitor present in the methyl acrylate. Neither prolonged irradiation nor a large excess of methyl acrylate could completely consume all of the imide.

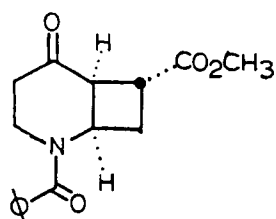
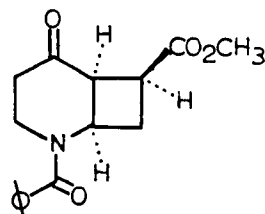
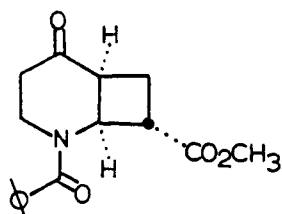
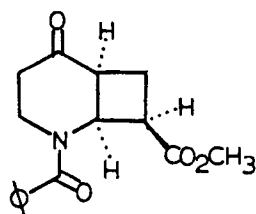
173174175

The major products (93% yield) of the reaction were demonstrated to be epimeric [2+2] photoadducts as evidenced by their cmr spectra and equilibration experiments. Isolation of both ketoesters was made possible by repetitive passage through silica gel columns with chloroform, providing the pure compounds in a 70:30 ratio. (Chromatography in this way did not change the ratio of products, as

determined by tlc.) Routine pmr and cmr analysis of the pure compounds was inconclusive toward resolving the regiochemical issue, nor did it completely ascertain that a single epimeric pair was present. In fact, the pmr spectra of each compound were quite different; the minor isomer exhibiting remarkably broad signals, though integration ratios were consistent with a 1:1 adduct. (See Appendix.)

Treatment of the 70:30 reaction mixture with 0.5M sodium methoxide in anhydrous methanol converted it into one estimated to be greater than 90:10 by the tlc and cmr analysis. Furthermore, equilibration of a 50:50 mixture produced the same 90:10 ratio, as did analogous treatment of the pure minor isomer. The major component remained unchanged under prolonged treatment (24 hours) with this base, and little, if any, formation of the minor isomer could be detected in this reaction. In all cases, the major isomer produced in the photoaddition was identical to the major component in the equilibration reactions. This suggests that the epimeric pair must possess a cis ring fusion at the end of the photoaddition, as cis-fused bicyclo[4.2.0]octane systems are thermodynamically more stable than their trans counterparts. This being the case, then, the epimeric pair produced in the photoaddition must be either 176 and 177 or 178 and 179.

Assuming that the ring fusion is indeed cis at the end of the photoaddition, then the equilibration reaction must be allowing the ester to adopt the more favored configuration. Molecular models

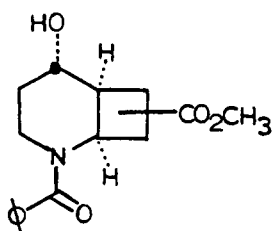
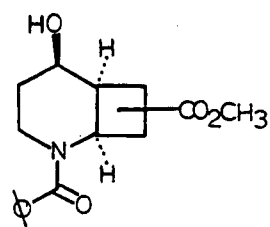
176177178179

show that when the ester is in a pseudoequatorial position (as in 176 and 178), the fewest number of steric and electronic interactions occur and this is assumed to be the thermodynamically preferred position for this group. This is true for either 176 or 178.

Knowledge of the relative stereochemistry of the asymmetric centers was very important. Of more importance was the position of the ester, as 176 and 177 possess the correct relationship between the oxygens required for necine base synthesis, where 178 and 179 find application only in model studies. Therefore, it was thought that conversion of one of the ketoesters into its corresponding alcohol ester followed by treatment with a strong, non-nucleophilic base would provide a lactone whose ketonic infrared absorption would aid in assigning regiochemistry. This is because five- and

six-membered lactones have characteristically different absorption energies in the infrared.

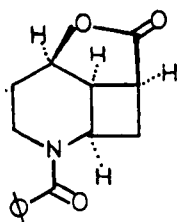
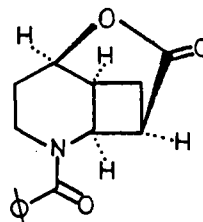
Treatment of the equilibrated photoproduct mixture with excess sodium borohydride in methanol provided a 55:45 mixture of two alcohol esters in quantitative yield. The mixture of epimeric alcohols was easily separated on silica gel, and each displayed cmr methine resonances⁶⁶ (70.7 and 61.8 ppm) consistent with equatorial and axial hydroxy substitution. All other resonances in the cmr spectra, in addition to respective pmr, ir and ms data, were consistent with the two alcohol esters 180 (major) and 181 (minor), shown below in a generalized manner.

180181

The mixture of alcohol esters was treated with excess sodium hydride (necessary to deprotonate the alcohol and epimerize the ester to the less favorable pseudoaxial position) in anhydrous THF with removal of solvents at reflux to afford a new compound in good yield, based on recovered starting material. Both alcohol esters were present in the recovered oil, but the percentage of 181 was significantly reduced. This suggests that 181 possesses the axial alcohol, as a lactone cannot be formed from the equatorial

position. Further, since all of 181 was not consumed, then the lactonization must be under equilibrium control. Unfortunately, continued reflux with removal of solvent never completely consumed all of 181.

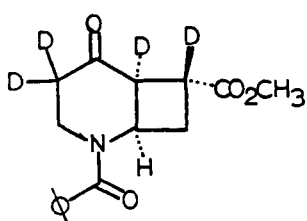
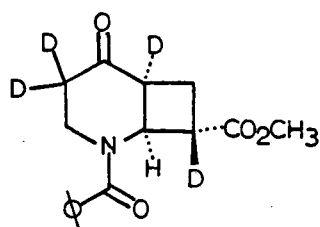
The cmr data from the crystalline lactone was inconclusive toward resolving the regiochemical question, but did confirm its formation by the loss of the methyl signal and the downfield shift of the methine under oxygen (72.8 ppm). This being the case, the bond from the four-membered ring must be pseudoaxial, as Dreiding models do not permit formation of a lactone with the acid portion occupying a pseudoequatorial position. Therefore, the lactone could be represented as either 182 or 183.

182183

The pmr spectrum supported the contention that the alcohol portion of the lactone is axially bonded due to a broad multiplet at 4.9 ppm integrating for one proton. This is in good agreement with similarly bonded bicyclic lactone systems.⁵³ High resolution pmr would no doubt provide the necessary information on the regiochemistry of this molecule, but was unavailable. Finally, the infrared spectrum of this material had an absorption at 1756 cm^{-1} which, unfortunately,

did not provide conclusive proof that the lactone was five- or six-membered. This particular absorbance falls between the acceptable ranges for lactones of this type, and these overlap to a degree.

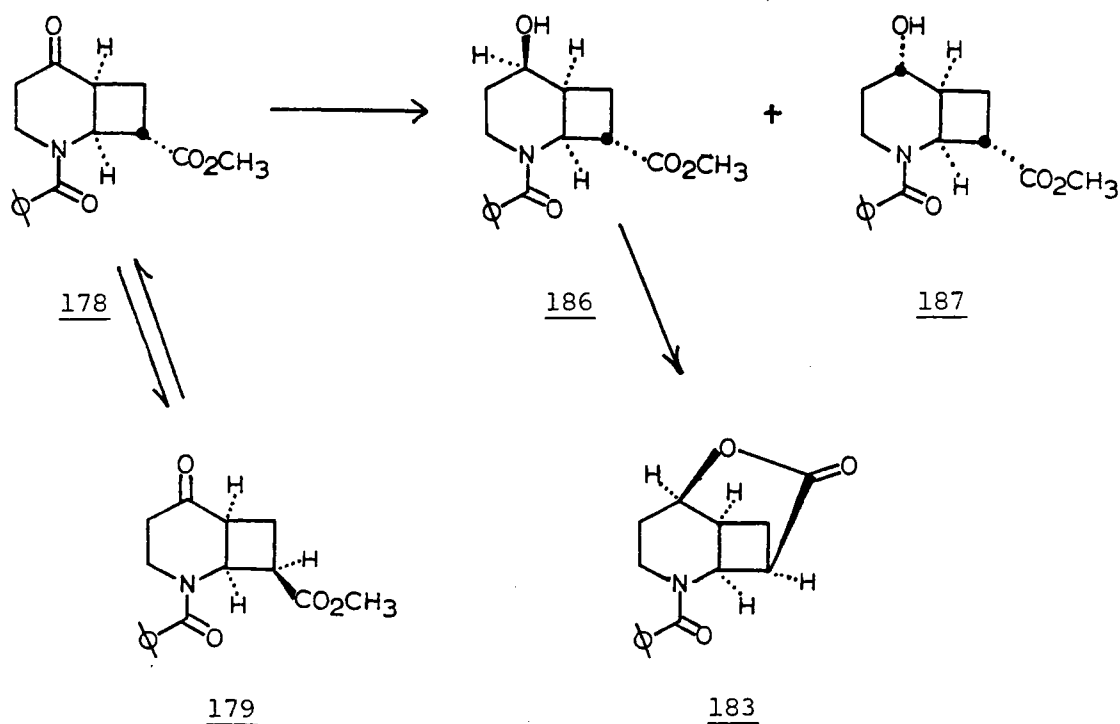
Since addressing the problem in this way provided only marginal information on regiochemistry, a deuteration experiment was conceived. The rationale was that if all hydrogens exchange for deuterium at positions alpha to the ketone and ester in the equilibrated photoadduct, then a relatively simple pmr spectrum would result. If the orientation were head-to-head as in 176 (p 48) one would obtain, upon deuteration, the tetradeuterio derivative 184. Similarly, 178 (p 48) would provide 185.

184185

Thus, stirring a room temperature solution of equilibrated ketoester in 0.1M sodium methoxide in methanol-d for 18 hours did provide a new ketoester which was fully deuterated. This was supported by disappearance of appropriate signals (43.4 and 42.6, CH; 40.9, CH₂) in the cmr due to the loss of nuclear Overhauser effect on relaxation. Evaluation of the pmr spectra (see Appendix) before and after the reaction clearly showed the collapse of the resonance at

5.1 ppm into a broadened singlet. Assuming that this resonance arises from the methine under nitrogen, it should not lose all of its coupling upon deuteration if 184 (p 51) had been obtained. Thus, 185 (p 51) must be the deuterated ketoester and the photoadduct mixture must be composed of the ester epimers 178 and 179 (p 48). With regiochemistry known, specific structures can be drawn for the aforementioned compounds, and are illustrated schematically below. (Scheme 29).

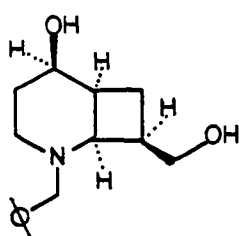
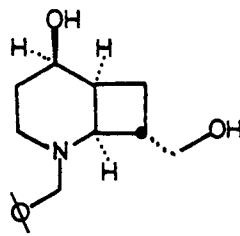
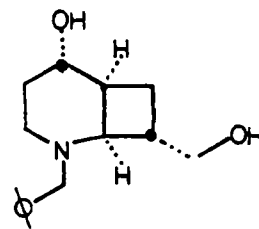
Scheme 29

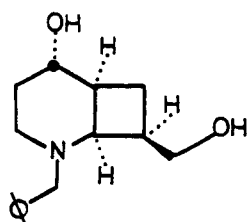
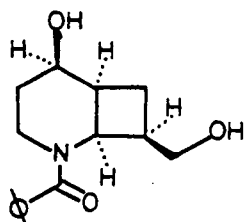
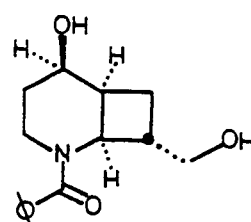
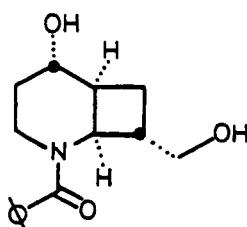
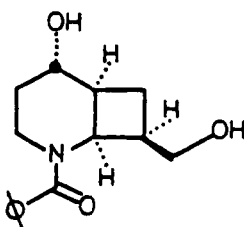


Reagents: 1) NaBH_4 , CH_3OH ; 2) NaOCH_3 , CH_3OH ; 3) NaH , THF

Although these results were unfavorable toward natural pyrrolizidine diol synthesis, it was felt that these compounds would provide an excellent model study upon which could be based other syntheses of pyrrolizidines. This decision was made because of their ready availability and also to test their versatility to stereospecific modifications.

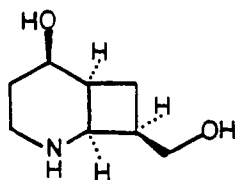
As was mentioned earlier, the synthetic strategy was designed to fix the stereochemical centers prior to rearrangement of the N-chloroamine. Thus, the next intermediate stage focused upon the conversion of the equilibrated ketoesters 178 and 179 (p 48), and their derivatives, into the two diol series illustrated below. The amino diols 188-191 were chosen because it appeared that protection of the alcohols, followed by hydrogenolysis of the benzyl group would provide a reasonable route to the requisite secondary amines needed for rearrangement. Alternatively, the amido diols 192-195 were also viewed as viable targets by protection of the alcohols, then hydrolysis of the tertiary amide. In the paragraphs that follow a brief description of each diol synthesis will be given. This will be followed by a discussion of stereochemistry for each diol series on the basis of their cmr spectra.

188189190

191192193194195

Exposure of a tetrahydrofuran solution of lactone 183 (p 50) to a large excess of lithium aluminum hydride at room temperature provided a mixture of products. Following chromatography on silica gel the major constituent (62%) was identified as 188 (p 53) on the basis of its cmr spectrum. Unfortunately, the minor products were largely uncharacterized. However, due to the familiar odor of benzaldehyde present in the oil after workup, it was felt that one of the minor products could be 196, or its related Grob fragmentation or retro-Mannich products. Accounting for formation of 196 is not difficult to envision as expulsion of the amine could occur from incomplete reduction products during aqueous workup. Production of 196, or its analogs, could be minimized by using a large excess of

lithium aluminum hydride, but they could not be eliminated. Finally, attempts to isolate 196 failed, perhaps due to its solubility in aqueous media.



196

In a similar fashion, 189 and 190 (p 53) could be obtained by reduction of the equilibrated ketoester 178 (p 48) with lithium aluminum hydride. Unfortunately, the aforementioned problems attendant to analogous lactone reduction were amplified, and low yields of the desired diols resulted. A better method involved reduction of the mixture of alcohol ester epimers 186 and 187 (p 52) with excess lithium aluminum hydride. Although separation of the alcohol esters was easily accomplished, it was discovered that separation of the diols by column chromatography was facilitated just as readily, thereby eliminating the need for the initial chromatography. Thus, 189 and 190 (p 53), reflecting the ratio of epimers produced in the sodium borohydride reduction, were obtained in 89% yield from a 55:45 mixture of 186 and 187 (p 52), respectively.

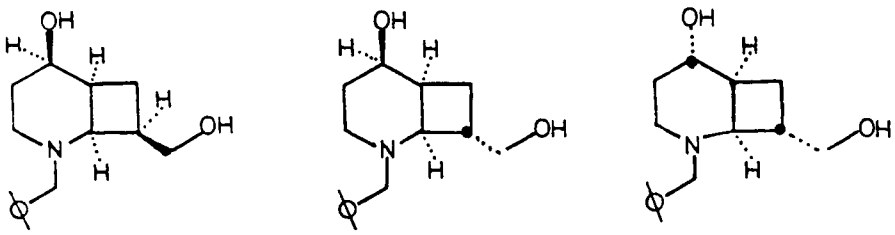
No attempt was made to synthesize 191 (p 54) even though it should be available via a reductive sequence originating from photo-product 179 (p 48). This was not pursued due to the difficulties

encountered in the isolation of 179 (p 48) and its propensity to equilibrate to 178 (p 48) on standing.

Careful evaluation of the resonances listed in Table I, coupled with the knowledge of expected products from these reductions, allow assignment of relative stereochemistry for each of the amino diols with reasonable surety. (It is assumed that the cis relationship enjoyed by the bridgehead hydrogens has been maintained through this point in the synthesis. Indeed, there should be no reason ring fusion stereochemistry should change.) Additionally, these data also support the regiochemical assignments made earlier. Thus, there are interesting, though expected, features in these spectra that warrant some attention. Further, this discussion will simplify the analysis of the amido-diols 192-195 (p 54) later in the chapter.

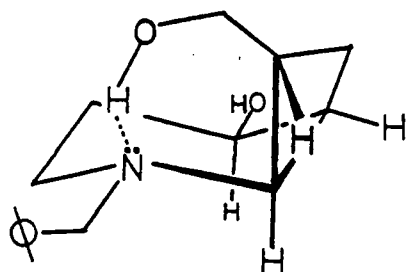
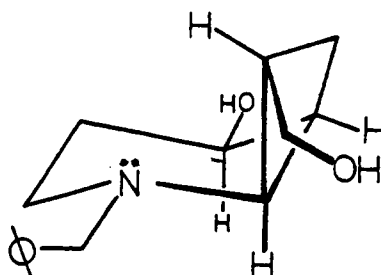
The most useful discussion of stereochemistry stems from the fact that diol 188 (p 53) is produced from lactone 183 (p 50). Evaluation of this molecule with Dreiding models indicates that, in the most stable conformation (fewest number of gauche interactions), the C₅ hydroxy substituent occupies an equatorial position on the six membered ring. This analysis also shows that the C₉ hydroxyl proton can hydrogen bond with the lone pair of electrons on nitrogen, where the atoms involved can adopt a conformation similar to the chair form of cyclohexane. Though difficult to depict, this is illustrated below in structure 197. Comparison of the chemical shifts for 188

TABLE I
CARBON NMR DATA FOR AMINO DIOLS 188-190

			
Carbon	Chemical Shift		
	<u>188</u>	<u>189</u>	<u>190</u>
1	63.5	60.4	59.4
3	48.0	45.0	45.4
4	31.0	30.0	31.9
5	67.1	65.4	71.9
6	35.5	34.8	37.9
7	19.6	20.3	24.1
8	36.3	41.0	39.5
9	62.4	63.6	65.2
10	62.0	57.0	58.1

vs. 189 (p 53) clearly reflect this latter phenomenon. One would expect that the carbons neighboring the nitrogen would be most dramatically affected, as the concomitant reduction in electron density would increase the polarity and cause a downfield chemical shift. This explains why C_1 , C_3 and C_{10} in 188 (p 53) appear at significantly lower field than in 189 (p 53). This may also explain why C_4 , C_5 and C_6 also appear at slightly lower field in 188 (p 53) relative to 189 (p 53). Other explanations may be possible, but it is felt that these must focus on the relationship of the pseudoaxial hydroxymethylene relative to the electronic environment of these

carbons in 188 (p 53). When C₉ occupies the pseudoequatorial position as it does in 189 (p 53), the hydrogen bonding arrangement is not possible (198).

197198

Another interesting observation is the similarity of chemical shift values for the cyclobutane methylenes (C₇) in 188 and 189 (p 53). At first glance, one might expect them to be quite different due to dissimilar C₈ configuration and therefore a difference in the magnitude of the γ -effect. Since this is not the case, then the C₅ equatorial hydroxy must be dominating its electronic environment. On closer inspection this might be expected due to the gauche relationship which exists between the C₅ equatorial position and C₇ in 188 and 189 (p 53). (This also supports the assignment of regiochemistry observed in the photoaddition in that this relationship would not exist for the alternate regioisomer.) Finally, C₈ chemical shifts for 188 and 189 (p 53) are different as would be expected for reversed configuration, and C₉ in both molecules appears at an expected position for a primary aliphatic alcohol.

The evaluation of 190 (p 53) in a similar fashion is difficult. Since the ring position of the C₅ hydroxy substituent seems to dictate the overall conformation of these molecules, one expects 190 (p 53) to be no different. However, placement of the C₅ hydroxy group in an equatorial position forces the molecule to adopt a conformation which is different from that in 188 and 189 (p 53). Because many factors are known to influence chemical shifts (including conformation), direct comparison of 190 (p 53) to 188 or 189 (p 53) is not appropriate. It can be said that severe gauche interactions exist in 190 (p 53) and that these might force the molecule to adopt a skewed chair form. Nevertheless, it should be indicated that C₇ and C₅ in 190 (p 53) appear at significantly different field strengths than in 188 and 189 (p 53), thereby confirming the difference in relative C₅ stereochemistry.

These data, coupled with information presented in earlier paragraphs, fully support the assignment of stereochemistry and regiochemistry as indicated in structures 188, 189 and 190 (p 53). Thus, with the three isomers now in hand, a means of continuing the synthetic plan was sought.

A variety of hydroxyl protecting groups are known and this list continues to grow as increasing demands on their resiliency to attack by acids and bases becomes more crucial.⁶⁷ Since no outstanding requirement was anticipated of the protected diols, the use of dihydropyran was believed sufficient. Further, in addition to being a

non-selective protecting group, dihydropyran has been introduced into systems using a wide array of methodologies.

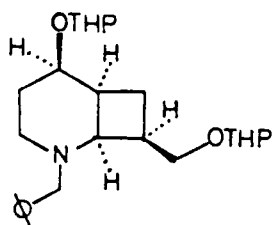
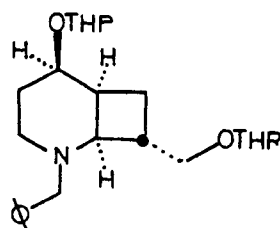
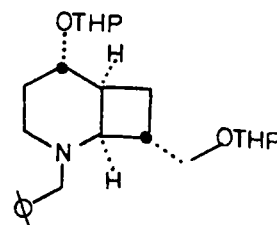
After several attempts had been made with limited success, it was discovered that the molar quantity of acid used and the water content were the two most important variables governing the success of the reaction. Reasonable yields were realized when *p*-toluene-sulfonic acid was used (particularly when first made anhydrous by azeotropic removal of water with benzene) in anhydrous tetrahydrofuran. A better method, published at a fortuitous time, was developed by Grieco.⁶⁸ He suggests the use of pyridinium *p*-toluenesulfonate, which does not form a hydrate and has the added advantage of being a very mild acid. Thus, a room temperature, anhydrous tetrahydrofuran solution of the diol and 1.5-2.0 equivalents of the acid was prepared and allowed to stir for 30 minutes under dry argon. During this time the solution becomes cloudy, perhaps due to partial precipitation of the ammonium sulfonate; then five equivalents of dihydropyran are added and the solution is stirred for 18-24 hours. Workup from aqueous sodium bicarbonate afforded respectable yields (60-75%) of bis-protected material after chromatography on silica gel. Some starting material is recovered after chromatography, but not enough to account for yields higher than 75%.

In retrospect, the initial difficulties encountered probably were due to insufficient molar quantities of the acid catalyst. Apparently, competition by dihydropyran for the proton is

unsuccessful in the presence of the amine. Using the large molar excess of acid circumvents this problem; once this was learned, most of the reactions attempted succeeded.

Spectral analysis of the desired products was, by and large, nebulous. The success of the reaction was typically evaluated on the basis of loss of hydroxyl content in the infrared spectrum. Because a mixture of diastereomers is produced the cmr spectra of the protected compounds possessed a plethora of lines, thus making precise interpretation very difficult. Likewise, the proton nmr spectra of these materials exhibited very broad resonances, and comparisons of aliphatic to aromatic integration ratios afforded the only significant characterization information.

All three bis-protected diols (199, 200, and 201) were synthesized in the aforementioned manner, and are illustrated below.

199200201

Although hydrogenolysis⁶⁹ of benzylamines is well known, successful completion of this reaction required a significant amount of developmental chemistry. Usually, reactions of this type are

conducted in a hydrogen pressurized container in the presence of a catalyst and an acid or alcohol. Reaction progress is monitored by uptake (loss of pressure, or decrease in volume) of the gas. Unfortunately, the yields of secondary amine were less than adequate. However, it was found that running the reaction under rigidly maintained anhydrous conditions provided marginal amounts of desired product. For example, glacial acetic acid had to be distilled from acetic anhydride and the hydrogen gas passed through Drierite before contacting the reaction solution. Additionally, the starting benzyl amines were vacuum dried for 24 hours at 0.01 mmHg.

All of the hydrogenolyses were conducted at room temperature with palladium-on-carbon as the catalyst. Usually, the hydrogen pressure was maintained for a minimum of 18 hours, but no longer than 48 hours. Workup of the reaction was accomplished by cautious, dropwise addition of the mixture into concentrated potassium hydroxide or sodium bicarbonate solutions, filtration through Celite, and extraction of the organic materials with methylene chloride. Evaporation of the organic solvents left oils which reddened on exposure to air and were thus stored under argon until needed.

Characterization of the product was made on the basis of its proton nmr spectrum. Thus, disappearance of the aromatic signal present in all of the materials at 7.3 ppm indicated that debenzylation had occurred. That the tetrahydropyranyl groups remained intact was evidenced by the absence of hydroxyl adsorption in the infrared

spectrum, and the presence of the four peak pattern typical of acetals. Reproduction of these spectral properties of products isolated from reaction to reaction seemed to indicate that the hydrogenolysis was reproducible to some degree. Unfortunately, attempts to scale-up this last reaction were not fruitful, and due to the poor yield of desired product, the alternate route from the amido diols was pursued.

The synthesis of the amido-diols 192-195 (p 54) from keto-ester 178 (p 48) requires a reductive sequence whereupon the ketone and ester or lactone can be reduced but the amide retain its integrity. Since C₅ configurational isomers 186 and 187 (p 52), and lactone 183 (p 50) were available, reduction of the ester (lactone) in the presence of the amide became the critical objective. Toward that end, it was found that K-Selectride⁷¹ (potassium tri-sec-butylborohydride in THF, Aldrich) provided excellent yields of amido-diols 192, 193 and 194 (p 54) from their respective precursors, where lithium borohydride did not. In fact, the latter reagent was completely unreactive. Reduction of the lactone with K-Selectride is in some respects novel, as it has been used as a reagent in the formation of bicyclic, cis-fused lactones from appropriate ketoesters upon adjustment of pH.⁷¹ Once again, isomer 195 (p 54) was not synthesized for the reasons discussed earlier in this chapter. However, some additional work was performed on the pseudoaxial photoproduct 179 (p 48) with K-Selectride which will be reported later in this chapter.

Reaction of lactone 183 (p 50) with 2.2 equivalents of K-Selectride in THF at reflux provided, after chromatography, a single product in 95% yield. Identification of this product as diol 192 (p 54) was straightforward on the basis of its spectral properties. Thus, the infrared spectrum displayed alcoholic O-H stretching at 3400 cm^{-1} (broad, intense) and an absorption at 1620 cm^{-1} assigned as the amide carbonyl. High resolution proton nmr data were unavailable, but at 60MHz the integration ratio between aromatic and aliphatic hydrogens provided evidence that the lactone was fully reduced. Full characterization was made on the basis of the cmr spectrum (to be discussed later) which was in complete accord with the assigned structure.

In a similar fashion, amido diols 193 and 194 (p 54) were available from their corresponding alcohol esters 186 and 187 (p 52) by treatment of the latter with 2.2 equivalents of K-Selectride at -15° . Isolated yields (after chromatography) of these diols were comparable to that obtained from the lactone. However, 186 (p 52) produced a small amount (5-18%) of lactone 183 (p 50) in this reaction and reduced the amount of diol obtained. Fortunately, this was not a disadvantage as the lactone is of use for production of isomer 192 (p 54). These diols also possessed the characteristic infrared absorptions and proton nmr integration ratios expected from molecules of this type. A discussion of their cmr spectra, upon which characterization is based, will be included with that of diol 192 (p 54).

Since K-Selectride was found to be so versatile, several other reactions were conducted on various intermediates with this reagent to see if its full potential had been exploited. Attempts to produce both 193 and 194 (p 54) directly from ketoester 178 (p 48) failed, in the main, because the reducing agent selectively produces axial alcohols from rigid cyclohexanones. Also, crude mixtures of all three diols resulted when three equivalents of the reducing agent were applied to the ketoester. However, treatment of 178 (p 48) with one equivalent afforded alcohol ester 186 (p 52) in 95% yield and became the method routinely used for its synthesis. Unfortunately, a stereospecific route to 187 (p 52) was unavailable.

Reaction of ketoester 179 (p 48) with K-Selectride further substantiated the claim that the C₈ hydroxymethylene substituent in this isomer is pseudoaxial. Thus, treatment with one equivalent of the reducing agent provides a respectable yield (50% by tlc) of lactone 183 (p 50) when the reaction is conducted at lowered temperatures. Apparently, the ester is trapped by the reduced oxygen before it can equilibrate to its more stable configuration. By maintaining the lowered temperature (-15°) the lactone remains resistant to reduction and the only other product isolated was identified as 186 (p 52). Sodium borohydride treatment of ketoester 179 (p 48) did not result in lactone formation, presumably because the oxygen-boron bond here is more covalent than the one produced above and the electrons on oxygen are unavailable to attack the ester.

In a manner analogous to the amino diols 188-190 (p 53) the amido diols 192-194 (p 54) can be characterized on the basis of their cmr spectral properties. (Table II). By and large, the trends noted earlier are prevalent here and similar arguments can be invoked for chemical shift differences among skeletal carbons. Notable exceptions exist and will be briefly discussed below. Finally, as in the amino diols, the amido diols are also assumed to possess the cis relationship of the bridgehead hydrogens.

TABLE II

CARBON NMR DATA OF AMIDO DIOLS 192-194

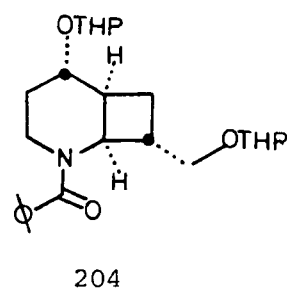
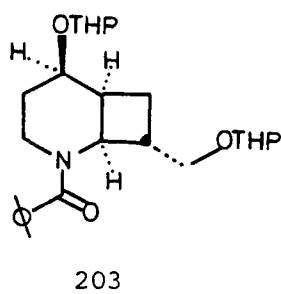
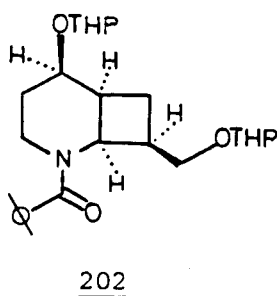
Carbon	Chemical Shift		
	<u>192</u>	<u>193</u>	<u>194</u>
1	53.4	52.0	52.5
3	45.7	41.0	44.0
5	29.4	29.9	31.9
6	65.5	62.8	71.0
6	34.1	34.8	39.2
7	19.9	18.6	22.9
8	35.4	45.2	43.2
9	61.6	65.3	64.8

The most striking difference is that exhibited by carbons 1 and 3 (C_{10} is now a part of the amide system) with their marked upfield

shift. This is to be expected as the lone pair of electrons on nitrogen are, essentially, completely involved in the pi-system of the carbonyl, and the latter with the aromatic ring. The net result is a reduction in electron density (and polarity) which affects the shielding so observed. As can be seen in Table II, characteristic resonances are displayed for C₄, C₅, C₆ and C₉ in each of the diols, and C₇ shows a significant γ-effect difference when the conformation of the molecule changes on going from 193 to 194 (p 54). Similarly, C₈ resonates at different field strengths when the hydroxymethylene substituent changes from pseudoaxial (192, p 54) to pseudoequatorial (193, 194, p 54). Thus, the stereochemistry and regiochemistry can be rationalized in a manner similar to the amino diols presented earlier.

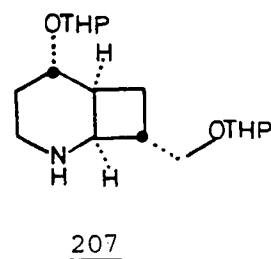
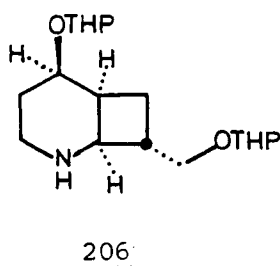
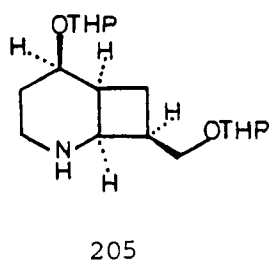
Protection of these diols as their tetrahydropyranyl ethers was much less difficult to complete than in the previous cases. Presumably, because the nitrogen is now part of an amide system, competition for protons is reduced, and good yields of the protected diols could be realized. Each diol (192, 193, 194, p 54) was protected in the same way, so a general procedure will suffice to demonstrate the method used. An anhydrous THF solution of the diol was heated to 60° and treated with a few crystals of pyridinium p-toluenesulfonate. After the acid had dissolved (30 minutes), 2.2 equivalents of dihydropyran was added and stirring was continued at this temperature for 18-24 hours. Aqueous, basic workup followed by extraction with methylene

chloride and chromatography of the oil on silica gel provided yields in excess of 80% of the desired bis-tetrahydropyranyl ethers 202, 203 and 204. Some starting material was always recovered from these reactions; however, quantitative conversion was not possible by the method used. Further, no vigorous attempt to maximize the yield of this reaction was ever pursued, though it is felt that quantitative yields would be possible under the proper set of conditions.



Characterization of these intermediates was difficult for reasons already discussed (*vide supra*). The disappearance of the hydroxyl absorption and the appearance of the acetal quartet in the infrared spectrum was one indication that the reaction had succeeded. The proton nmr spectrum provided little information other than the expected integration ratios between aliphatic and aromatic regions. The carbon nmr spectrum of each displayed a large number of lines due to the diastereomeric nature of the protecting groups and their different influence on the chemical shifts of neighboring carbons. These data are listed under the appropriate compound name in Chapter III.

Hydrolysis of the amide was accomplished according to the procedure of Gassman.⁷² As before, all of the bis-protected amides were treated identically, so a single procedure will be given. To one equivalent of the amide in a 50:50 mixture of anhydrous tetrahydrofuran and diethylether, and 8-9 equivalents of potassium tert-butoxide was added two equivalents of distilled water via syringe. Upon addition of the water a glistening white precipitate formed (presumed to be potassium hydroxide) and the solution was stirred for 30-60 minutes under argon at 0°. The temperature was then raised to 60° and the reaction allowed to continue for 24 hours. Addition of crushed ice produced two layers, and the organic materials were extracted with diethyl ether. Chromatography of the yellow-brown oil on silica gel afforded colorless-to-yellow secondary amines 205, 206 and 207 in yields between 80 and 90%. Because these amines were subject to oxidation on standing in air, they were typically prepared on an as-needed basis and stored under a blanket of dry argon. It was discovered that chlorinated hydrocarbon solvents also initiated some decomposition, but tetrahydrofuran solutions of the amines were stable for a considerable length of time.



Once again, the tetrahydropyranyl groups interfered with interpretation of the spectral data for these compounds. However, loss of the aromatic signal in the pmr clearly demonstrated that the reaction had succeeded. Furthermore, loss of the aromatic ring greatly enhances the fine structure in the pmr - unlike the typically broad signals observed in the other tetrahydropyranyl derivatives. Interestingly, the carbon nmr spectra were not as compromised due to the tetrahydropyranyl groups as was experienced in the other protected derivatives. In fact, some of the downfield lines appear in pairs (notably the acetal methines) reflecting each of the diastereomers present. Carbon atoms near these centers (C_5 and C_9) also appear as two lines where other skeletal carbons do not. Loss of the aromatic portion of the molecule is also quite clearly evident in this spectrum as it is in the infrared spectrum. On the basis of this evidence, it was concluded that the protecting groups and ring system survived this vigorous reaction intact.

It is worthy of mention at this time that production of the requisite secondary amines needed for rearrangement is much more easily accomplished via the amide route. For example, 206 (p 69) was produced in greater than 70% yield from the ketoester 184 (p 51) by the reduction/protection/hydrolysis sequence just described. Obtention of 206 (p 69) from the benzyl amine intermediates falls quite short of this value. This is without question a result of the ease with which amides can be handled relative to amines. Nonetheless, having the benzyl amine diols available for spectral analysis proved

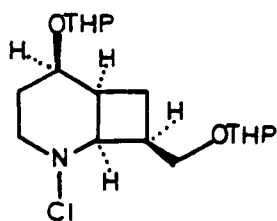
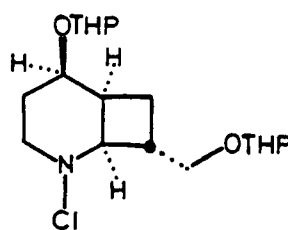
to be of significant value in assignment of regio- and stereo-chemistry of the amido diols. Further, they will provide useful information for comparison to a system which possesses the correct regiochemistry. This will be discussed at the close of this chapter.

From this point forward, only 205 and 206 (p 69) were exposed to rearrangement conditions. This decision was made primarily because of isolation problems encountered in the final stages of this model study. It is well known that the pyrrolizidine diols are water soluble to the extent that continuous extraction with a variety of solvents provides only negligible amounts of material.^{7,56,57} The experience with these model compounds also provided a considerable challenge with regard to isolating pure materials from aqueous media. Experimental details are presented in Chapter III and will not be discussed here. In addition to the above problem, rearrangement of 207 (p 69) was not pursued because of the results obtained from rearrangement of amine 205 (p 69). For the same reasons, isomer 206 (p 69) was not fully investigated: a pure product was not isolated, but the rearrangement was shown to be reproducible.

Additional justification for leaving two of the isomers incomplete is twofold. First, the work performed clearly demonstrated that stereochemical modification of the photoproduct(s) was possible. Second, a vinylogous amide system, similar to the vinylogous imide 173 (p 46), was investigated with respect to its photochemical potential. The results of this latter investigation led to the decision to forego extensive examination of 206 and 207 (p 69) in lieu of

pursuit of this new photoactive vinylogous amide. Following a brief description of the chlorination and rearrangement of 205 and 206 (p 69), this new system will be discussed.

Exposure of the secondary amines to a slight molar excess of N-chlorosuccinimide in methylene chloride provided, after a bicarbonate wash, quantitative yields of crystalline N-chloroamines. Due to their propensity to decompose, 208 and 209 were prepared just prior to rearrangement and stored under vacuum until needed. Relative purity was gauged by their tlc properties (they are much less polar than secondary amine on alumina plates). Residual succinimide could be removed by repetitive sodium bicarbonate washes without jeopardizing the integrity of the desired N-chloroamine, or reducing its yield. No further purification was deemed necessary, or was attempted.

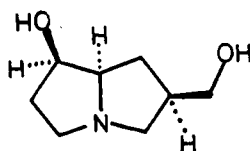
208209

Rearrangements were conducted according to the method of Schell and Ganguly.⁶² Thus, a benzene solution of silver tetrafluoroborate was made anhydrous by azeotropic removal of water into a Dean-Stark apparatus. Cooling to 50°, followed by addition of an

anhydrous benzene solution of the N-chloroamine over a 15-45 minute period commenced immediate precipitation of silver chloride as a pale gray powder. The solution was permitted to stir for 4-8 hours at the elevated temperature, then lithium chloride was added and the solution was allowed to cool to room temperature. The solution was filtered through celite and the solids washed well with methylene chloride. Combination and evaporation of the organic solvents left a pale yellow oil which was immediately dissolved in methanol and added to a stirring methanolic sodium cyanoborohydride solution containing an excess of the reducing agent. After being stirred for 12 hours, the solution was poured into excess 3M potassium hydroxide and the organic products extracted with methylene chloride. Evaporation of the solvent left a yellow oil which was hydrolyzed with dilute hydrochloric acid in tetrahydrofuran. After stirring for 24 hours at room temperature, two major products could be detected by tlc. Isolation of the hydroxytetrahydropyran was straightforward. However, isolation and characterization of the second material, presumed to be a hydrochloride salt of the amine, was tedious and difficult. A full description of the two isolation procedures used is presented in Chapter III.

When amine 205 (p 69) was chlorinated, treated with silver tetrafluoroborate, reduced and hydrolyzed in the manner just described, only moderate yields of nitrogenous materials could be realized. However, cmr analysis of this product clearly demonstrated

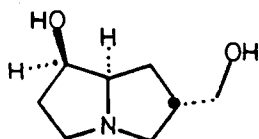
that the pyrrolizidine nucleus had been obtained. The product, 210, possessed the correct and expected resonances in the decoupled and undecoupled spectra. Thus, downfield methylene (69.9 ppm) and methine (61.7 ppm) signals attributable to carbons under oxygen were easily distinguished. The remaining ring carbons (69.1 and 43.4 ppm, methine; 61.7, 57.5, 50.9, 34.2 and 25.2 ppm, methylene) were also consistent with the proposed structure. The infrared spectrum also clearly displayed a broad hydroxyl absorption with no additional functional group absorbances. Finally, though each of the analytical data was similar, none was identical to that for platynecine (88, p 24).



210

In a manner analogous to 208 (p 72), N-chloroamine 209 (p 72) was subjected to rearrangement conditions. Unfortunately, isolation of a pure product from the mixture was not possible. However, repetitive rearrangements did provide materials whose cmr spectra were identical, which indicates that the reaction was at least reproducible. No explanation exists regarding why the isolation of a pure material was so difficult, except to indicate that the water solubility of the diols severely inhibits routine approaches. Because the rearrangement of 208 (p 72) was successful,

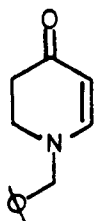
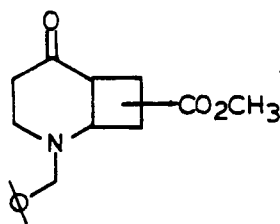
and the resonances appeared at appropriate chemical shifts in the cmr spectrum, it is assumed that 211 was formed, though no concrete proof exists.



211

As mentioned earlier, a similar vinylogous system, 212, was available for investigation. This compound, prepared from the corresponding hydroxypyridine by a reductive alkylation sequence, also reacted with methyl acrylate in the presence of ultraviolet light. Thus, exposure of the amide to a large excess of the unsaturated ester in 10:1 cyclohexane:tert-butanol for 4.5 hours provided a new ketoester (213, 84%) in addition to some polymeric or oligomeric material. Chromatography on silica gel provided a colorless oil whose cmr spectrum indicated a mixture of materials of similar structure. Resolution of the mixture by tlc was not possible; therefore, no attempt was made to purify the components by chromatography. Nevertheless, the cmr was sufficiently clean to indicate that a 1:1 photoadduct had been obtained, and that the mixture was composed of isomers.

Once again, orientation of the methyl acrylate portion of the molecule was of premier importance. Because the diol series

212213

188-190 (p 53) was available for comparison, it was decided that reduction of this new ketoester to a diol amine, and evaluation of its cmr spectrum, would provide sufficient evidence regarding the regiochemistry of the addition.

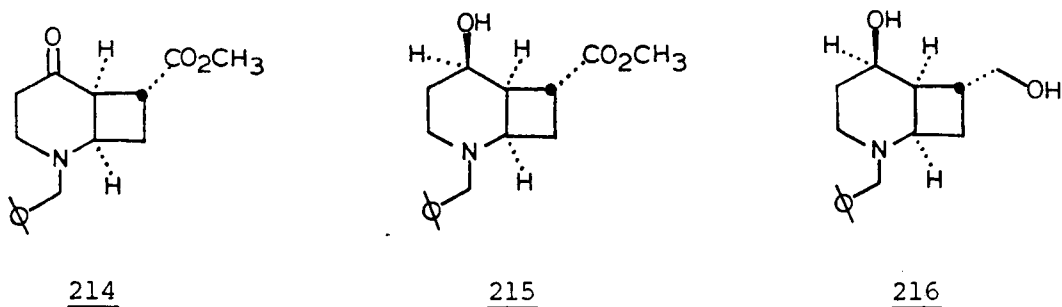
Exposure of the mixture to a slight excess of K-Selectride at -15° , then acidic workup, afforded an alcohol ester in 42% yield. The reduced yield is a consequence of the workup procedure (see Chapter III) in addition to the relative susceptibilities of both the starting material and product to decompose. In fact, the routine workup procedure used with K-Selectride reductions (hydrogen peroxide) completely destroyed the product. Little developmental work was performed on improving the procedure, but it was found that acetic acid workup, followed by aqueous sodium hydroxide, gave adequate results. Chromatography on silica gel provided an alcohol ester as a colorless-to-pale-yellow oil. The cmr spectrum of this material clearly indicated that the hydroxyl group occupied a position similar to that in compound 186 (p 52) on the six-membered ring, and also indicated that the product was pure and not a mixture

of isomers of any kind. This may lead to the conclusion that the photoproduct mixture is one composed of ester epimers as in the case of 178 and 179 (p 48), and that the reduction conditions allow the ester to equilibrate to the most stable position. Finally, satisfactory ir and pmr spectra were recorded for the alcohol ester.

In an effort to reproduce the relative stereochemistry of lactone 183 (p 50), the alcohol ester was treated with sodium hydride in tetrahydrofuran at elevated temperature. The progress of the reaction was monitored by tlc which indicated a slow and progressive decomposition of the starting material. Since no meaningful product could be isolated, this approach was abandoned.

Assuming that the ester occupies the pseudoequatorial position on the cyclobutane ring, and that the ring fusion is cis, then reduction of the ester with lithium aluminum hydride should provide a diol with the relative stereochemistry of diol 189 (p 53). (As a matter of note, attempted equilibration of the photoproduct with sodium methoxide in anhydrous methanol resulted in decomposition of the starting material). Treatment of a tetrahydrofuran solution of the alcohol ester with a slight excess of the reducing agent afforded a colorless oil which was air sensitive. Both cmr and tlc analysis of the oil confirmed that a single product was formed. Comparison of this cmr spectrum with those obtained from the amino diols 188-190 (p 53) showed that this new diol was clearly different. If the prior assumptions are correct, the only conclusion must be

that this diol possesses different regiochemistry: the hydroxymethylene must be attached to C₇, and not C₈, of the cyclobutane ring. Appropriate analytical data are listed in the experimental section. The photoproduct, alcohol ester, and diol must be 214, 215 and 216, respectively.



With this result, and the prior development work completed, it is concluded that necine base synthesis is possible by the synthetic route outlined in this chapter. Though problems may be encountered with the removal of the benzyl group by hydrogenolysis, these can be overcome. Furthermore, it was shown that vinylogous imide 173 (p 46) also reacted photochemically with other suitably functionalized alkenes,⁷³ and with proper choice of reaction conditions, could feasibly provide an azabicyclo[4.2.0]octane with the proper regiochemistry. This latter approach would provide a system where the nitrogen would be protected as an amide, and therefore be much easier to handle and manipulate than the corresponding benzyl amines.

CHAPTER III

EXPERIMENTAL DATA

Anhydrous solvents were prepared in the following manner: tetrahydrofuran and benzene were distilled from sodium-benzophenone ketyl under anhydrous argon; diethyl ether was distilled from lithium aluminum hydride under dry argon; diglyme was distilled under reduced pressure from calcium hydride after stirring at elevated temperature for 24 hours; methanol and ethanol were distilled from their magnesium salts generated by treating the solvent with magnesium metal and sublimed iodine under argon. All chromatographic solvents were distilled through a three-foot Vigreux column in which the first 500 mL of distillate was discarded.

Proton magnetic resonance spectra were recorded on a Varian T-60 Spectrometer using deuteriochloroform as the solvent and tetramethylsilane as the internal standard unless otherwise specified. Carbon-13 magnetic resonance spectra were recorded on a Nicolet TT-14 Spectrometer equipped with a multinuclear frequency synthesizer using deuteriochloroform as solvent and internal standard or a Jeol FX90Q multinuclear nmr. Chemical shifts are reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded on either a Perkin-Elmer 257 Grating Spectrophotometer or a Digilab FTS-20 Fourier Transform Spectrophotometer through sodium chloride plates as either solutions, films, melts or neat, as indicated. Infrared absorptions are reported in cm^{-1} and are standardized using an appropriate

polystyrene absorption. Mass spectra were recorded on a Hewlett-Packard HP-5982A GC-Mass Spectrometer equipped with a HP-5934 Data Package by injecting a methylene chloride solution of the compound directly into the probe and ionizing at 70eV.

Analytical thin-layer chromatography plates were prepared from Merck Alumina G or Merck Silica Gel G by dipping a microscope slide in a chloroform slurry of the adsorbent. They were visualized by passing iodine vapors over the dry plates after development. Preparative chromatography plates were used as supplied from Analtech Laboratories.

Melting points were taken on a Thomas 40 Micro Hot Stage apparatus equipped with a polarizing field viewer and are uncorrected.

Reactions requiring anhydrous conditions were conducted in flame-dried or oven-dried glassware cooled in a stream of anhydrous nitrogen or argon.

Silver tetrafluoroborate (Alfa Corporation) was stored and transferred into anhydrous glassware sealed with rubber septa under argon in an inert atmosphere glove box (Vacuum Atmospheres Corporation Model 43-Z). K-Selectride was obtained from Aldrich Chemical Company as either 0.5M or 1.0M THF solutions, and used as supplied.

Photolyses were conducted using a Hanovia 450-W medium pressure mercury arc lamp suspended in a water cooled Ace glass immersion well (Pyrex) or by irradiating from the same source into solutions held in Pyrex tubes. In either case, the apparatus was equipped for degassing the solutions with pre-purified nitrogen.

1,6-cis α -8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5-one,
178 (p 48) and 1,6-cis α -8 β -carbomethoxy-2-(N-benzoyl)azabicyclo
[4.2.0]octan-5-one 179 (p 48)

A degassed methanol solution (800 mL) containing 7.5 g (0.037 mole) of vinylogous imide 173 (p 46) and 3.85 g (0.044 mole, 1.2 equivalents) of methyl acrylate was irradiated through Pyrex for four hours. The solvent was evaporated under reduced pressure leaving 11.8 g of a yellow oil consisting of three products and some residual starting imide. Repetitive chromatography on silica gel with chloroform gave 9.73 g (93%, 0.034 mole) of the ketoester mixture 178 and 179 (p 48) in a 70:30 ratio (approximate), 0.15 g of recovered imide (0.0005 mole) and 0.4 g (0.001 mole) of an imide dimer, 174 or 175 (p 46). Spectral properties of the products are as follows: 178 (p 48); cmr δ 207.9 (aliphatic C=O), 171.4 (ester C=O), 170.0 (amide C=O), 134.2 (aromatic C), 129.4, 127.7, 126.3 (aromatic C), 54.7 (broad, CH), 51.1 (CH₃), 43.4 (CH), 42.6, 40.9 (CH₂), 39.1 (broad, CH₂), 21.8 (CH₂); pmr δ 7.4 (s, 5H), 5.15 (bt, 1H), 5.0-4.4 (broad hump, 1H), 3.65 (s, 3H), 3.3 (dd, 3H), 2.8-2.1 (overlapping m, 4H); 179 (p 48); cmr δ (significant broadening of most all resonances) 207.4 (aliphatic C=O), 172.4 (ester C=O), 170.8 (amide C=O), 135.1 (aromatic C), 129.9, 128.3, 126.5 (aromatic CH), 54.8 (CH), 51.8 (CH₃), 43.8 (CH), 42.6, 39.6 (CH₂), 24.6, 22.0 (CH₂); pmr δ (all resonances very broad) 7.35 (s, 5H), 5.5-4.8 (hump, 2H), 3.68 (s, 3H), 3.7-3.0 (overlapping m, 3H), 2.6 (bt, 4H).

This photoaddition can also be accomplished in cyclohexane, which has the added feature of suppressing dimer formation, but is of limited use due to the low solubility of vinylogous imide 173 (p 46) in this solvent. In neither reaction can all of the starting material be consumed; perhaps due to the inhibitor present in the methyl acrylate.

Repeated passage of the 1:1 photoadduct mixture through silica gel with chloroform does not change the relative ratio of the two; however, stirring the mixture in anhydrous sodium methoxide/methanol for several hours (depending on the amount of methoxide added) does produce an equilibrium mixture that is approximately 9:1 178:179 (p 48) or greater as judged by cmr analysis.

Deuteration of Equilibrated Ketoester 178 (p 48)

Under anhydrous conditions, ketoester 178, (p 48) (0.36 g, 0.0012 mole) was dissolved in 10 mL of CH_3OD at room temperature under argon. While stirring, 5 mL of a 0.4M solution of $\text{CH}_3\text{ONa}/\text{CH}_3\text{OD}$ was injected into the solution and the mixture permitted to stir for 18 hours. It was poured into 25 mL of D_2O and extracted three times with 25 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated to afford 0.26 g (72%) of colorless oil identified as 185 (p 51). Depressed yield is due to inefficient extraction. Spectral data: cmr δ 208.6 (aliphatic C=O), 172.0 (ester C=O), 170.8 (amide C=O), 134.7 (aromatic C), 130.2, 128.4, 126.9 (aromatic CH), 55.3 (N- CH_2), 51.8 (CH_3), 39.9

(NCH), 22.2 (CH₂); pmr δ 7.4 (s, 5H), 5.15 (bs, 1H), 3.62 (s, 3H), 3.35 (bd, 2H), 2.2 (d, 2H).

Conversion of Ketoester 179 (p 48) into its Epimer by Treatment with Sodium Methoxide Solution

Several grams of the pseudo axial ester photoproduct 179 (p 48) were dissolved in 100 mL of anhydrous methanol. The pH of the solution was adjusted to 13 by the addition of 5 mL of a freshly prepared, anhydrous sodium methoxide/methanol solution. The reaction solution was stirred at room temperature under argon for 24 hours. TLC analysis of an aliquot removed from the reaction mixture showed that equilibrium had been reached. The solution was poured into water and extracted several times with 100 mL portions of methylene chloride which provided, after drying, filtering and evaporating the solvent a quantitative return of the equilibrated ketoester mixture: 178 (p 48) and 179 (p 48), 90:10 by cmr.

Reduction of Ketoester 179 (p 48) with Potassium tri-sec-Butylborohydride

Ketoester 179 (p 48), 0.52 g (0.0018 mole) was dissolved in 75 mL of anhydrous THF under argon and the solution temperature lowered to -20°. The K-selectride solution (3.7 mL, 1 equivalent) was added to the reaction mixture dropwise over a 45-minute period, and the solution stirred an additional one hour. Standard workup procedure for this reaction was employed (4 mL 3M sodium hydroxide, stir; 5 mL 30% hydrogen peroxide, stir; 4 mL 3M hydrochloric acid,

stir) at -10° ; then the solution was allowed to warm to 20° . It was poured into 100 mL of distilled water and extracted four times with 75 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated to provide 0.57 g of a colorless oil consisting of two products by tlc. Chromatographic and spectroscopic evidence suggested that the two products were formed in nearly equal amounts and were lactone 183 (p 50) and presumably the pseudoaxial alcohol ester which slowly equilibrated to 186 (p 52) upon exposure to air.

1,6-cis α -8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 α -ol
(187, p 52)

To a stirring room temperature solution of 3.7 g (0.0129 mole) of equilibrated ketoester 178 (p 48) in 150 mL of methanol was added a large excess of sodium borohydride. The reaction mixture was allowed to stir for one hour when tlc indicated that complete consumption of starting material had occurred. The solution was poured into 100 mL of distilled water and extracted four times with 75 mL portions of methylene chloride. The organic layers were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure leaving 3.7 g of a colorless oil. Repetitive chromatography on silica gel with chloroform eluted two alcohol esters 186 and 187 (p 52) in a 45:55 ratio (mass yield = 100%). Each column was flushed with 10% methanol:90% chloroform at the end of each separation. This served to remove residual alcohol ester 187 (p 52) which has a smaller tlc r_f value in a variety of solvent systems. Spectral data

for 187 (p 52) is as follows: cmr δ 172.1 (amide C=O), 170.7 (ester C=O), 135.1 (aromatic C), 129.1, 127.7, 126.0 (aromatic CH), 70.7 (CHOH), 53.5 (broad, CH), 51.1 (CH₃), 42.6, 39.9 (CH₂), 37.5 (broad, CH₂), 31.8, 23.6 (CH₂); pmr δ 7.38 (s, 5H), 2.9-2.5 (m, 2H), 2.3-1.6 (complex m, overlapping signals, 5H); ir cm⁻¹ 3400 (OH), 1730 (ester carbonyl), 1624 (amide carbonyl).

1,6-cis α -8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol
(186, p 52)

To 2.54 g (0.0088 mole) of equilibrated ketoester 178 (p 48) dissolved in 250 mL of anhydrous THF maintained at -10° under argon was added 18.5 mL (0.0095 mole) of a 0.5M THF solution of potassium tri-sec-butylborohydride dropwise over a one hour period. The yellow solution was allowed to stir for an additional hour at -10°, then warmed to 0° and the following sequence accomplished: addition of 8 mL of 3M sodium hydroxide and stirring for 15 minutes; cautious addition of 8 mL of 30% hydrogen peroxide solution and stirring for 15 minutes (decolorizes); addition of 12 mL of 3M hydrochloric acid and stirring for 15 minutes. The reaction mixture was poured into 200 mL of brine and extracted four times with 100 mL portions of methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford 2.70 g of a colorless oil. Chromatography on silica gel with chloroform produced 2.30 g (0.0079 mole, 95% based on recovered 178) of alcohol ester 186 (p 52); 0.130 g (0.0004 mole)

recovered ketoester 178 (p 48); and 0.11 g (0.00073 mole, 5%) of lactone 183 (p 50). The major product, 186 (p 52), had the following spectral data: cmr δ 173.2 (amide C=O), 171.2 (ester C=O), 135.9 (aromatic C), 128.0, 126.4 (aromatic CH), 62.8 (axial CHOH), 52.4 (CH), 51.3 (CH₃), 44.8, 36.3 (CH), 29.8, 19.7 (CH₂), ir cm⁻¹ (chloroform solution) 3410 (OH), 1740 (ester carbonyl), 1639 (amide carbonyl), pmr δ 7.26 (s, 5H); 4.8-3.8 (m, 3H), 3.5 (bs, 3H), 3.4 (m, 4H), 2.8-1.6 (m, 5H); ms m=286; calc. 287.3.

1,4-cis-1,9-cis-5,9-cis-4,5-cis-6-(N-benzoyl)aza-2-oxa-tricyclo
[4.3.1.0^{1,9}]decan-3-one(183, p 50)

To 200 mL of anhydrous THF containing 3.1 g (0.01 mole) of alcohol ester 186 (p 52) was added an excess of sodium hydride. The solution was refluxed under argon with solvent removal accomplished with a Dean-Stark trap. When 150 mL of the THF/methanol mixture had distilled, the solution was cooled, filtered through celite which was washed well with anhydrous THF and the solvent evaporated leaving an orange oil. Chromatography on silica gel with chloroform afforded 1.65 g (0.0064 mole, 88% based on recovered starting material) of lactone 183 (p 50) and 0.80 g (0.0027 mole) of recovered alcohol ester 186 (p 52). Spectral data of the lactone are as follows: cmr δ 173.0 (amide carbonyl), 170.8 (ester carbonyl), 135.4 (aromatic C), 129.5, 128.1, 126.0 (aromatic CH), 72.8 (axial OCH), 49.0 (CH₂), 46.9 (CH), 37.5 (CH); 36.4 (CH), 27.6, 23.4 (CH₂); pmr δ 7.35 (s, 5H), 4.9 (bs, 1H), 4.7-4.2 (m, 1H); 4.0-3.1 (m, H), 2.7 (m, H), 2.6-1.5 (m, H);

ir cm^{-1} (chloroform solution) 1748 (lactone carbonyl), 1643 (amide carbonyl); ms $m=257$; calc. 257.3.

1,6-cis α -8 β -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol (192, p 54)

To a stirring solution containing 1.30 g (0.005 mole) of lactone 183 (p 50) in 100 mL anhydrous THF maintained at 50° under argon was added in one portion via syringe 24 mL (0.012 mole, 2.2 equivalents) of a 0.5 molar THF solution of potassium tri-sec-butylborohydride (K-selectride, Aldrich). The yellow solution was refluxed for one hour, cooled to 0° and the following sequence accomplished: 6 mL of 3M sodium hydroxide and stirring for 15 minutes; 6 mL of 30% hydrogen peroxide and stirring for 15 minutes (decolorizes); 8 mL of 3M HCl and stirring for 15 minutes. The solution was then poured into 100 mL of water, extracted ten times with 50 mL portions of methylene chloride which were combined, washed once with 100 mL brine, dried over anhydrous potassium carbonate, filtered and the solvent evaporated under reduced pressure to provide 1.25 g (0.0048 mole, 95%) of 192 (p 54) as needles after recrystallization from chloroform. Spectral data: cmr δ 174.8 (C=O), 136.0 (aromatic C), 129.9, 128.5, 126.7 (aromatic CH), 65.4 (CH), 61.6 (CH₂), 53.4 (CH), 45.6 (CH₂), 39.3, 34.1 (CH), 29.3, 19.9 (CH₂); pmr δ 7.4 (s, 5H), 4.47 (t, 1H), 4.0-3.3 (m, 5H), 3.3-2.6 (m, 4H), 2.2-1.6 (m, 4H); ir cm^{-1} 3400 (b, OH), 1620 (amide carbonyl); ms $m=261$, calc. 261.3.

1,6-cis α -8 α -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol (193, p 54)

To a stirring, refluxing solution of 1.1 g (0.0038 mole) of alcohol ester 186 (p 52) in 100 mL anhydrous THF under argon was added 19.7 mL (0.0098 mole, 2.5 equivalents) of potassium tri-sec-butylborohydride as a 0.5M THF solution. The mixture was permitted to stir at reflux for two hours when it was cooled to room temperature, then immersed in an ice bath. The reaction mixture was treated successively with 6 mL 3N sodium hydroxide, stirred for 15 minutes, 6 mL of 30% hydrogen peroxide, stirred for 15 minutes, and 8 mL of 3N hydrochloric acid and stirred for 15 minutes. The binary mixture was diluted with 100 mL of distilled water and exhaustively extracted with methylene chloride. The organic layers were combined, dried over anhydrous potassium carbonate, filtered and evaporated to provide 1.05 g of a pale yellow oil. Chromatography on silica gel initially with chloroform produced a 0.18 g (0.0007 mole, 18%) of lactone 183 (p 50). Changing the solvent system to 3% methanol:97% chloroform eluted 0.74 g (0.0028 mole, 85%) of diol 193 (p 54) as a colorless oil. Increasing the polarity of the solvent system further with methanol eluted an additional 0.035 g of material composed mainly of the required diol and the diol corresponding to reduction of the lactone (by tlc). Spectral properties of the major product are as follows: cmr δ 171.7 (C=O), 135.4 (aromatic C), 129.4, 128.0, 126.4 (aromatic CH), 65.3 (CH₂), 62.8 (CH), 52.0, 45.2 (CH), 41.0

(CH₂), 34.8 (CH), 29.9, 18.6 (CH₂); pmr δ 7.3 (s, 5H), 4.18 (m, 2H), 3.9 (bs, 2H), 3.43 (m, 4H), 2.7 (m, 2H), 2.2-1.5 (m, 4H); ir cm⁻¹ (chloroform solution) 3380 (OH), 1605 (C=O).

1,6-cis α -8 α -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 α -ol (194, p 54)

A solution of 0.97 g (0.0033 mole) of alcohol ester 187 (p 52) in 150 mL of anhydrous THF was brought to gentle reflux under argon. To this hot solution was added, in one portion, an excess of potassium tri-sec-butylborohydride as a THF solution. Reflux was continued for three hours when the solution was cooled to 0° and 5 mL of 3N sodium hydroxide was added. After stirring for 15 minutes, 5 mL of 30% hydrogen peroxide was added followed by 8 mL of 3N hydrochloric acid after the solution had cooled. Dilution with 150 mL of distilled water and extraction with four 100 mL portions of methylene chloride provided, after drying over anhydrous potassium carbonate, filtering and evaporation of the solvent under reduced pressure, 0.738 g of a colorless oil. Saturation of the aqueous layer with sodium chloride solution and reextraction with eight 50 mL portions of methylene chloride which were combined, dried, filtered and evaporated as before afforded an additional 0.104 g of oil, chromatographically identical with the oil obtained in the first series of extractions. Chromatographic and spectroscopic analysis of the oil [identified as 194 (p 54)] indicated no further purification was necessary: 0.842 g (0.0032 mole, 97.6%). Spectral data as follows:

pmr δ 7.33 (s, 5H), 4.45 (t, 2H), 3.8 (m, 1H), 3.58 (m, 2H), 3.35 (s, 2H), 3.2-2.2 (overlapping m, 3H), 1.75 (m, 4H); ir cm^{-1} (chloroform solution) 3380 (OH), 1600 (C=O); cmr δ 172.4 (C=O), 135.1 (aromatic C), 129.6, 128.0, 126.4 (aromatic CH), 71.2 (CH), 64.8 (CH_2), 52.7, 43.9 (CH), 43.1 (CH_2), 39.3 (CH), 27.6, 18.7 (CH_2).

1,6-cis α -7 α , β -carbomethoxy-2-(N-benzyl)azabicyclo[4.2.0]octan-5-one
(213, p 76)

A solution (400 mL, 10:1 cyclohexane:tert-butanol) containing 2.0 g (0.011 mole) of vinylogous amide 212 (p 76) and a large excess (10 mL) of methyl acrylate was irradiated 4.5 hours through Pyrex under nitrogen. During the course of the reaction the temperature of the solution increased to approximately 50°, and no attempt was made to cool the vessel. After cessation of the irradiation, the Pyrex tube was immersed in an ice water bath, the solids filtered and the solvent evaporated to provide 4.0 g of a pale yellow oil. Chromatography on silica gel with chloroform afforded 2.45 g (84%) of a mixture of two 1:1 photoadducts. Thin layer alumina chromatograms indicated that one isomer clearly dominated the mixture. However, cmr data provided evidence to the contrary, suggesting a 60:40 or 50:50 mixture of the ester epimers of 213, (p 76) had been obtained: cmr δ (of the mixture) 210.3, 208.8 (C=O), 173.9 (ester C=O), 137.4 (aromatic C), 128.1, 127.8, 126.7 (aromatic CH), 62.1 (CH), 57.1, 57.0 (CH_2), 51.4, 51.1 (CH_3), 47.0 (CH), 46.6, 45.9 (CH_2), 42.9 (CH), 40.6, 39.6 (CH_2), 38.4, 37.7 (CH), 27.7, 22.4 (CH_2); pmr δ 7.2

(s, 5H), 4.1 (dt, 1H), 3.65 (s, 3H), 3.60 (s, 2H), 3.38 (m, 2H), 3.1-2.85 (m, 2H), 2.6-2.1 (m, 4H); ir cm^{-1} (neat) 1735 (ester C=O), 1605 (C=O).

1,6-cis α -7 α -carbomethoxy-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol
(215, p 78)

To an anhydrous THF solution (125 mL) containing 1.7 g (0.0062 mole) of the ketoester epimer mixture 214 (p 78) maintained at -15° under argon was added dropwise 9.0 mL (0.009 mole, 1.5 equivalents) of a 1.0M THF solution of K-selectride over a one-hour period. The solution was allowed to stir for 30 minutes, then 0.8 mL (0.67 equivalents based on R_3B) of glacial acetic acid was added which produced a white precipitate. Stirring for five minutes, followed by addition of 10 mL of 1N sodium hydroxide dissolved the precipitate. The reaction mixture was poured into 100 mL of brine and extracted four times with 100 mL portions of methylene chloride. The organic layers were combined and washed once with 200 mL of brine, dried over anhydrous potassium carbonate, filtered and evaporated to give a crude yellow oil. Chromatography on silica gel with chloroform provided 0.71 g of a pale yellow oil (42%) with the following spectral characteristics: cmr δ 175.1 (ester C=O), 138.6 (aromatic C), 128.4, 127.9, 126.7 (aromatic CH), 65.9 (CHOH), 58.0 (CH_2), 56.2 (CH_3), 51.1 (CH), 46.5 (CH_2), 40.8 (CH), 36.7 (CH), 31.2 (CH_2), 29.4 (CH_2); pmr δ 7.28 (s, 5H), 3.72 (s, 2H), 3.68 (s, 3H),

3.58 (t, 2H), 3.0 (bt, 2H), 2.8-2.4 (m, 2H), 2.2-1.6 (m, 5H); ir cm^{-1} (neat) 3440 (broad, OH), 1735 (ester C=O).

1,6-cis α -7 α -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol (216, p 78)

A solution of lithium aluminum hydride (0.15 g, 0.004 mole, 4 equivalents) in 100 mL of anhydrous THF under argon was prepared and allowed to stir for 30 minutes prior to the addition of 0.55 g (0.002 mole) of alcohol ester 215 (p 78) in 30 mL of anhydrous THF. The reaction mixture was stirred for 15 minutes and cautious addition of 1M sodium hydroxide destroyed the excess hydride. The solvent was decanted from the solid residue into 100 mL of brine, the precipitate washed well with THF and combined with the former. Extraction with four 75 mL portions of methylene chloride provided, after drying over anhydrous potassium carbonate, filtering and evaporation of the solvent, 0.48 g (97%) of a colorless oil which reddened on exposure to air and chloroform: cmr δ 139.0 (aromatic C), 128.6, 128.0, 126.7 (aromatic CH), 66.3 (CH_2), 65.8 (CH), 58.2 (CH_2), 56.9 (CH), 47.3 (CH_2), 45.6 (CH), 37.0 (CH), 32.4 (CH_2), 28.1 (CH_2): pmr δ 7.2 (s, 5H), 3.9-3.5 (m, 1H), 3.6 (s, 2H), 3.6 (bs, 2H, OH), 3.22 (t, 2H), 2.95 (m, 2H), 2.7-2.2 (m, 2H), 1.75 (dt, 5H); ir cm^{-1} (neat) 3400 (broad, OH).

Reduction of Ketoester Mixture of 213 (p 76) with Lithium Aluminum Hydride

To a room temperature, anhydrous THF solution (75 mL) containing a large excess of lithium aluminum hydride under argon was added over a period of one hour 0.45 (0.0016 mole) of the ketoester epimer mixture of 214 (p 78) in 10 mL of anhydrous THF. After completion of the addition the reaction mixture was stirred for 20 minutes, then excess lithium aluminum hydride was destroyed using 1N sodium hydroxide. The solution was poured into 100 mL of brine, the white precipitate washed well with THF and the aqueous layer was extracted exhaustively with methylene chloride (400 mL). The organic layers combined, dried over anhydrous potassium carbonate, filtered and evaporated to provide 0.35 g of a pale yellow oil which consisted of several products (by tlc). The major product comprised approximately 75% of the mixture and was shown to be identical to that listed in the previous experiment: 216, (p 78). The minor product, roughly 15% of the mixture, had cmr resonances different from any of the other diols (ppm 138.4, 128.6, 128.1, 126.9, 72.1, 69.1, 63.1, 58.0, 56.8, 48.6, 47.3, 36.5, 28.8), and is presumed to be the C₅ equatorial hydroxy epimer of 216 (p 78).

1,6-cis-8 β -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol (192, p 54)

A solution of 0.285 g (0.0011 mole) of lactone 183 (p 50) in 10 mL of anhydrous THF was prepared and added dropwise to a large

excess of lithium aluminum hydride in 50 mL of anhydrous THF maintained at 22° under argon. The solution was stirred for six hours and excess lithium aluminum hydride was consumed with 1N sodium hydroxide until precipitation of the white solid was complete. The colorless reaction solution was diluted with 100 mL of methylene chloride, filtered, washed once with 100 mL of saturated salt solution, dried over anhydrous potassium carbonate, filtered and evaporated to give 0.20 g of a colorless oil consisting of two products. The minor product, thought to be the parent secondary amine due to the characteristic smell of benzaldehyde in the oil, could not be isolated in appreciable amounts due to its apparent water solubility. Chromatography on silica gel initially with chloroform, then with a 1:1 chloroform:ethyl acetate mixture, provided 0.170 g (62%) of colorless prisms (mp 135-6°) after allowing the oil to stand overnight: cmr δ 137.2 (aromatic C), 129.4, 128.3, 127.3 (aromatic CH), 67.1, 63.5 (CH), 62.4, 62.0, 48.0 (CH₂), 36.3, 35.5 (CH), 30.9, 19.6 (CH₂); pmr δ 7.24 (s, 5H), 3.95 (d, 2H), 3.82 (bs, 1H), 3.7 (d, 1H), 3.5 (bm, 1H), 3.10 (d, 2H), 3.3-2.7 (bm, 2H), 2.6 (m, 4H), 1.7 (m, 3H).

1,6-cis-8 β -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol (193, p 54) and 1,6-cis-8 α -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 α -ol (194, p 54)

A solution of 1.7 g (0.006 mole) of the epimeric alcohols 186 and 187 (p 52) in 50 mL of anhydrous THF was prepared and added

dropwise to a large excess of lithium aluminum hydride in 125 mL of anhydrous THF at room temperature under argon. The solution was stirred vigorously for one hour upon completion of the addition and 5% (w/v) sodium hydroxide solution was added dropwise until precipitation was complete. The solution was decanted from the solid, the latter washed well with THF and the two organic layers poured into 100 mL of saturated salt solution. The brine was extracted three times with 75 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated to give 1.34 g of an oil consisting of principally two products. Chromatography on silica gel with 6% methanol in chloroform separated the diols cleanly. The minor product, 193 (p 54), comprised 45% of the mixture and had the following properties: $rf=0.5$ on alumina eluted with 5% methanol in chloroform; $cmr \delta$ (d_6 -acetone/ $CDCl_3$) 138.2 (aromatic C), 128.0, 127.3, 126.0 (aromatic CH), 65.4 (CH), 63.6 (CH_2), 60.4 (CH), 57.0, 45.0 (CH_2), 41.0, 34.8 (CH), 30.0, 20.3 (CH_2). The major product, 194 (p 54), 55% of the mixture, is characterized as follows: $rf=0.4$ in the same tlc system as above; $cmr \delta$ 138.2 (aromatic C), 128.4, 127.9, 126.7 (aromatic CH), 71.9 (CH), 65.2 (CH_2), 59.4 (CH), 58.1, 45.4 (CH_2), 39.5, 37.9 (CH), 31.9, 24.1 (CH_2).

1,6-cis-8 β -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (202, p 68)

To a stirring solution of 1.25 g (0.0048 mole) of diol 192 (p 54) in 125 mL anhydrous THF maintained at 60° under argon was

added a few crystals of pyridinium p-toluenesulfonate. The acid was allowed to dissolve and 1.0 mL (0.92 g, 0.01 mole, 1.1 equivalents) of dihydropyran was injected into the solution and the reaction mixture stirred for six hours. Analysis of an aliquot by tlc indicated starting material remained, thus an additional 1.0 mL of dihydropyran was introduced into the reaction mixture. Stirring an additional ten hours consumed all of the starting material (by tlc). The solution was cooled to room temperature, poured into 150 mL of half-saturated sodium bicarbonate solution and extracted six times with 75 mL portions of methylene chloride. The organic layers were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure to provide 2.51 g of a straw-yellow oil. Chromatography on silica gel with chloroform gave 1.74 g (0.0041 mole, 85%) of a colorless oil whose spectral data follows: cmr δ 171.4 (amide carbonyl), 136.7 (aromatic C), 129.0, 127.9, 126.5 (aromatic CH), 98.6, 98.5, 97.6, 96.0, 95.6, 95.3 (diastereomeric CH), 63.9 (CH), 66.9 (CH₂), 62.1 (CH₂), 51.3 (CH), 36.6, 30.4, 25.1 (CH₂); pmr δ 7.2 (bs, 5H), 4.5 (bs, 2H), 4.4-3.2 (m, 7H), 3.2-2.5 (m, 3H), 2.4-1.8 (m, 6H), 1.6 (bs, 12H); ir cm⁻¹ (neat) 1620 (amide carbonyl), 1130, 1115, 1070, 1030 (acetal).

1,6-cis-8 β -hydroxymethylene-2-azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (205, p 69)

To a stirring, room temperature solution of 3.1 g (0.0071 mole) of amide 202 (p 68), 100 mL of THF, 100 mL of diethyl ether and 7.02 g (0.062 mole, 8.5 equivalents) of potassium tert-butoxide under

argon was added 0.25 g (0.014 mole, 2 equivalents) of distilled water via syringe. Immediately upon addition of the water, a glistening white precipitate formed in the flask. The solution was heated at 65° for 18 hours, cooled to room temperature and several grams of ice added. The solution was allowed to stir until the layers separated and all of the precipitate had dissolved. The solution was diluted with 150 mL of water and extracted four times with 100 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure to provide 2.2 g of a brown oil. Chromatography on silica gel initially with chloroform, then with 5% methanol-chloroform eluted 1.95 g (85%) of the desired secondary amine 205 (p 69) as a yellow oil: cmr δ 98.9, 98.2, 96.6, 95.3 (diastereomeric CH), 71.9, 69.9 (CH), 66.8, 66.2, 62.3, 61.8 (CH₂), 54.5 (CH), 42.1 (CH₂), 35.4, 34.5 (CH), 30.5, 25.1, 22.9, 22.3, 19.5 (CH₂); pmr δ 4.6 (bs, 1H), 4.45 (bs, 1H), 4.0-3.2 (overlapping m, 7H), 3.04 (t, 1H), 2.85 (t, 1H), 2.6-2.05 (overlapping m, 4H), 1.9 (d, 4H), 1.55 (bs, 12H); ir cm⁻¹ 3320 (broad NH), 1130, 1080, 1030 (acetal).

1,6-cis α -8 β -hydroxymethylene-2-(N-chloro)azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (208, p 72)

To a solution of 0.5 g (0.0015 mole) of amine 205 (p 69) in 30 mL of distilled methylene chloride maintained at room temperature was added 15.5 mL of a 0.1 M N-chlorosuccinimide/methylene chloride solution (1.1 equivalents). The reaction mixture was allowed to

stand in the dark for ten minutes with occasional swirling, then washed twice with 100 mL portions of saturated sodium bicarbonate solution. The organic layer was dried over anhydrous potassium carbonate, filtered and the solvent evaporated under reduced pressure giving 0.56 g (0.0015 mole, 100%) of a pale yellow oil which crystallized as prisms under vacuum: m.p. 60° (charred); cmr δ 99.3, 98.9, 97.0, 95.9 (diastereomeric CH), 70.9, 70.5, 69.8, 67.8 (CH, 67.1, 66.4 (CH₂), 62.2, 59.1 (CH₂), 38.5, 37.2 (CH₂), 37.0, 36.2 (CH), 30.5, 27.6, 25.2, 19.3 (CH₂); decomposes to several products on prolonged exposure to air.

2 β -hydroxymethylene-7 β -hydroxy-8 α -pyrrolizidine(210, p 74)

The following procedure is typical for this reaction. A solution of 0.29 g (0.0015 mole) of silver tetrafluoroborate in 150 mL of anhydrous benzene was refluxed under argon into a Dean-Stark trap until 50 mL of benzene had been removed. The solution was allowed to cool to 45-50° and 0.56 g (0.0015 mole) of N-chloroamine 208 (p 72) dissolved in 10 mL of anhydrous benzene was added dropwise over a 30-minute period. Stirring was continued at 45-50° under argon for eight hours in the dark. Precipitation of silver chloride and the immonium salt began immediately upon addition of N-chloroamine and was considered complete when the benzene solution clarified, leaving a gummy gray solid on the interior wall of the flask. To complete precipitation of any excess silver tetrafluoroborate, lithium chloride (200 mg, oven-dried) was added, the

heat source removed, and the solution stirred until it reached room temperature. The reaction mixture was filtered through celite, the precipitate washed well with dry methylene chloride, the organic layers combined and evaporated under reduced pressure to provide 0.346 g of a pale yellow oil. The oil was immediately dissolved in distilled methanol (5 mL) and added to a methanolic sodium cyanoborohydride solution (100 mL) containing an excess of the reducing agent and stirred at room temperature for two hours. This produced a black precipitate presumed to be metallic silver, or a silver salt. The reaction mixture was filtered through celite into 100 mL of 1M sodium hydroxide and extracted five times with 100 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure to provide 0.247 g of a pale yellow oil consisting of two materials (by tlc): pmr evidence suggested some loss of tetrahydropyranyl groups occurred during the rearrangement. (See Appendix.)

Treatment of the oil with 0.5 mL of 3M hydrochloric acid in 20 mL of THF for 48 hours at room temperature resulted in the formation of a water-soluble residue presumed to be the hydrochloric salt of the parent diol. The THF was decanted and the residue washed well with THF. Combination of the THF layers, drying over anhydrous potassium carbonate, filtering and evaporation of the solvent left a colorless oil whose pmr, ir and cmr data were consistent with 2-hydroxy tetrahydropyran generated by acid-catalyzed addition of water to dihydropyran.

At this state in the isolation, pmr and cmr analysis of the hydrochloride salt were not useful due to the impurities present. Two isolation procedures were developed, the latter providing pure diol at its conclusion.

Method 1: Dissolution of the hydrochloride salt in a minimum amount of water and basification with 3N sodium hydroxide (5 mL) and concentrated ammonium hydroxide (1 mL), followed by exhaustive extraction with chloroform (250 mL total, taken 25 mL at a time). Workup of the chloroform extracts did not provide any recognizable diol, but apparently did remove some of the impurities (0.025 g). Evaporation of the aqueous phase produced a solid which was vacuum dried at 0.005 mm Hg for 24 hours. CMR analysis (D_2O , referenced to methyl resonance of acetone) indicated the presence of 210 (p 74).

Method 2: Hydrolysis of the rearranged bis-tetrahydro-pyranyl ether (0.16 g) is also accomplished by refluxing a methanolic (25 mL) solution in the presence of pyridinium p-toluenesulfonate (2 equivalents) for 36 hours. Evaporation of the solvent followed by dissolution of the solid residue in 5 mL of pyridine and 0.1 mL of acetic anhydride and stirring for 18 hours provided a new compound by tlc. The pyridine was removed under vacuum, the residue dissolved in 25 mL of methylene chloride and washed once with 50 mL of saturated sodium bicarbonate. The bicarbonate solution was washed twice with

50 mL portions of methylene chloride and combined with the original organic layer. Drying over anhydrous potassium carbonate, filtering and evaporation of the solvent left an oil (0.1 g) whose pmr clearly showed the presence of two acetyl methyl resonances. (Figure 19).

Combination of all aqueous phases, including extractive washes, and evaporation of the water left a white solid which was pulverized and placed in a cellulose thimble. Extraction of the powder with chloroform in a Soxhlet apparatus for 48 hours afforded, after evaporation of the chloroform, 0.061 g of a white solid, identified as 210 (p 74): cmr δ (D_2O , referenced to methyl resonance of d_3 -acetonitrile) 69.9, 69.1 (CH), 61.7, 57.5, 50.9 (CH_2), 43.4 (CH), 34.2, 25.4 (CH_2); ir cm^{-1} (chloroform solution) 3350 (broad, OH), 3000, 2960, 2935 (CH).

1,6-cis-8 α -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (203, p 68)

To a stirring solution of 1.5 g (0.0057 mole) of diol 193 (p 54) dissolved in 150 mL of anhydrous THF maintained at 65° under argon was added a few crystals of pyridinium p-toluenesulfonate. The acid was allowed to dissolve and 2.0 mL (0.184 g, 0.02 mole, 3.5 equivalents) of dihydropyran was added to the solution. The mixture was allowed to stir for 24 hours at 65° when it was cooled and poured into 200 mL of half-saturated sodium bicarbonate. It was extracted four times with 100 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and

evaporated under reduced pressure to give 2.2 g of a pale yellow oil. The oil was chromatographed on silica gel with chloroform which provided 1.98 g (0.0046 mole, 81%) of protected diol 203 (p 68) as a colorless oil. Depressed yield is probably due to loss of diol 193 (p 54) in the workup stage due to its water solubility. Spectral data for 203 (p 68) are as follows: pmr δ 7.38 (s, 5H), 4.7 (bs, 2H), 4.2-3.3 (broad m, 9H), 3.3-2.6 (broad, 3H), 2.6-1.8 (broad m, 4H), 1.6 (bs, 12H); ir (chloroform solution) 1620 (C=O), 1140, 1115, 1075, 1030 (acetal).

1,6-cis-8 α -hydroxymethylene-2-azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (206, p 69)

A solution of 1.3 g (0.003 mole) of benzamide 203 (p 68) and 2.7 g (0.024 mole, 8 equivalents) of potassium tert-butoxide in a 3:1 mixture of THF and diethyl ether (200 mL) was stirred at room temperature under argon until the base had dissolved. Addition of 0.108 g (0.006 mole, 2 equivalents) of distilled water produced a finely divided, white precipitate. The solution was brought to reflux (60°) and maintained for 20 hours. It was cooled to room temperature and ice was added until all of the precipitate had dissolved. Dilution with 100 mL of distilled water and extraction with four 100 mL portions of diethyl ether which were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure afforded 0.94 g of a brown oil. Chromatographic and spectroscopic analysis of this oil indicated no purification was

necessary; however passage through a short silica gel column with 5% methanol in chloroform decolorized the oil to a pale yellow color and provided 0.86 g (0.0027 mole, 90%) after vacuum evaporation of the solvents. Spectral data as follows: cmr δ 98.6, 98.4, 96.4, 96.0 (diaster eomeric CH), 70.3 (CH), 68.9, 68.8, 62.3, 62.1, 61.8 (CH₂), 54.3 (CH), 40.8, 40.3 (CH₂), 39.8, 34.3, 32.4 (CH), 30.3, 27.9, 25.2, 21.4, 21.1, 19.4 (CH₂); pmr δ 4.6 (bs, 2H), 4.05-3.2 (overlapping m, 10H), 3.2-2.2 (overlapping m, 7H), 1.6 (bs, 12H); ir cm⁻¹ (neat) 3320 (NH, broad), 1135, 1119, 1079, 1032 (acetal).

1,6-cis-8 α -hydroxymethylene-2-(N-chloro)azabicyclo[4.2.0]octan-5 β -ol-5,9-bis-tetrahydropyranyl ether (209, p 72)

To a solution of 1.12 g (0.003 mole) of amine 26 (p 69) in 50 mL of distilled methylene chloride maintained at room temperature was added 35 mL of a 0.1 M N-chlorosuccinimide/methylene chloride solution (1.2 equivalents). The reaction mixture was allowed to stand for five minutes in the dark then poured into 100 mL of saturated sodium bicarbonate solution. The aqueous solution was extracted four times with 50 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated under reduced pressure to provide 1.25 g (0.0029 mole, 98%) of a pale yellow semi-solid: pmr 4.65 (bs, 2H), 4.05-3.2 (overlapping m, 9H), 3.05-2.4 (overlapping m, 2H), 2.3-1.6 (overlapping m, 5H), 1.55 (bs, 12H); ir cm⁻¹ (neat oil) 2950 (CH), 1145, 1128, 1085, 1070 (acetal).

Rearrangement, Reduction and Hydrolysis of N-chloroamine 209 (p 72)
with Silver Tetrafluoroborate

A solution of 0.58 g (0.0029 mole) of silver tetrafluoroborate in 400 mL of anhydrous benzene was refluxed under argon into a Dean-Stark trap until 100 mL of benzene had been removed. The solution was allowed to cool to 50° and 1.25 g (0.0029 mole) of N-chloroamine 209 (p 72) dissolved in 8 mL of anhydrous benzene was added dropwise over a one hour period. Stirring was continued at 50° under argon for six hours when the analysis of the reaction mixture indicated no starting material remained. At this time the gray-white precipitate adhered to the walls of the flask and the benzene solution was clear and colorless. The solution was cooled to 22°, 1 g of oven-dried lithium chloride added, and the solution stirred for 15 minutes. The solution was filtered through celite, the solids washed well with methylene chloride, the organic layers combined and the solvent removed under reduced pressure to afford a yellow oil. The oil was immediately dissolved in 10 mL of methanol and added to a stirring, room temperature solution of a large excess of sodium cyanoborohydride in 400 mL of methanol. The reduction was allowed to continue for eight hours, the mixture was then filtered through celite to remove silver impurities into 200 mL of 1.5 M sodium hydroxide. The aqueous solution was extracted six times with 100 mL portions of methylene chloride which were combined, dried over anhydrous potassium carbonate, filtered and evaporated to give 0.9 g of a yellow oil which consisted

principally of two products. Chromatography on silica gel with chloroform eluted 0.30 g of the highest rf material. Increasing the polarity of the solvent with methanol in a step-gradient manner (5% initial) produced 0.306 g of a mixture of the two products. Finally, 10% methanol in chloroform eluted 0.188 g of the lowest rf spot. PMR spectra for each of these fractions (1, 2 and 3 respectively) are included in the Appendix. Fraction 1 and fraction 3 were each hydrolyzed separately as follows:

The upper rf material (fraction 1) was dissolved in 50 mL of THF containing 2 mL of 2% hydrochloric acid and was stirred for three hours (tlc changed completely). Pouring the reaction mixture into 150 mL of one-half saturated sodium bicarbonate and extracting eight times with 25 mL portions of methylene chloride provided, after drying, filtering and evaporating the solvents, a colorless oil whose pmr spectrum was consistent with 2-hydroxy tetrahydropyranyl-like materials. Continuous extraction of the aqueous layer with diethyl ether and with methylene chloride also proved fruitless. Evaporation of the water, pulverization of the residues and Soxhlet extraction of the powder with THF also did not produce any material. Unfortunately, fraction 1 did not produce any nitrogenous material by whatever isolation procedure was employed.

Fraction 3, when submitted to similar hydrolysis conditions, produced a brown, oily precipitate at the conclusion of the reaction. The THF was decanted, the oil washed for 24 hours in fresh THF, then

dried under vacuum for one hour to provide a tan colored solid whose pmr spectrum is shown in the Appendix (Figure 25).

From a different rearrangement of the same N-chloroamine, the crude product mixture (after reduction with sodium cyanoborohydride) was submitted to hydrolysis under more prolonged and vigorous conditions: 1 mL of 3N hydrochloric acid, 30 mL of THF, 0.45 g of the reaction mixture. After stirring for one week a light brown oil adhered to the sides of the flask. The oil was isolated by decanting the THF/acid solution, washing well with fresh THF (30 mL), and vacuum drying for four hours at 0.01 mmHg. The crude tan solid had the following cmr spectrum: δ (D_2O , ppm values referenced to residual chloroform) 74.2, 72.4 (CH_2), 66.2 (CH), 64.4 (CH_2), 59.0, 55.6, 48.1, 46.3, 43.7, 41.4 (broad), 36.7 (CH_2), 29.0, 27.7 (CH), 26.6 (CH_2). The pmr spectrum of this material was identical to that of fraction 3 described in the preceding paragraph. This material remains unidentified.

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APPENDIX

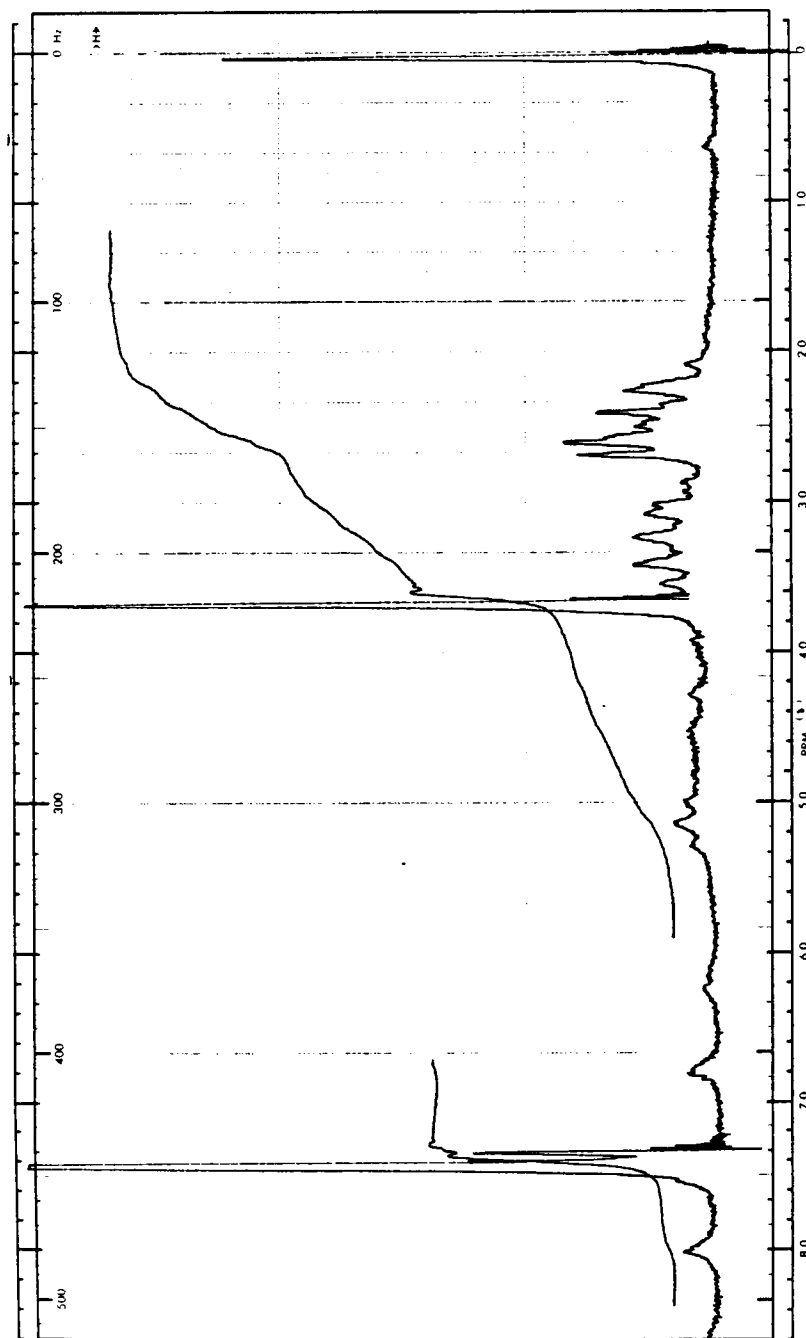


Figure 1. Proton magnetic resonance spectrum of 1,6-cis-8 α -carbomethoxy-2-(N-benzoyl)-azabicyclo[4.2.0]octan-5-one.

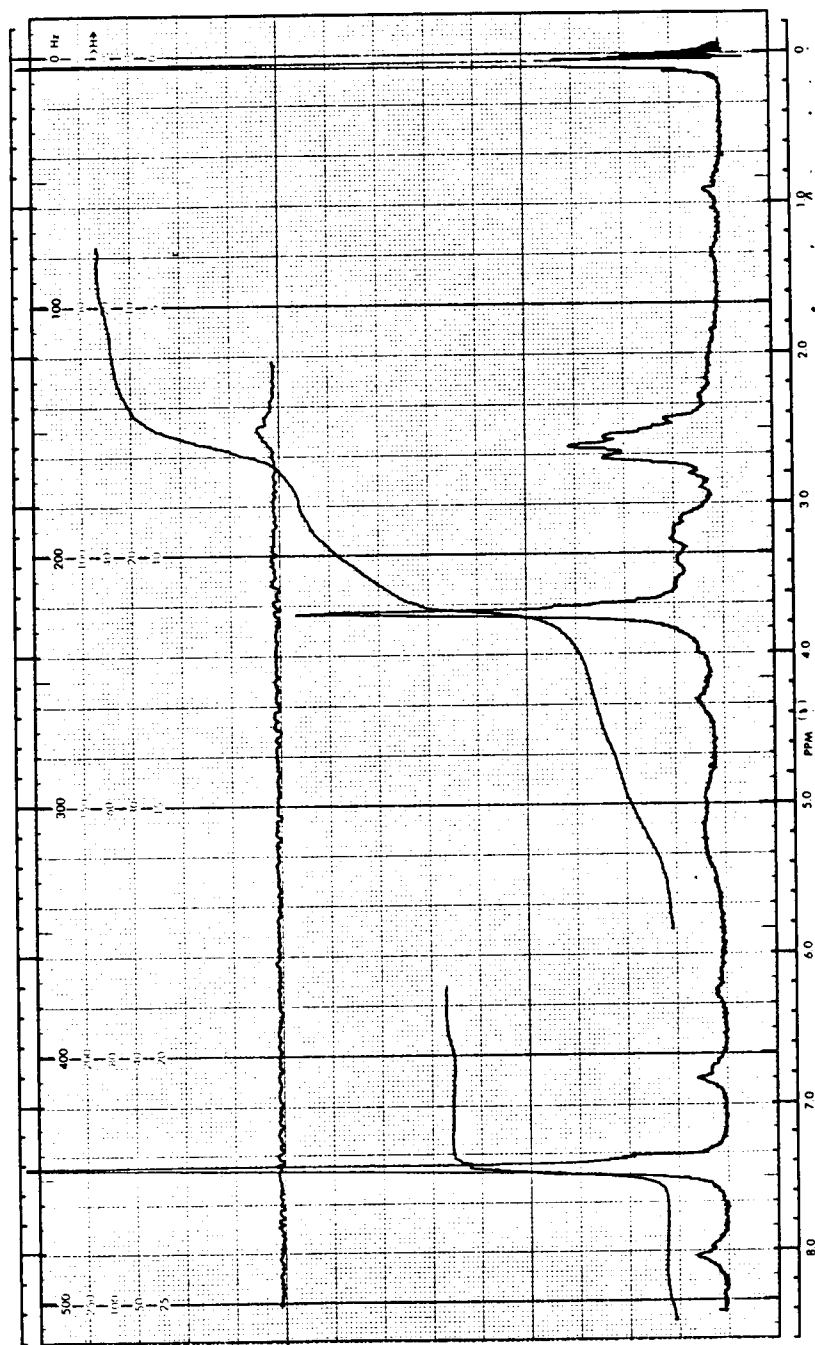


Figure 2. Proton magnetic resonance spectrum of 1,6-cis-8 β -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5-one.

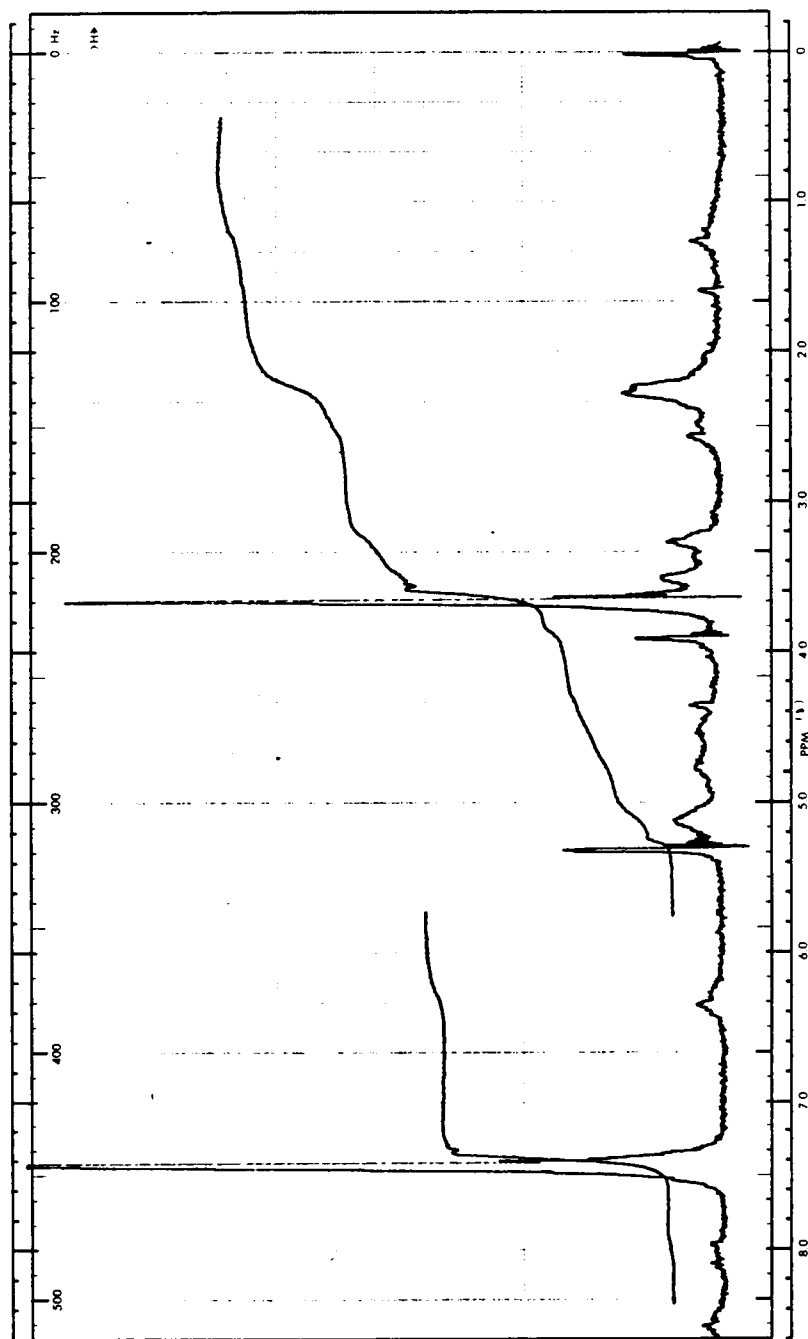


Figure 3. Proton magnetic resonance spectrum of the fully deuterated ketoester 185 (p 51).

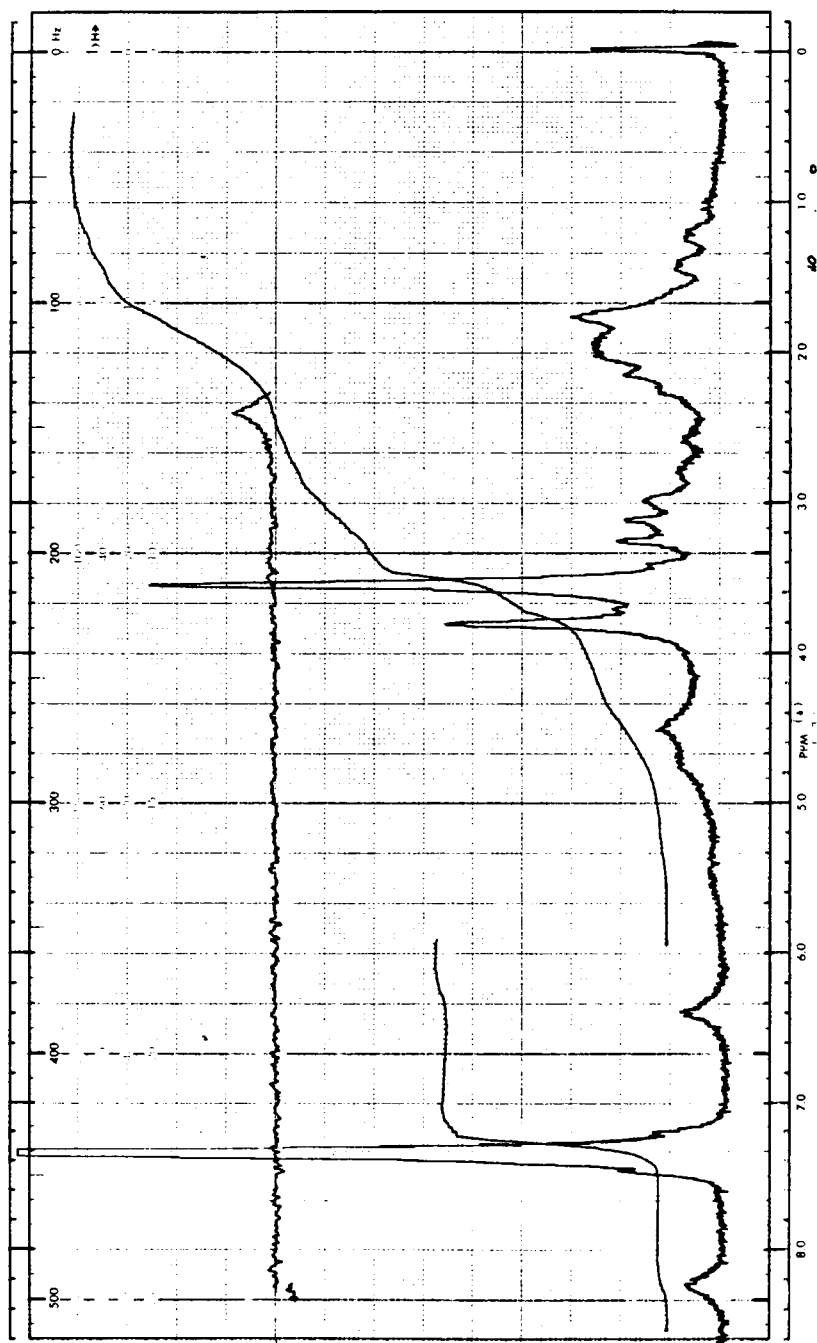


Figure 4. Proton magnetic resonance spectrum of 1,6-cis-8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 α -ol.

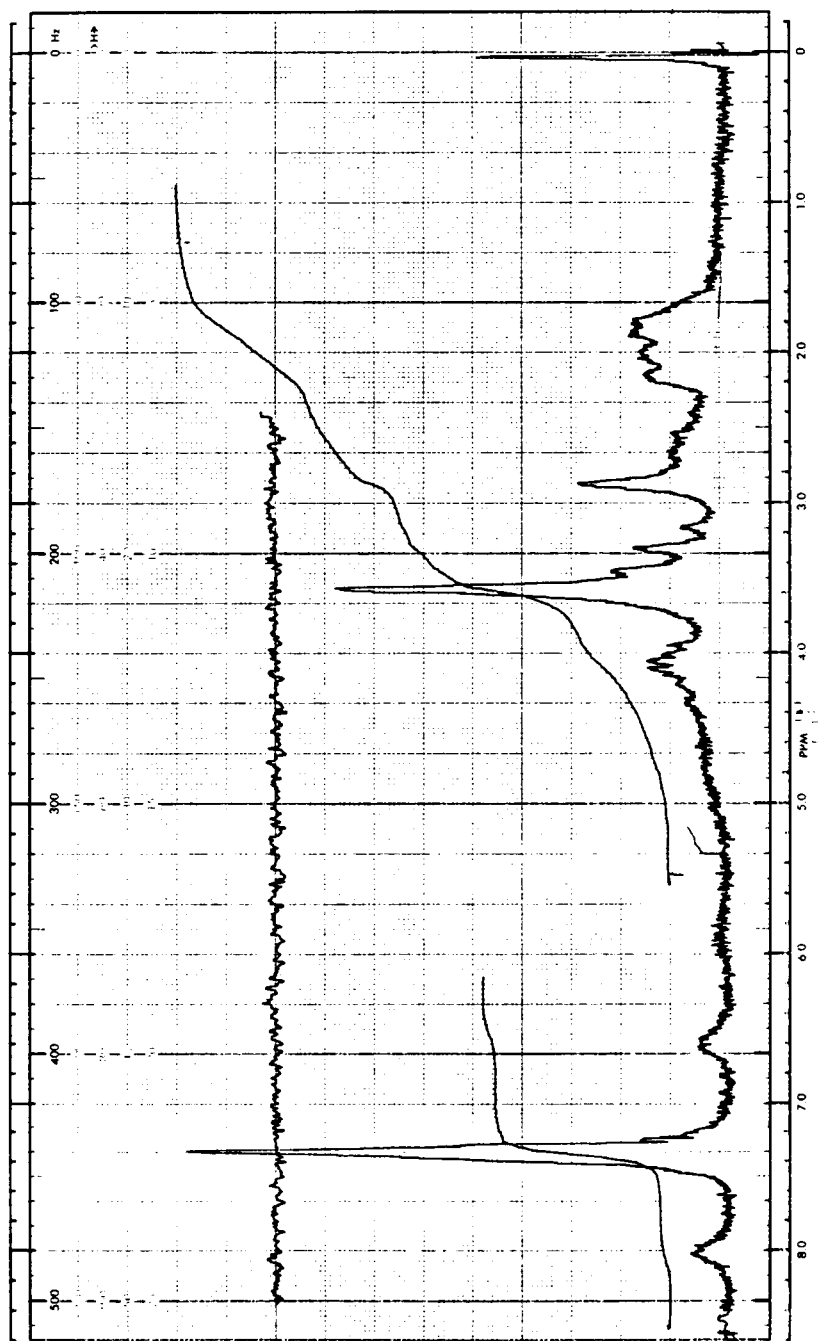


Figure 5. Proton magnetic resonance spectrum of 1,6-cis-8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol.

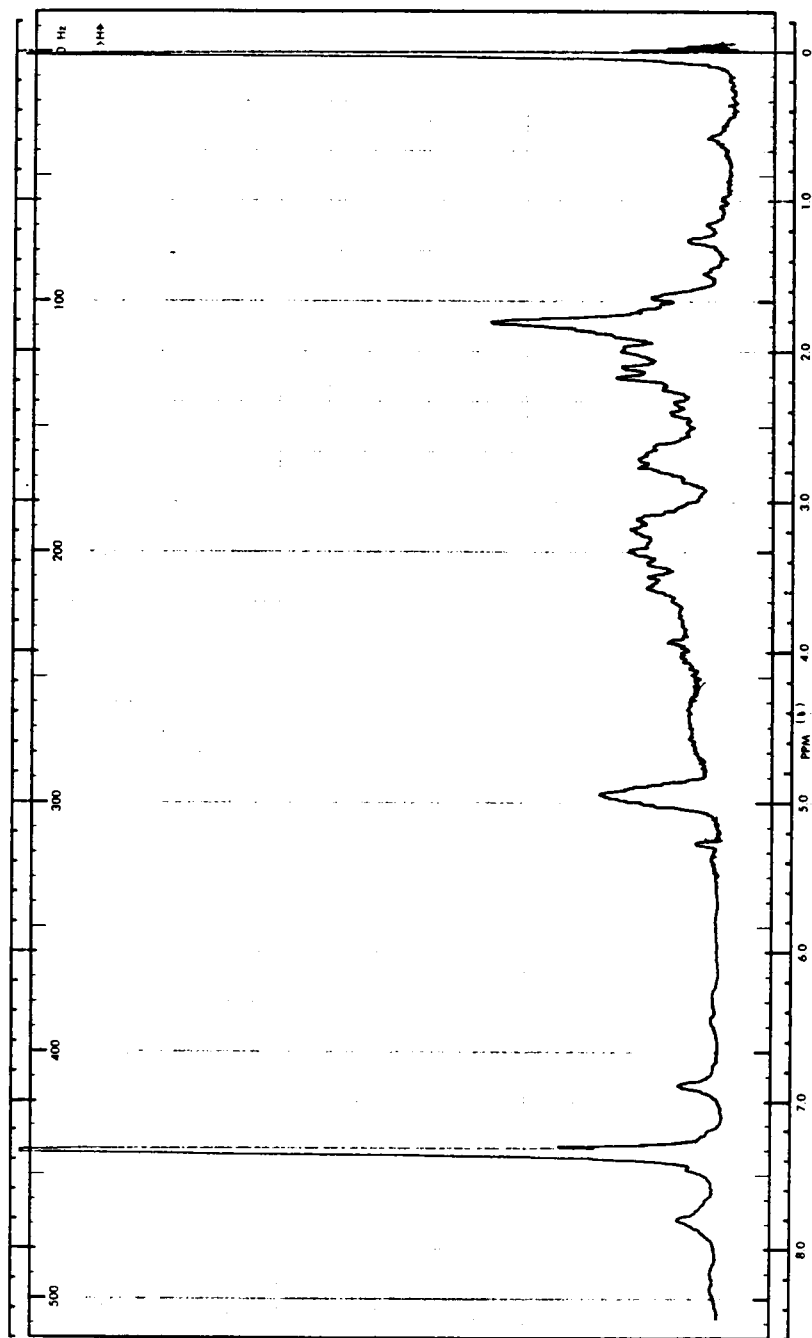


Figure 6. Proton magnetic resonance spectrum of 1,4-cis-1,9-cis-5,9-cis-4,5-cis-6-(N-benzoyl)aza-2-oxatricyclo[4.3.1.0^{1,9}]decan-3-one.

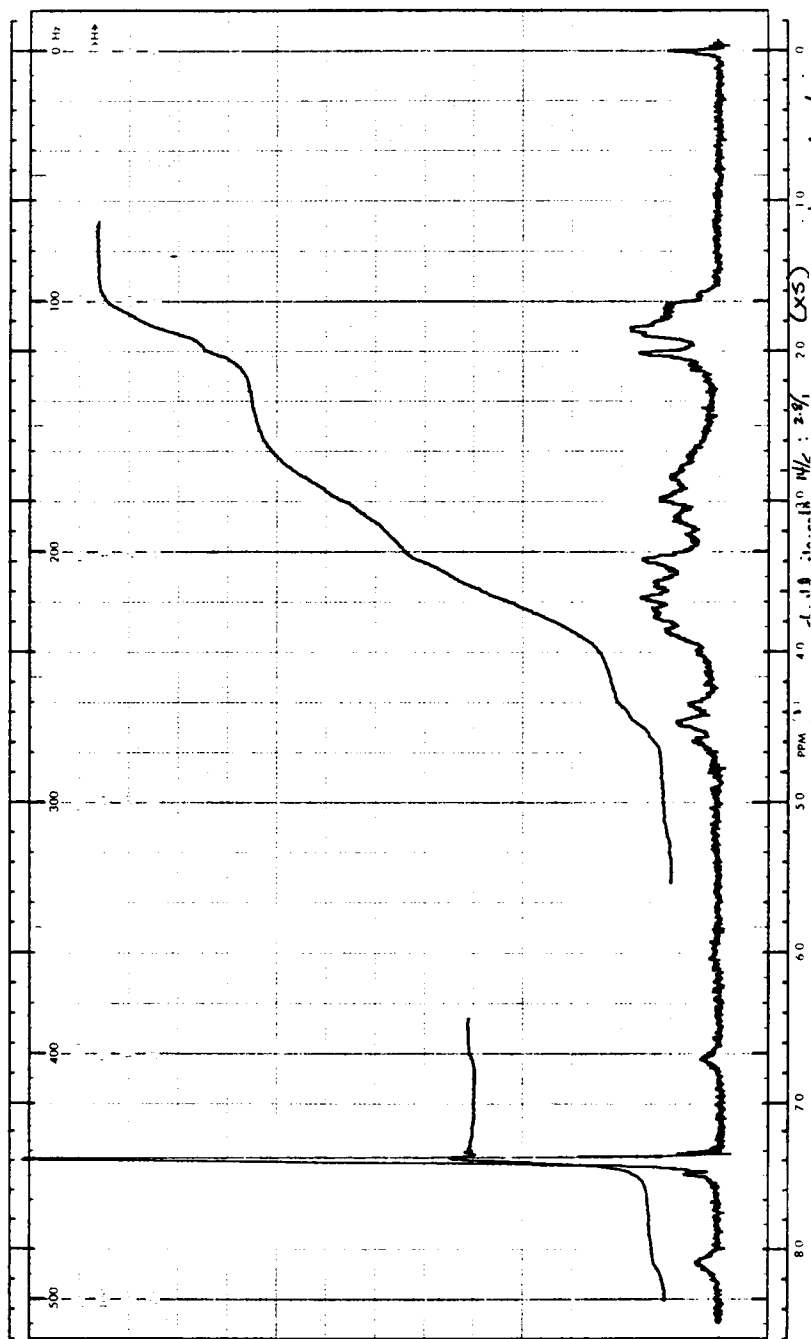


Figure 7. Proton magnetic resonance spectrum of 1,6-cis-8β-hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5β-ol.

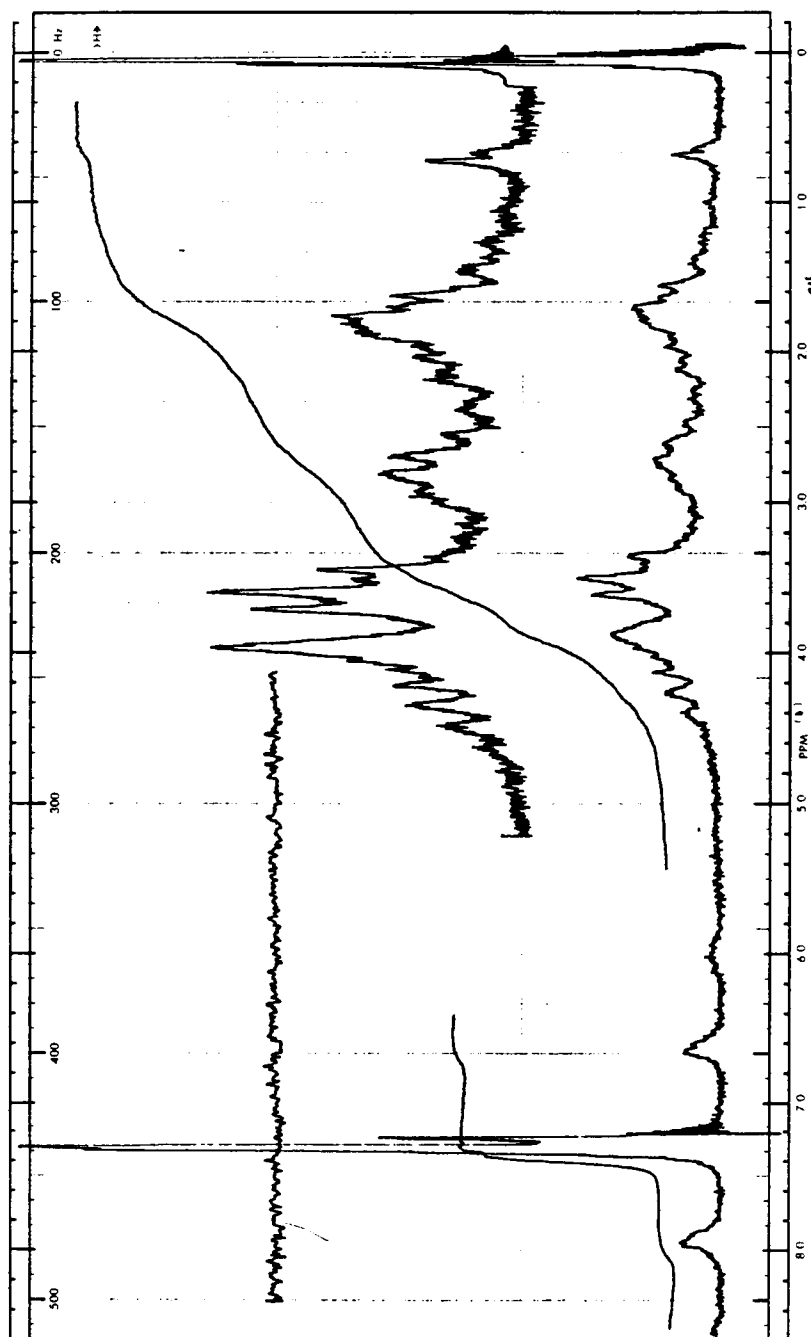


Figure 8. Proton magnetic resonance spectrum of 1,6-cis-8 α -hydroxy-methylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol.

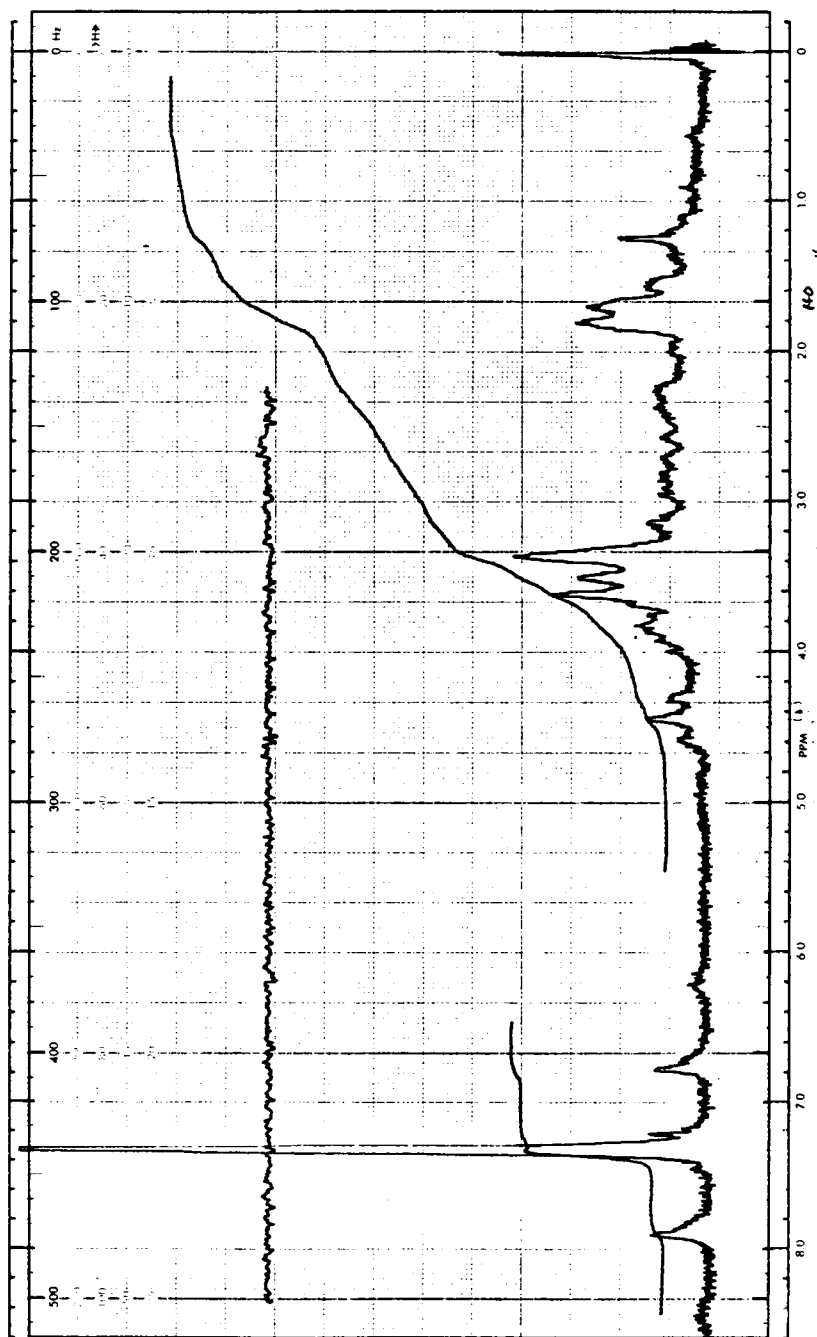


Figure 9. Proton magnetic resonance spectrum of 1,6-cis-8 α -hydroxy-methylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 α -ol.

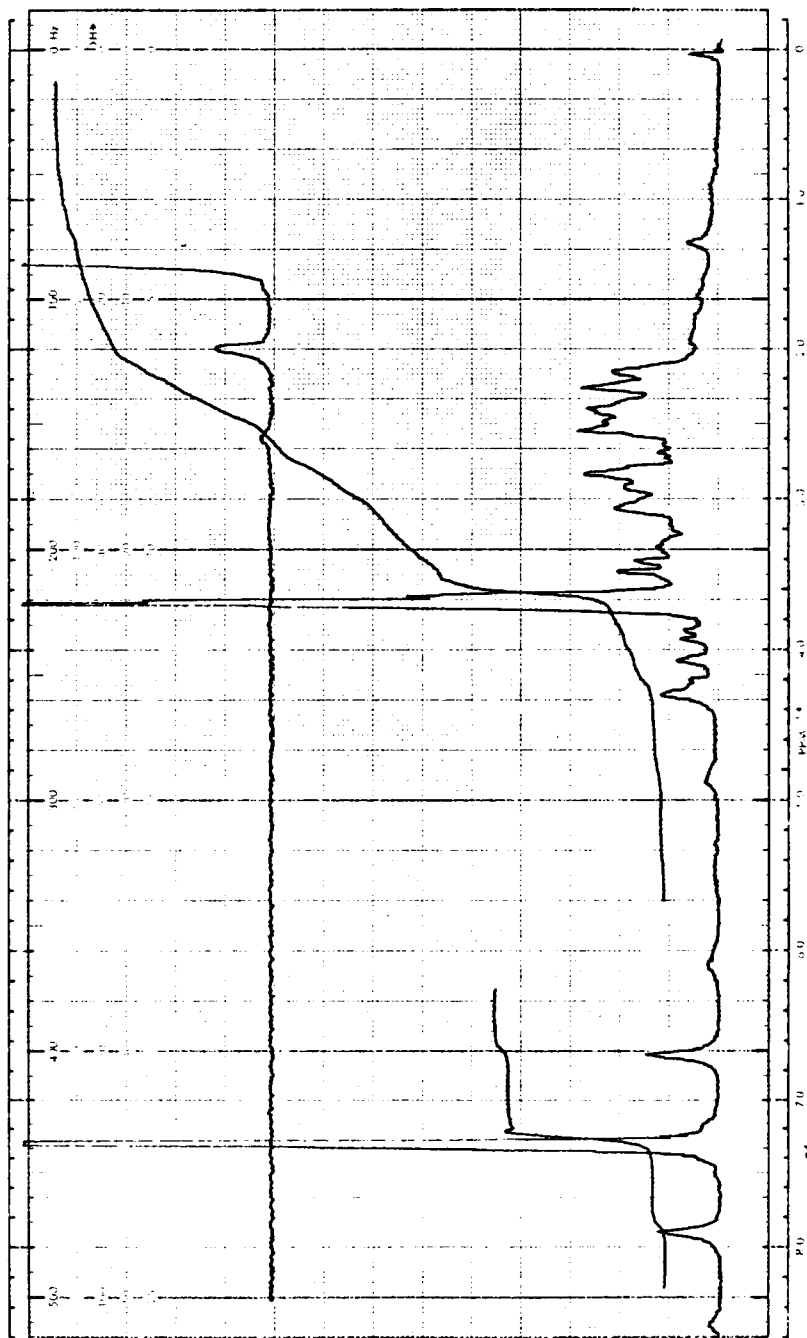


Figure 10. Proton magnetic resonance spectrum of the mixture arising from the photoaddition of vinyllogous amide 212 (p 76) and methyl acrylate, after chromatography.

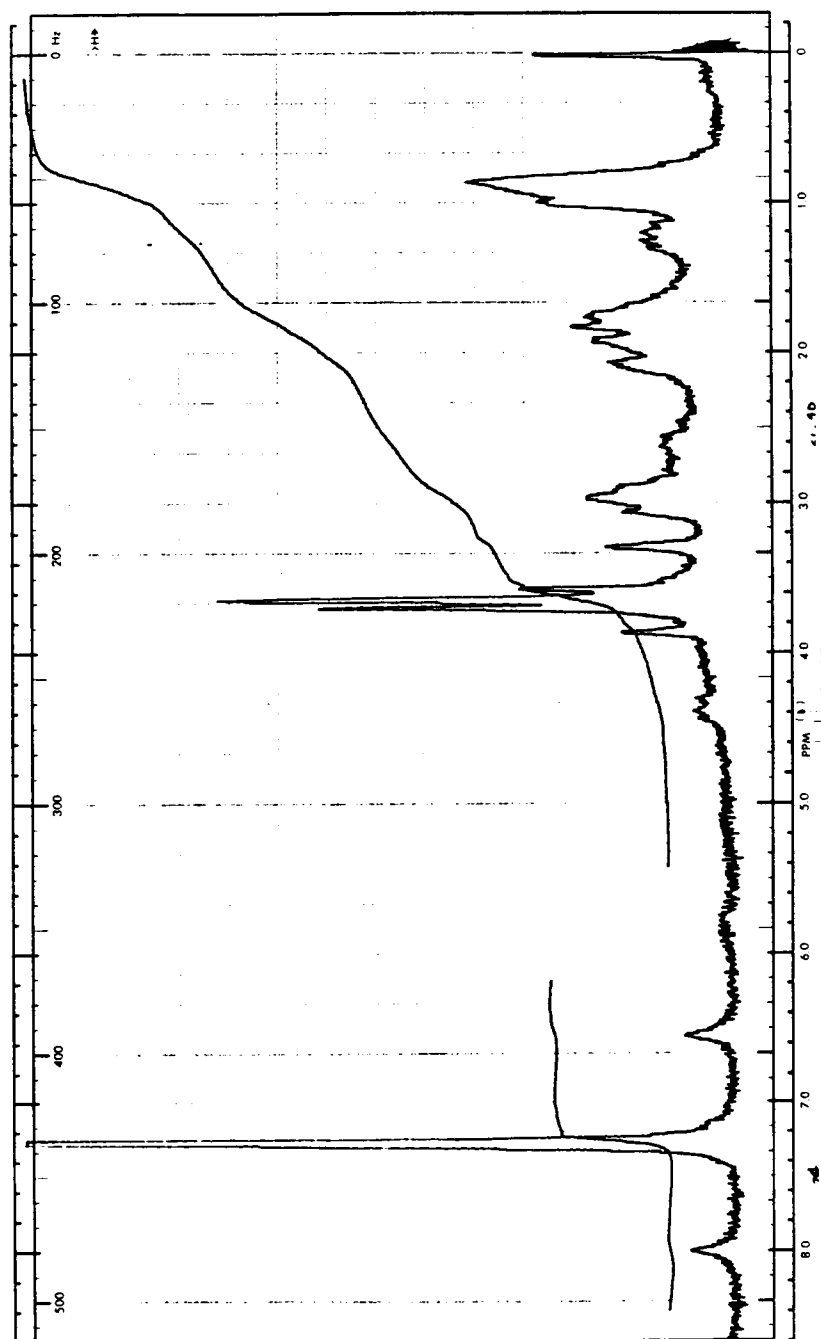


Figure 11. Proton magnetic resonance spectrum of 1,6-cis-7α-carbomethoxy-2-(N-benzyl)azabicyclo[4.2.0]octan-5β-ol.

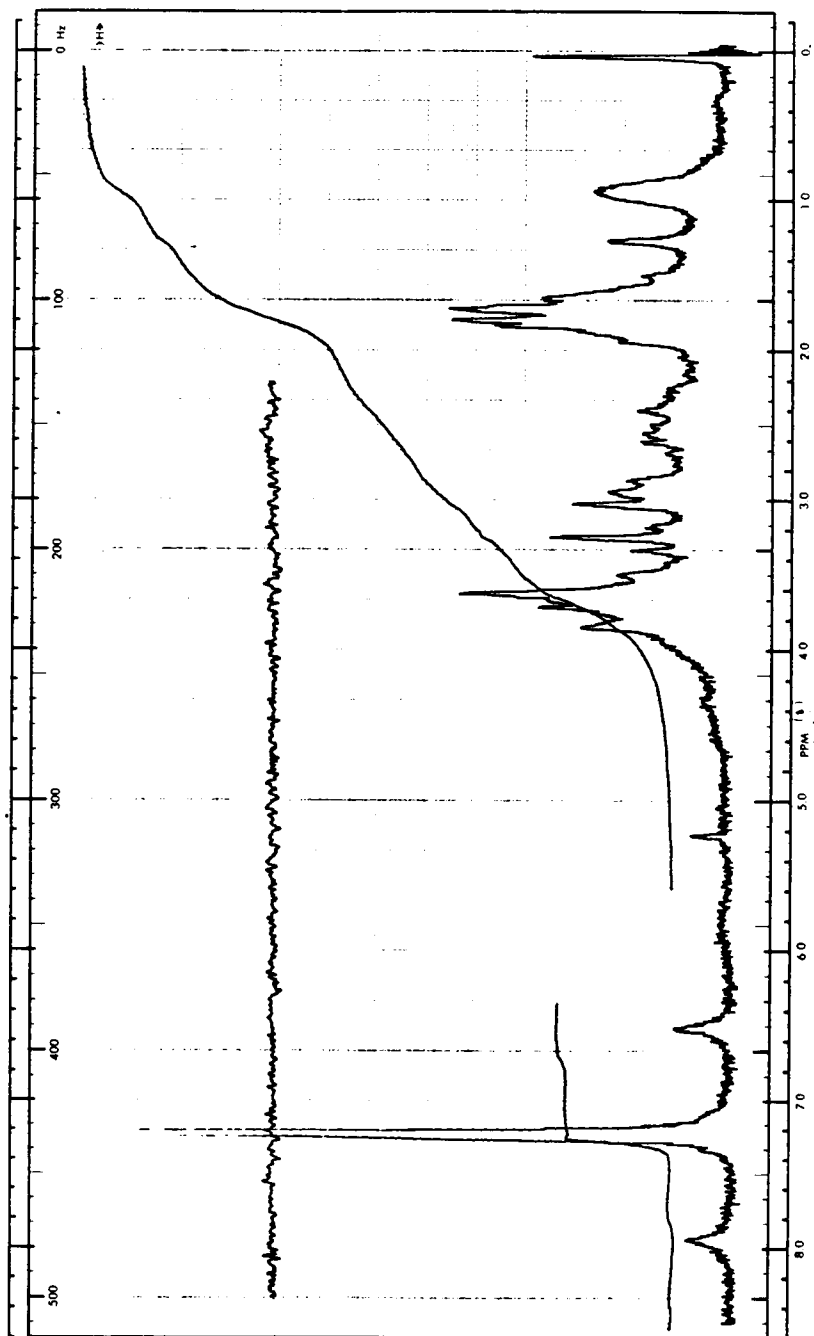


Figure 12. Proton magnetic resonance spectrum of 1,6-cis-7- α -hydroxy-methylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol.



Figure 13. Proton magnetic resonance spectrum of 1,6-cis α -8 β -hydroxy-methylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol.

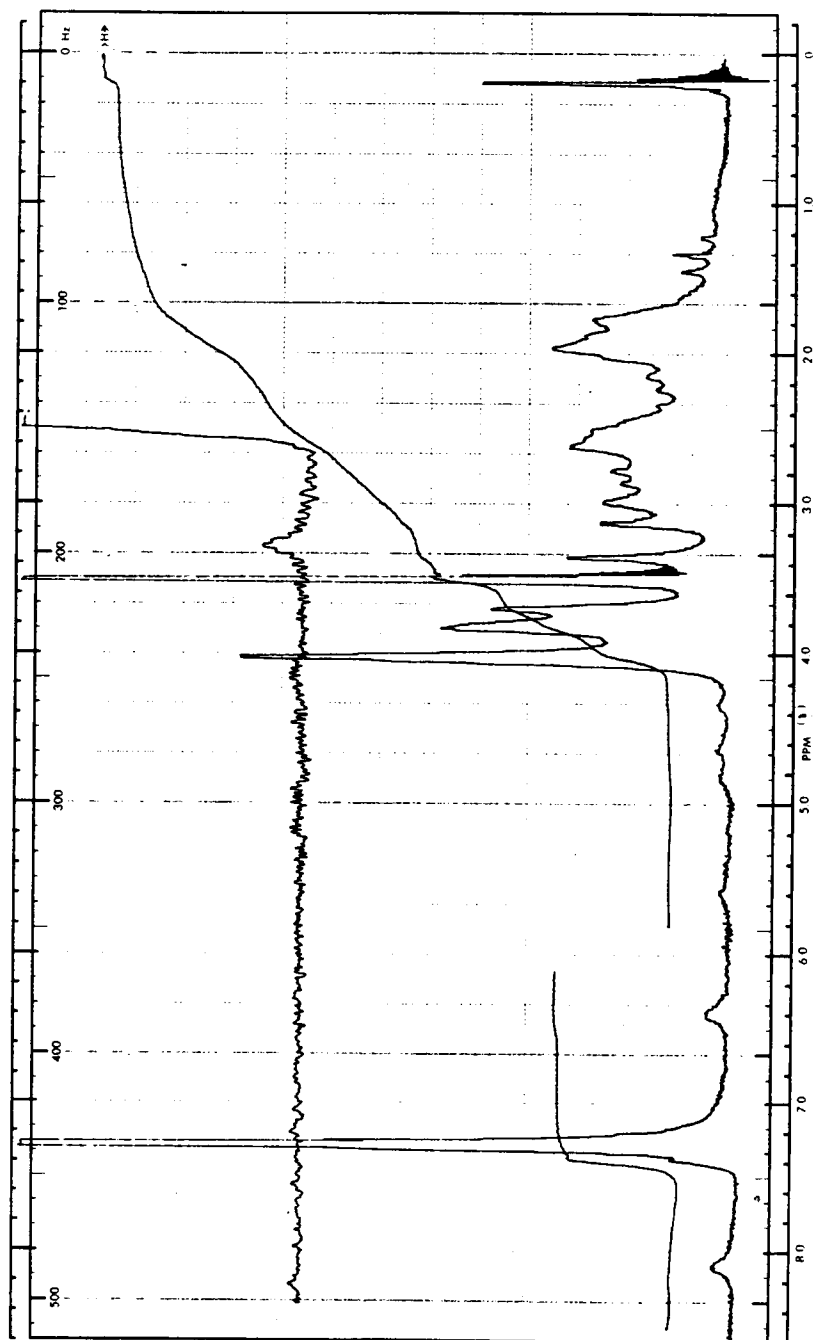


Figure 14. Proton magnetic resonance spectrum of 1,6-cis-8 α -hydroxy-2-methylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 α -ol.

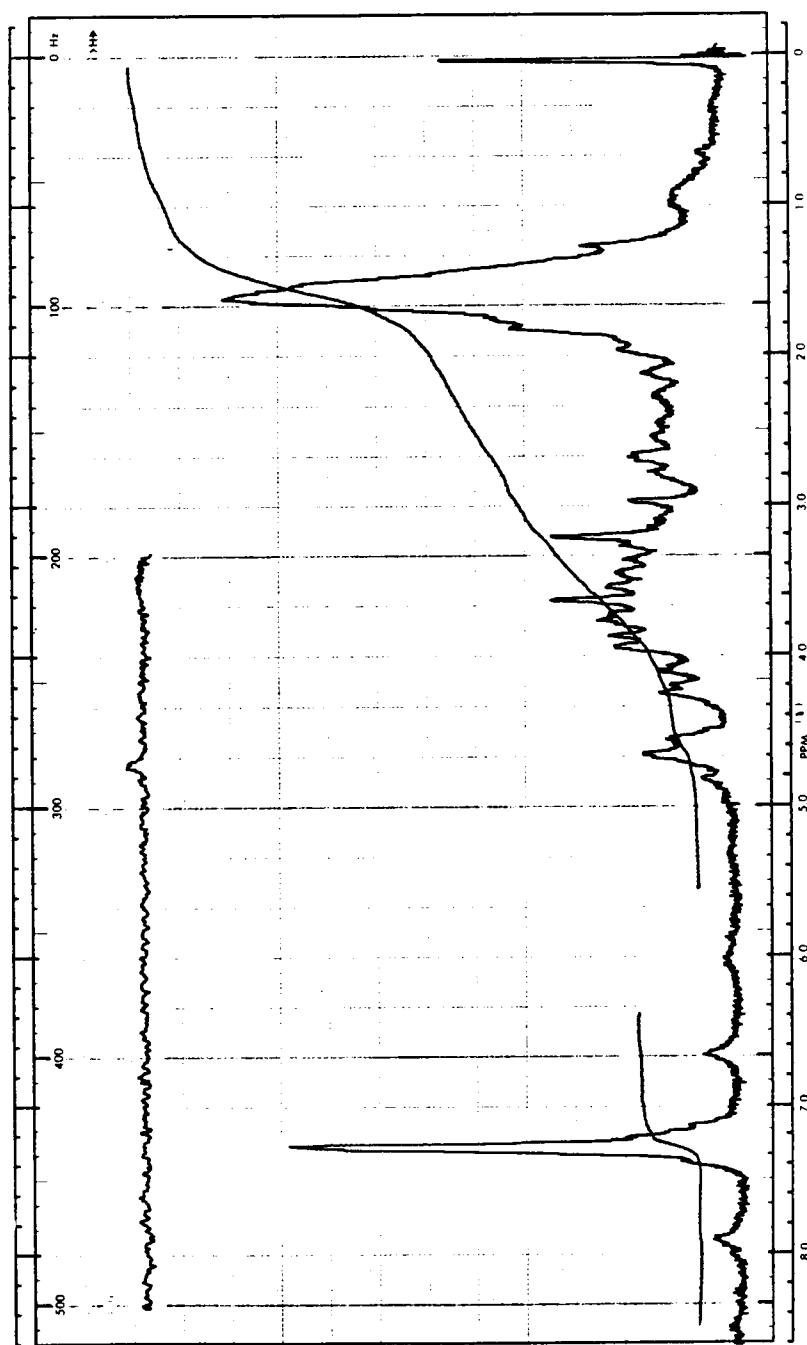


Figure 15. Proton magnetic resonance spectrum of 1,6-cis-8 β -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

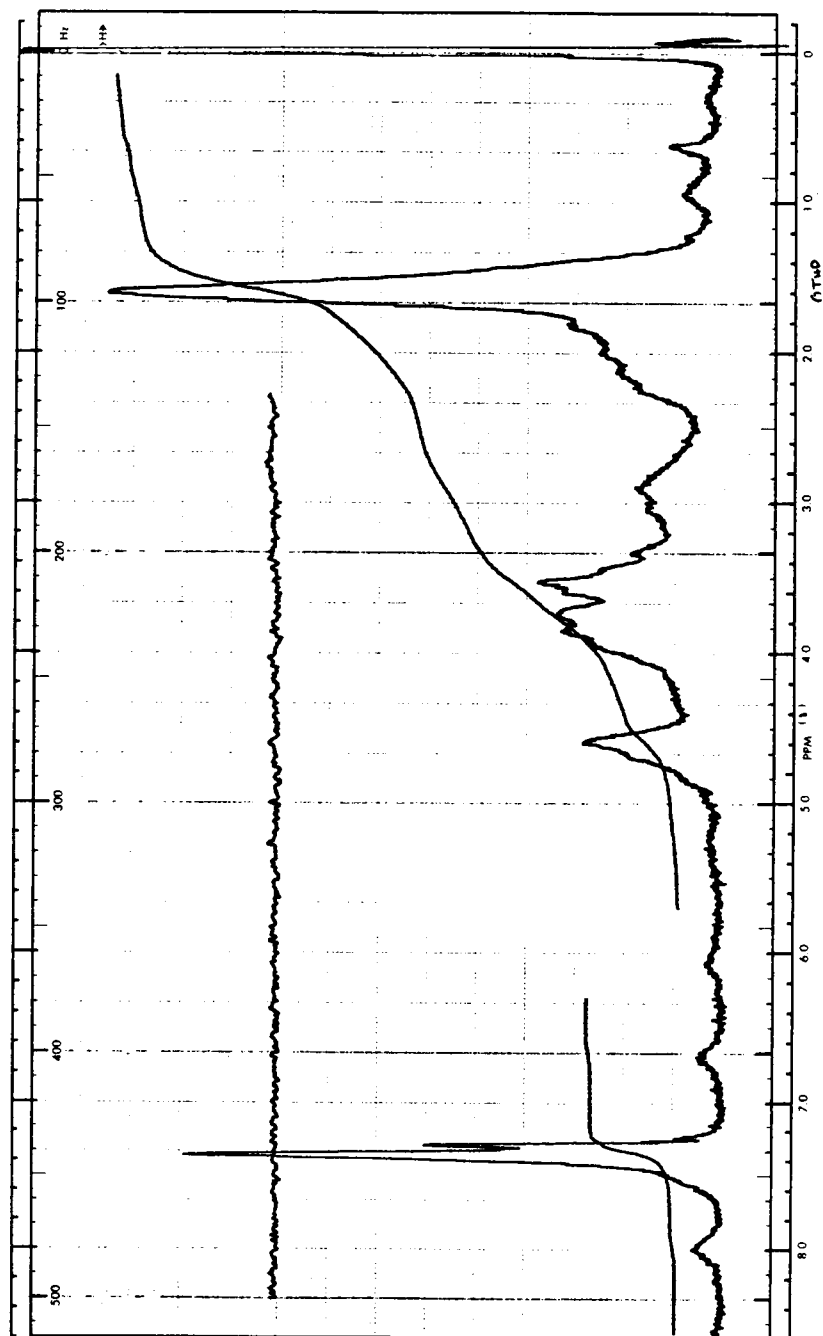


Figure 16. Proton magnetic resonance spectrum of 1,6-cis-8,8-hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5,9-bistetrahydropyranyl ether.

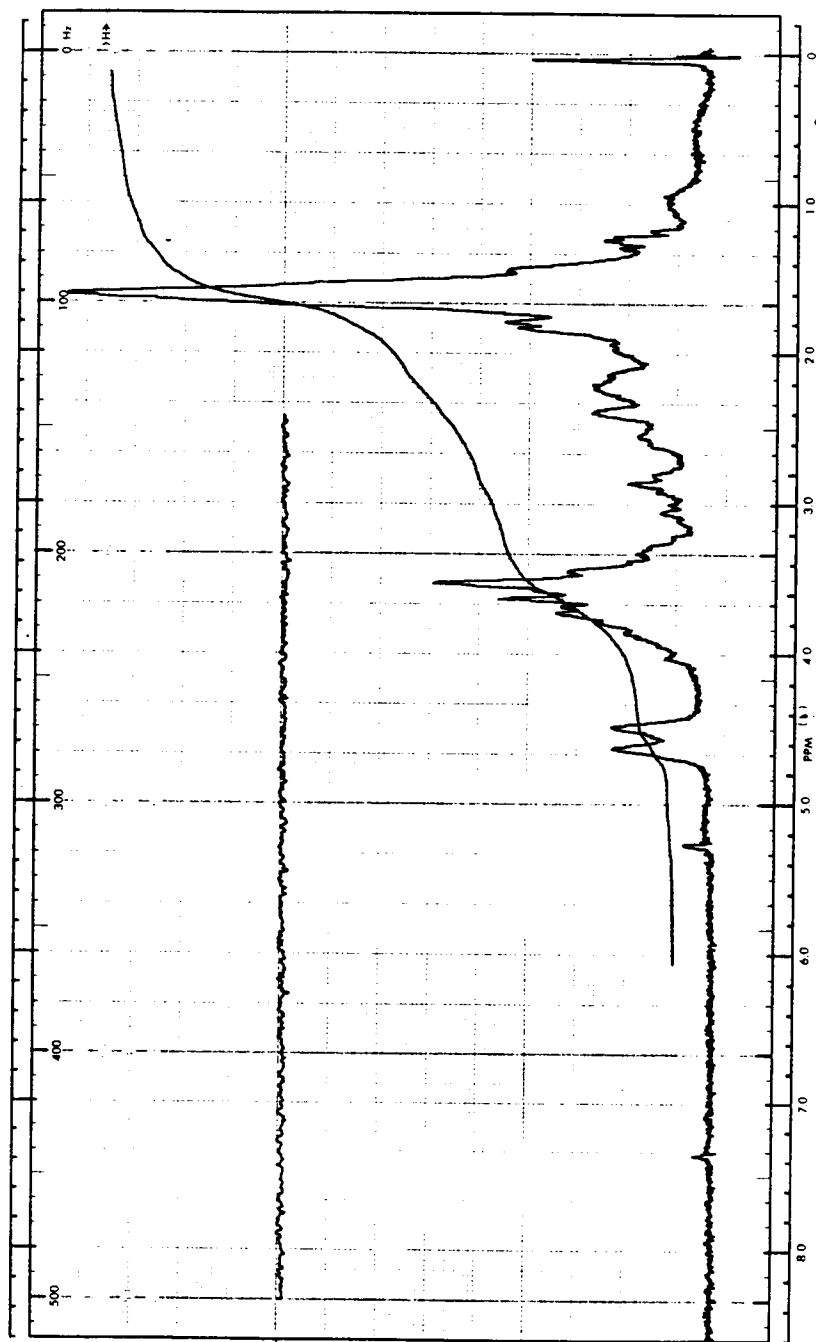


Figure 17. Proton magnetic resonance spectrum of 1,6-cis-8,8-hydroxymethylene-2-azabicyclo[4.2.0]octan-5-ol-5,9-bistetrahydropyranyl ether.

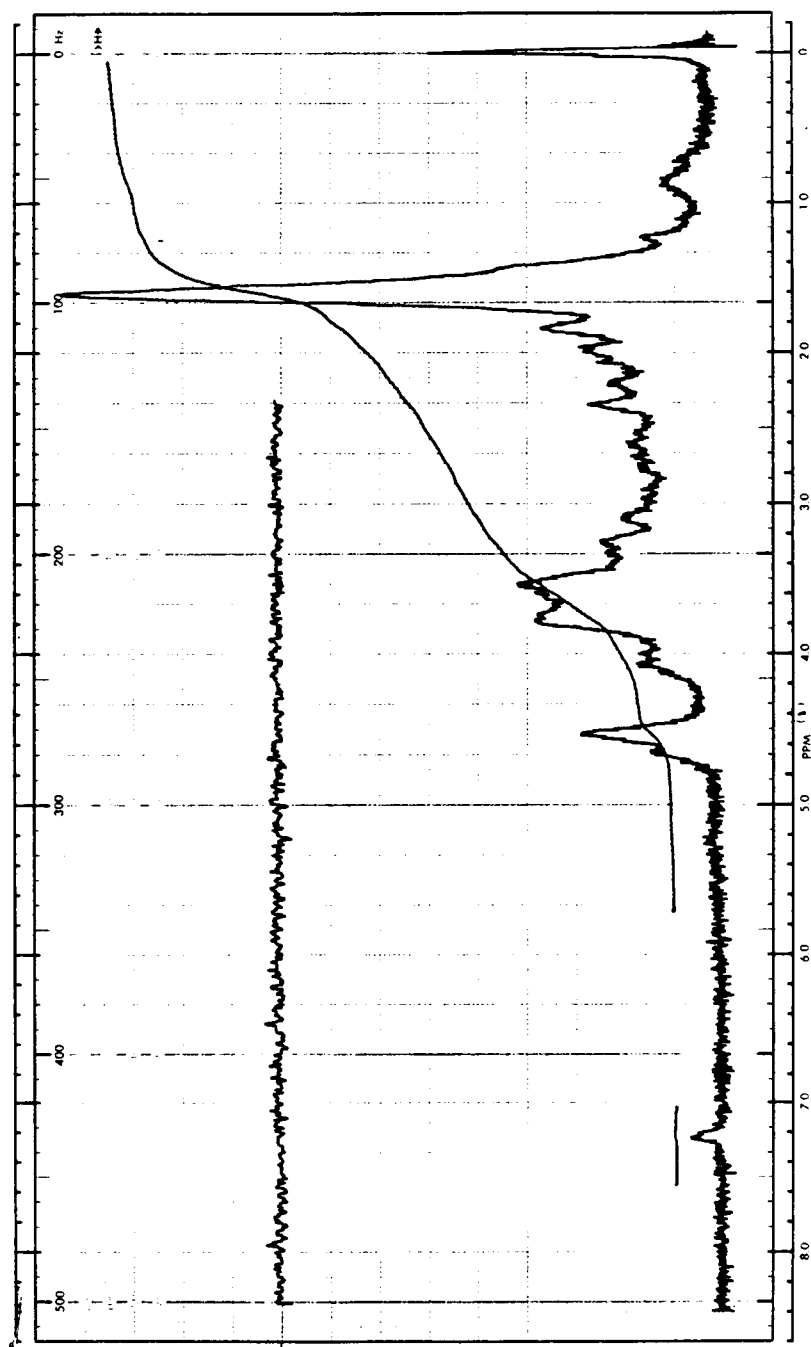


Figure 18. Proton magnetic resonance spectrum of the reaction mixture following rearrangement and reduction of N-chloroamine 208 (p 72).

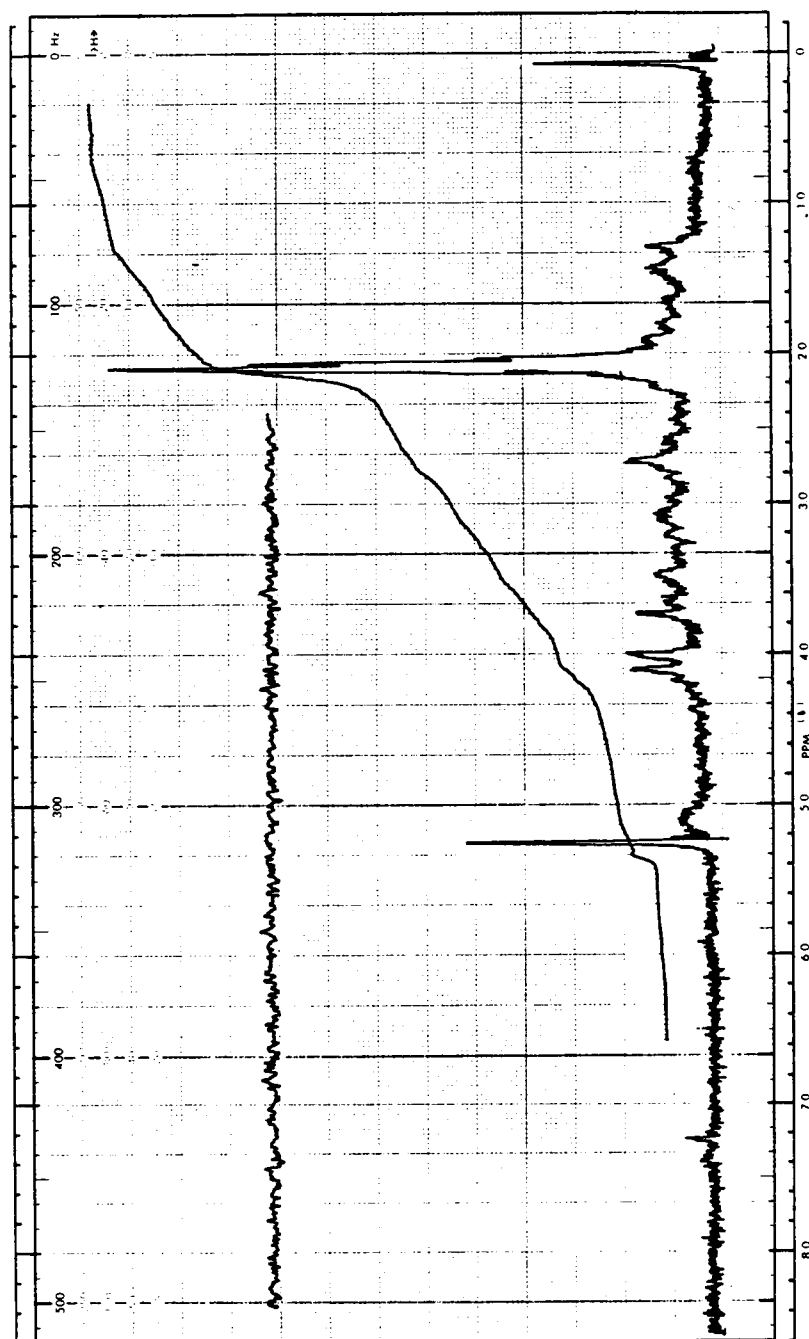


Figure 19. Proton magnetic resonance spectrum of the diacetate corresponding to diol 210 (p 74).

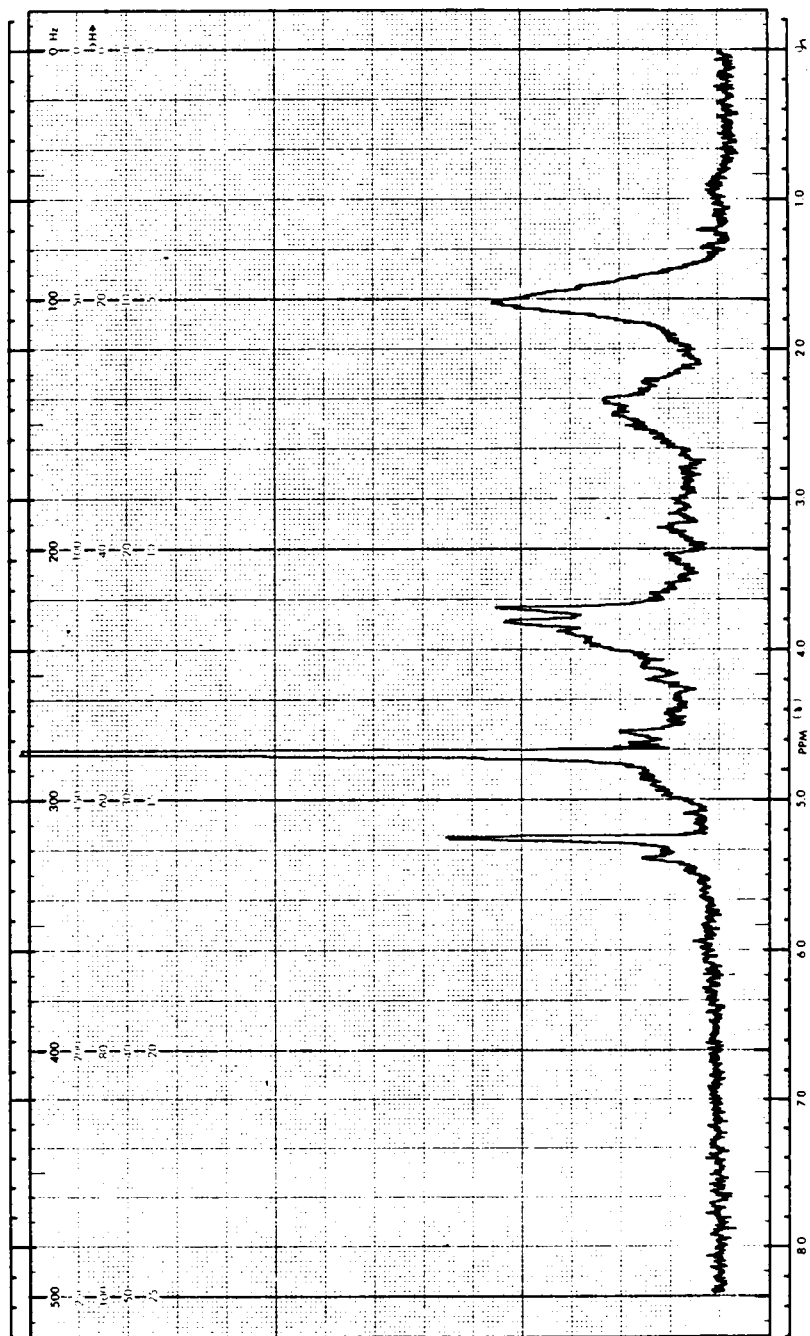


Figure 20. Proton magnetic resonance spectrum of 2β-hydroxymethylene-7β-hydroxy-8α-pyrrolizidine.

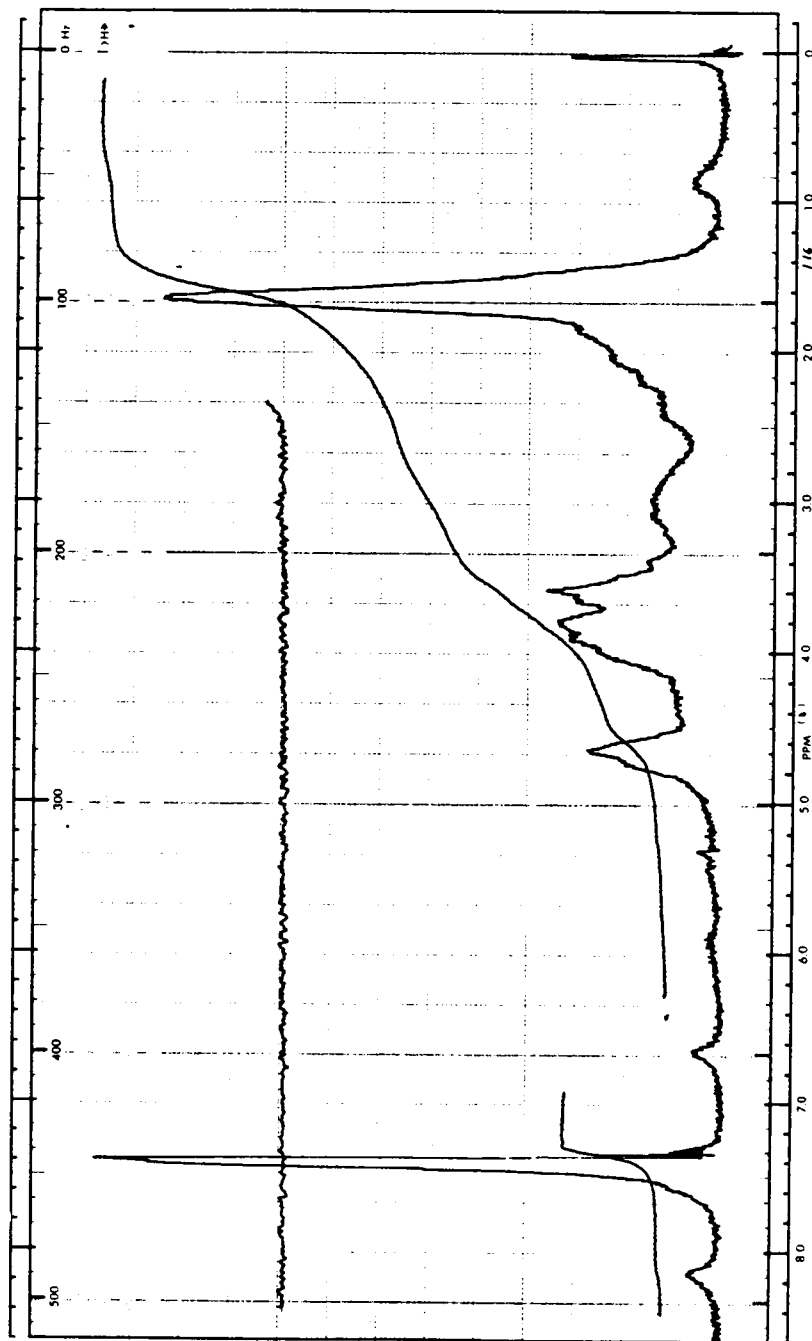


Figure 21. Proton magnetic resonance spectrum of 1,6-cis-8 α -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

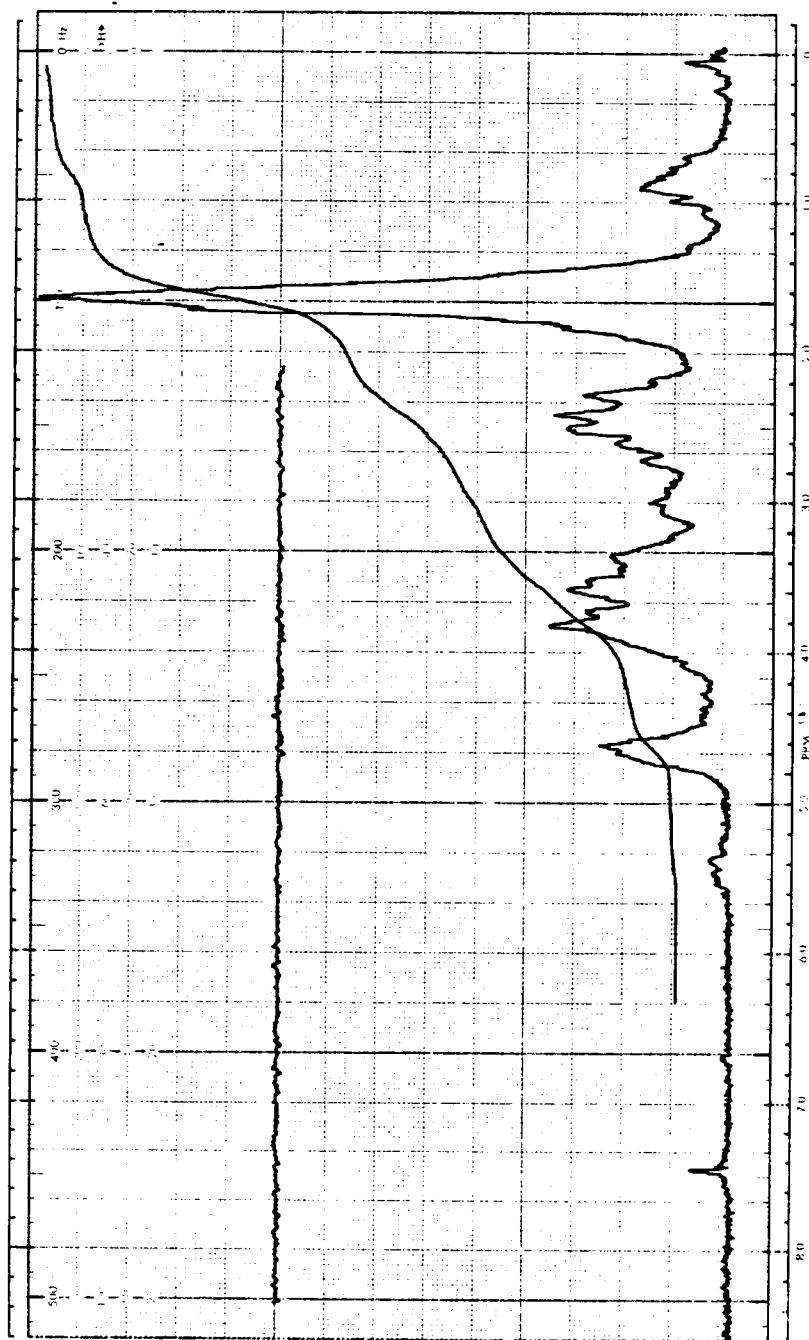


Figure 22. Proton magnetic resonance spectrum of 1,6-cis-8 α -hydroxymethylene-2-azabicyclo[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

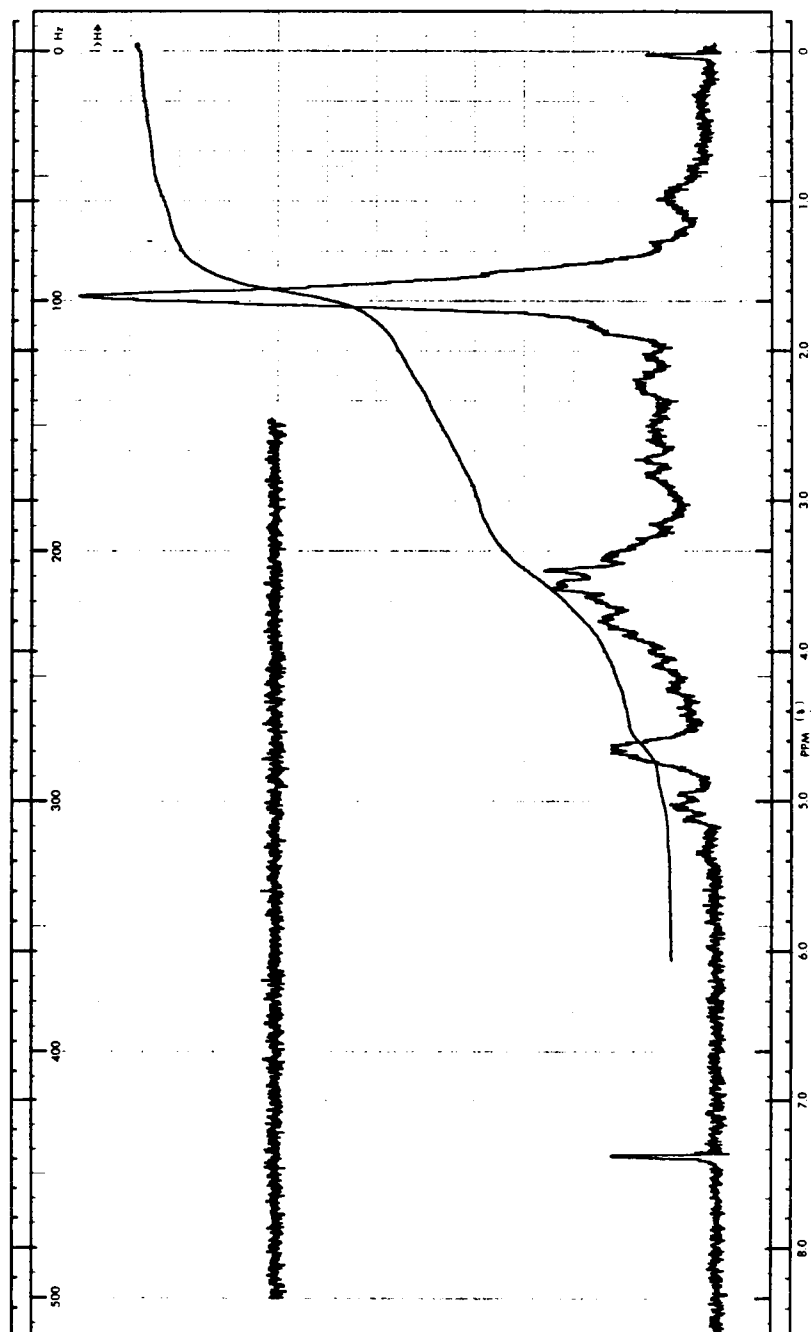


Figure 23. Proton magnetic resonance spectrum of the upper rf material obtained upon rearrangement and reduction of N-chloroamine 209 (p 72).

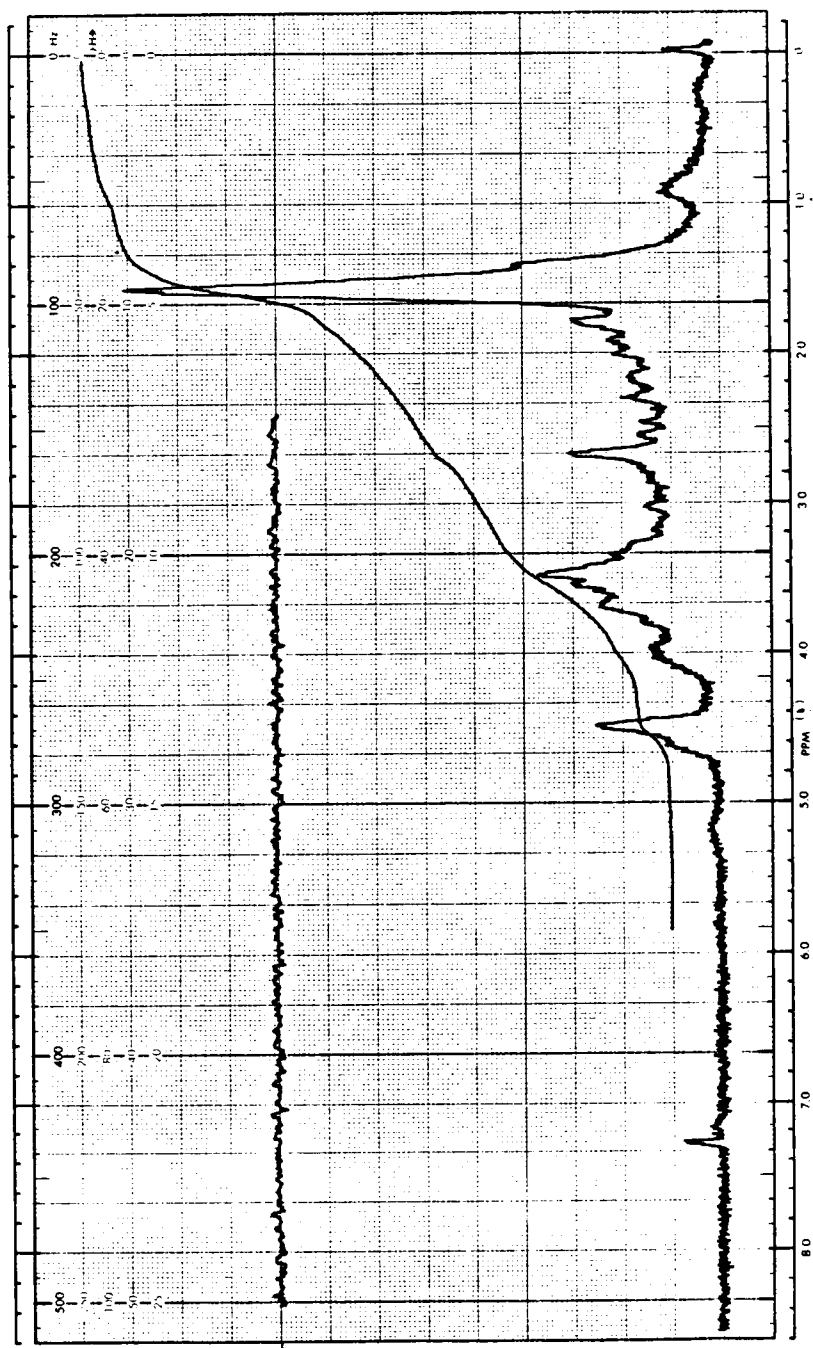


Figure 24. Proton magnetic resonance spectrum of the lower rf material obtained upon rearrangement and reduction of N-chloroamine 209 (p 72).

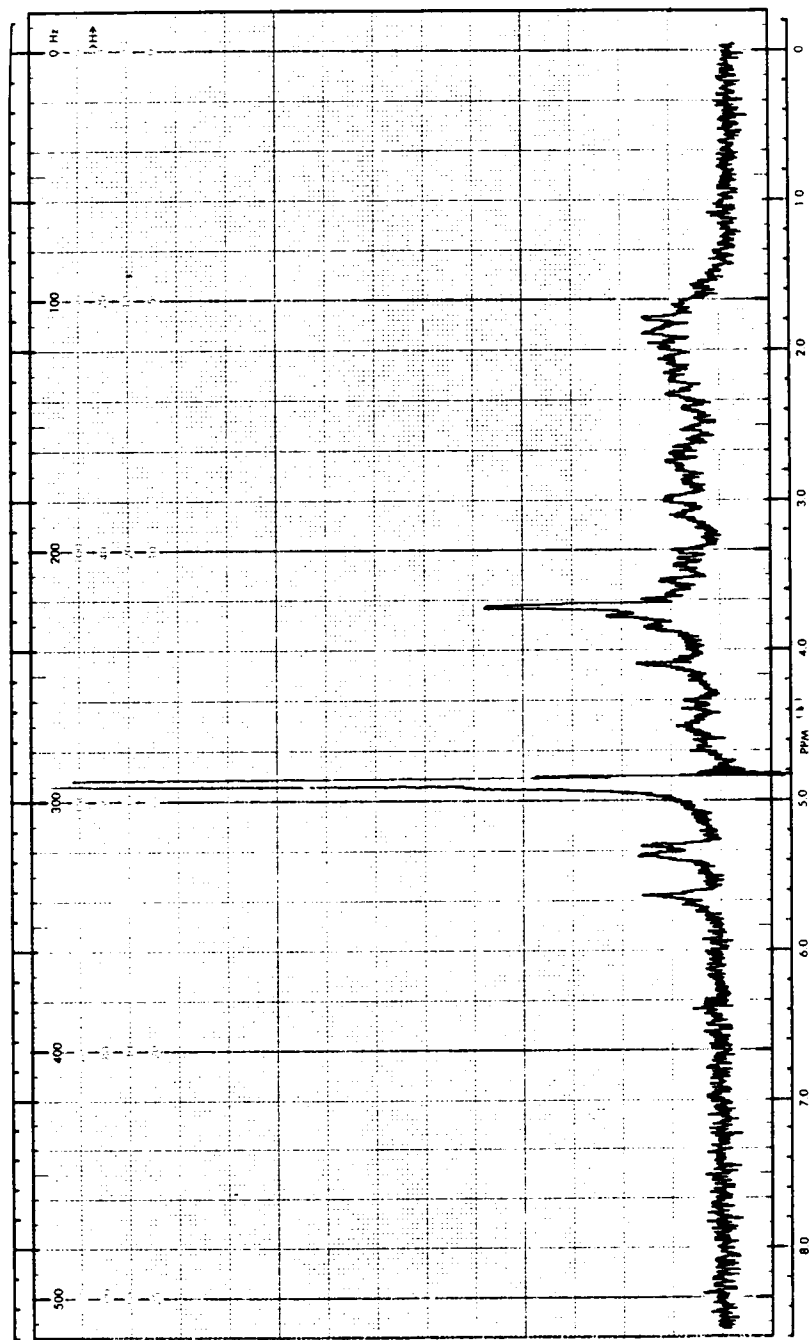


Figure 25. Proton magnetic resonance spectrum of the hydrolysis product believed to be the pyrrolizidine diol 211 (p 75).

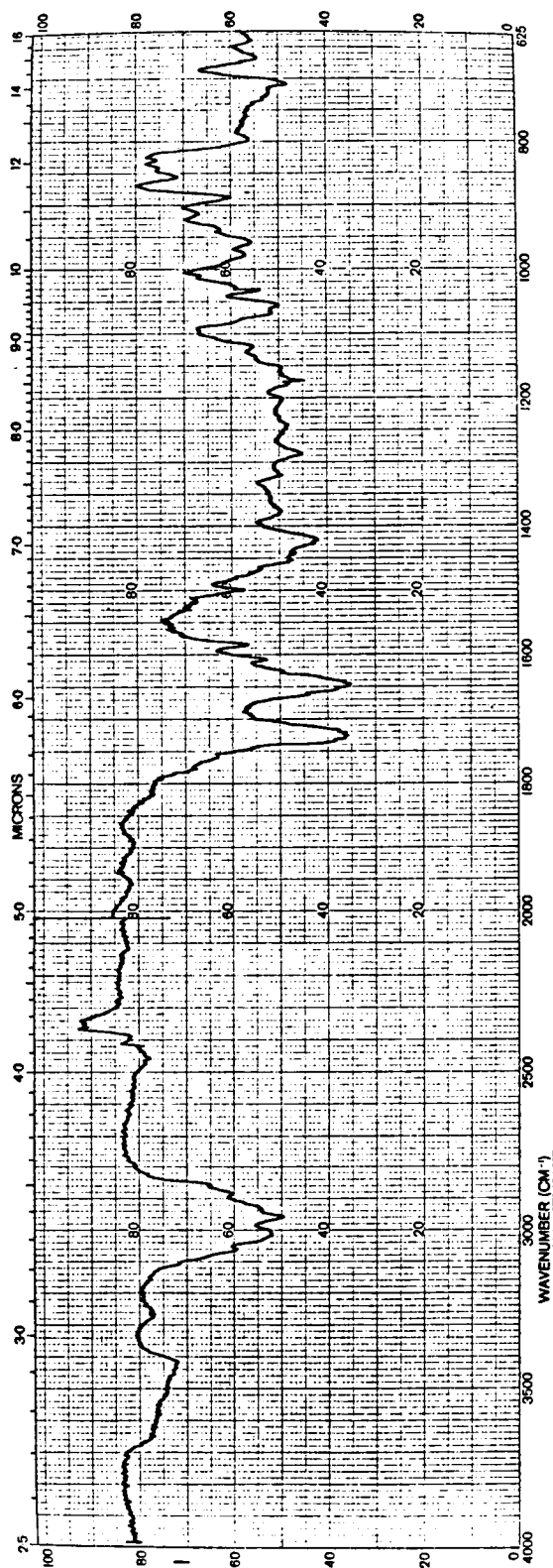


Figure 26. Infrared spectrum of 1,6-cis-8 α -carbomethoxy-2-(N-benzoyl)-azabicyclo[4.2.0]octan-5-one.

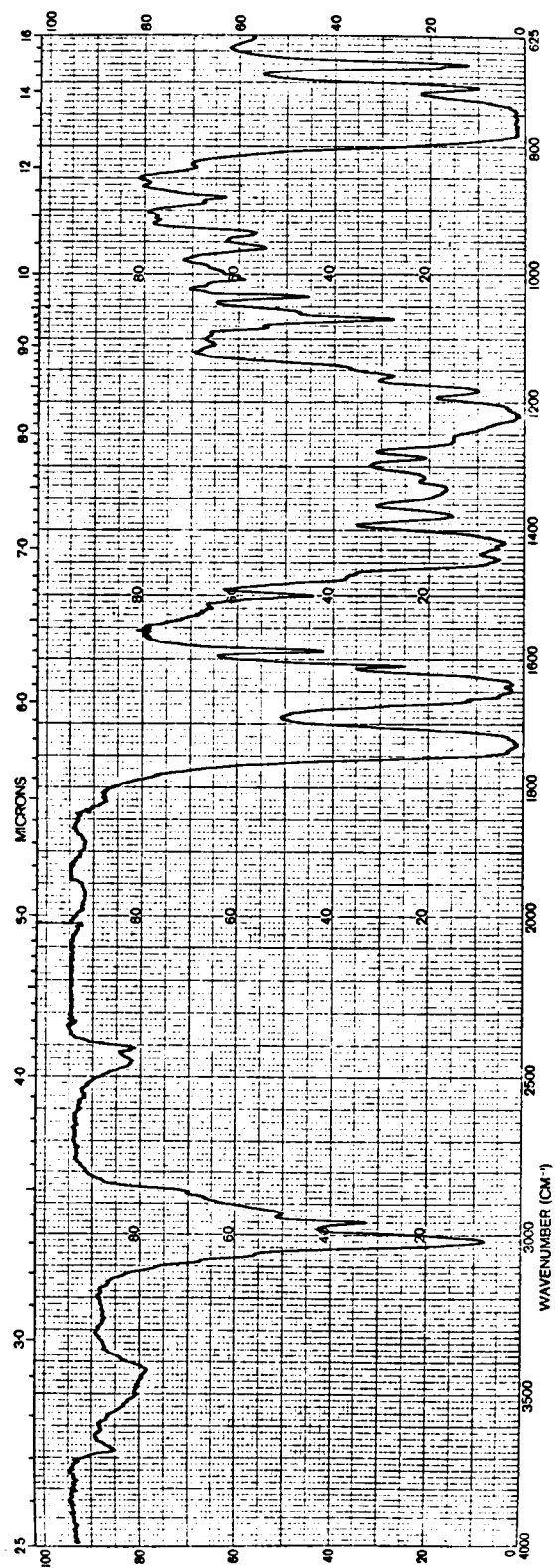


Figure 27. Infrared spectrum of 1,6-cis-8 β -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5-one.

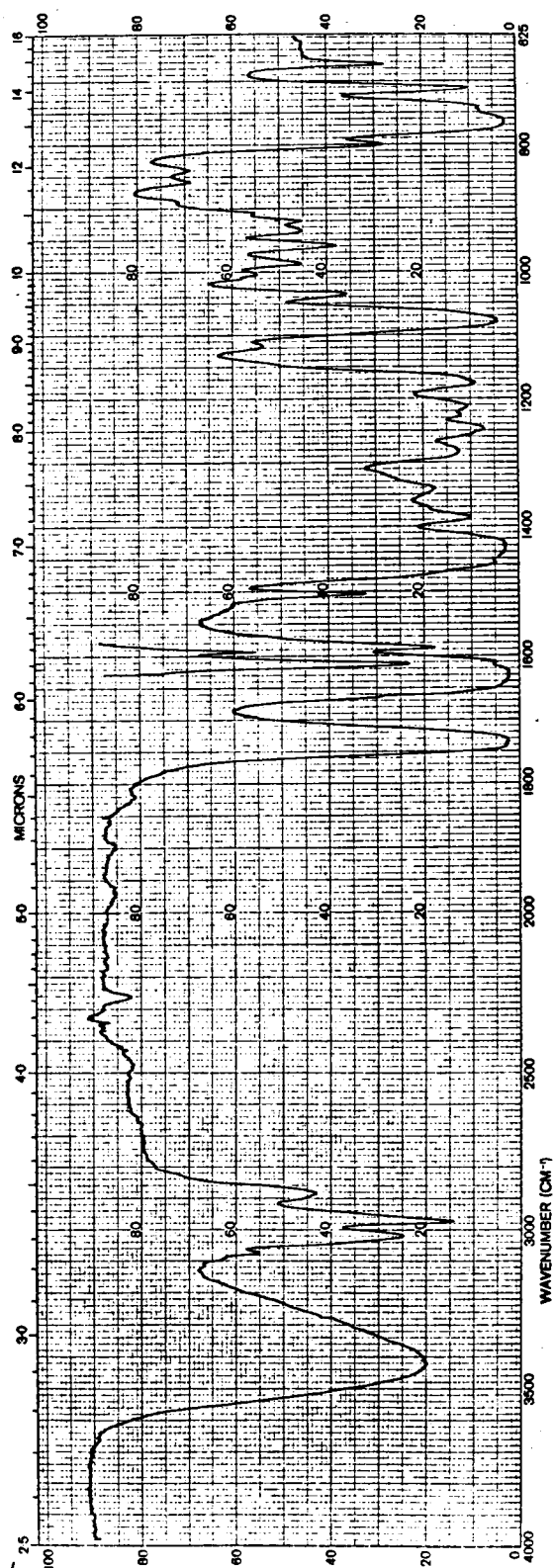


Figure 28. Infrared spectrum of 1,6-cis-8- α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 α -ol

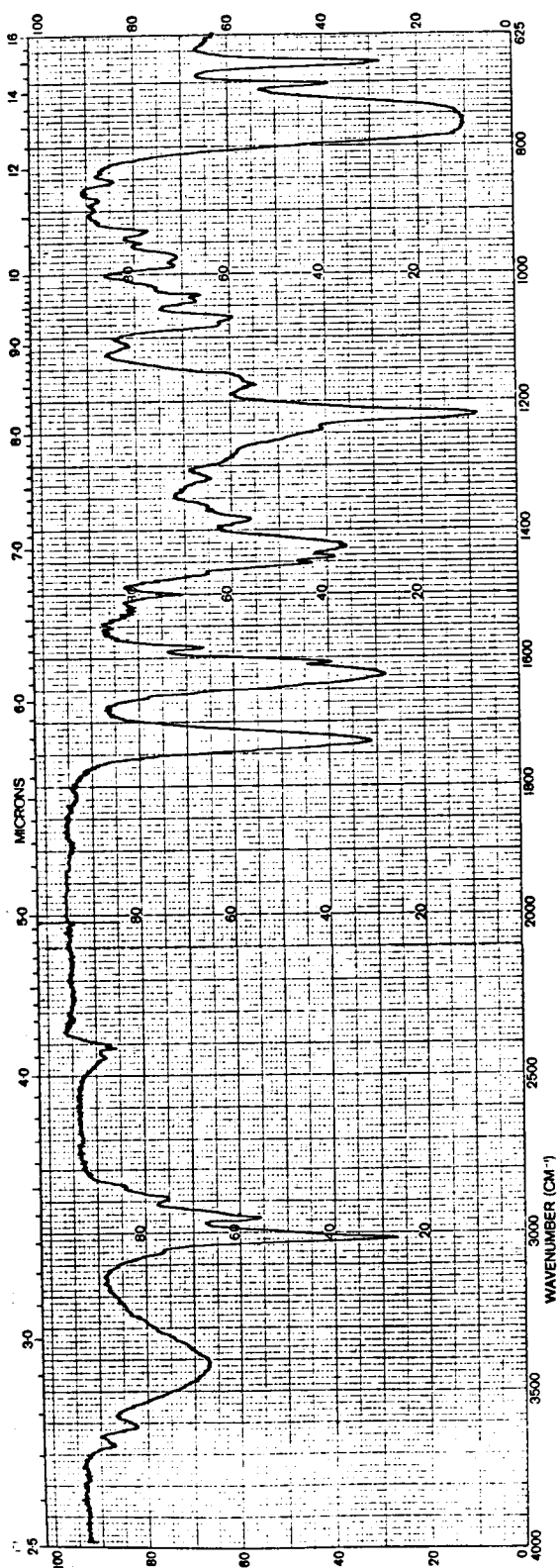


Figure 29. Infrared spectrum of 1,6-cis-8 α -carbomethoxy-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol.

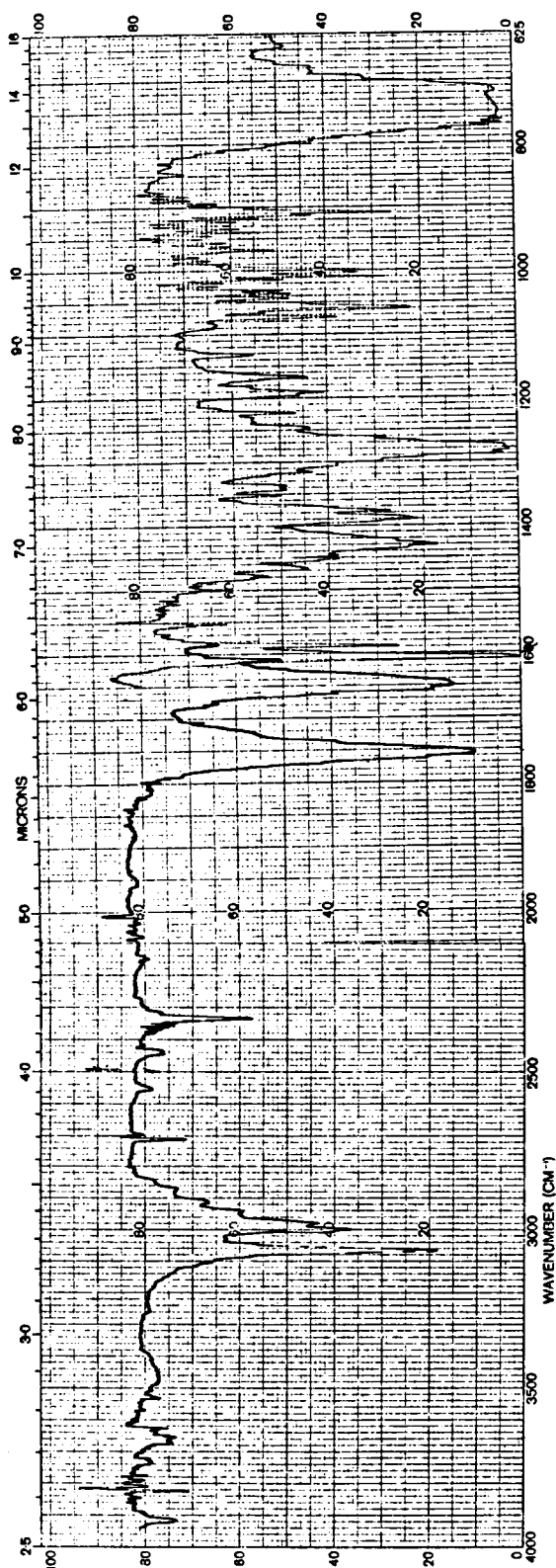


Figure 30. Infrared spectrum of 1,4-cis-1,9-cis-5,9-cis-4,5-cis-6-(N-benzoyl)aza-2-oxatricyclo[4.3.1.0^{1,9}]decan-3-one.

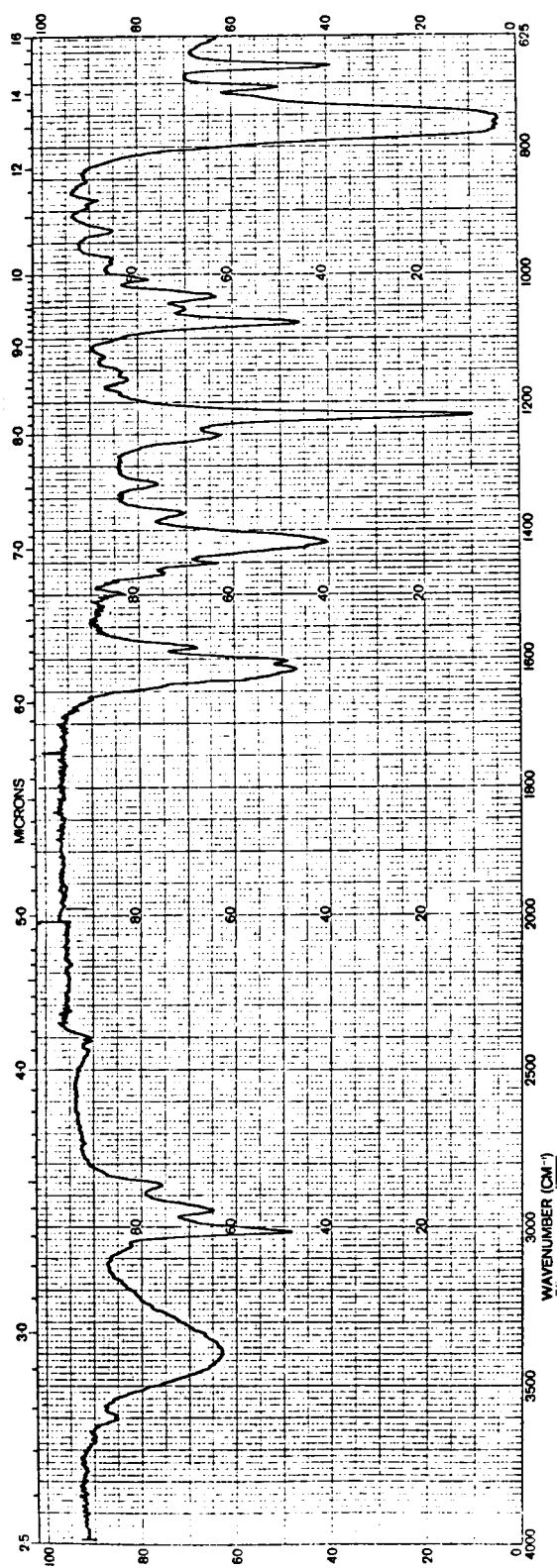


Figure 31. Infrared spectrum of 1,6-cisa-8β-hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5β-ol.

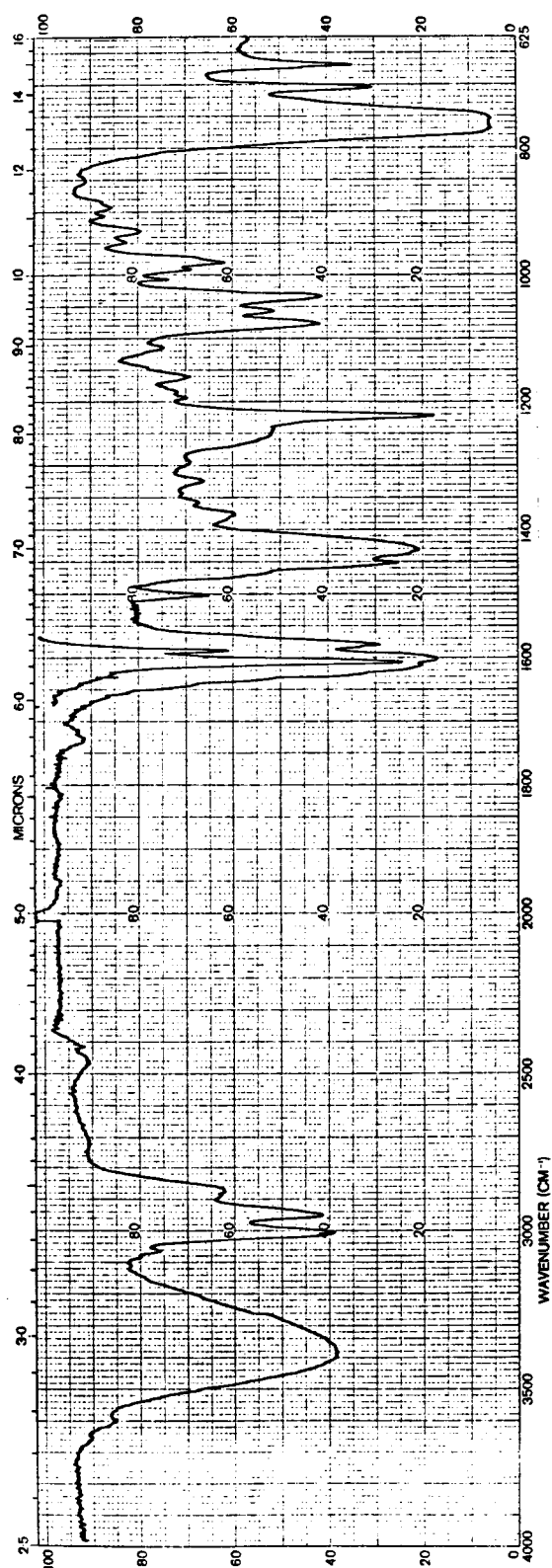


Figure 32. Infrared spectrum of 1,6-cis-8 α -hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5 β -ol.

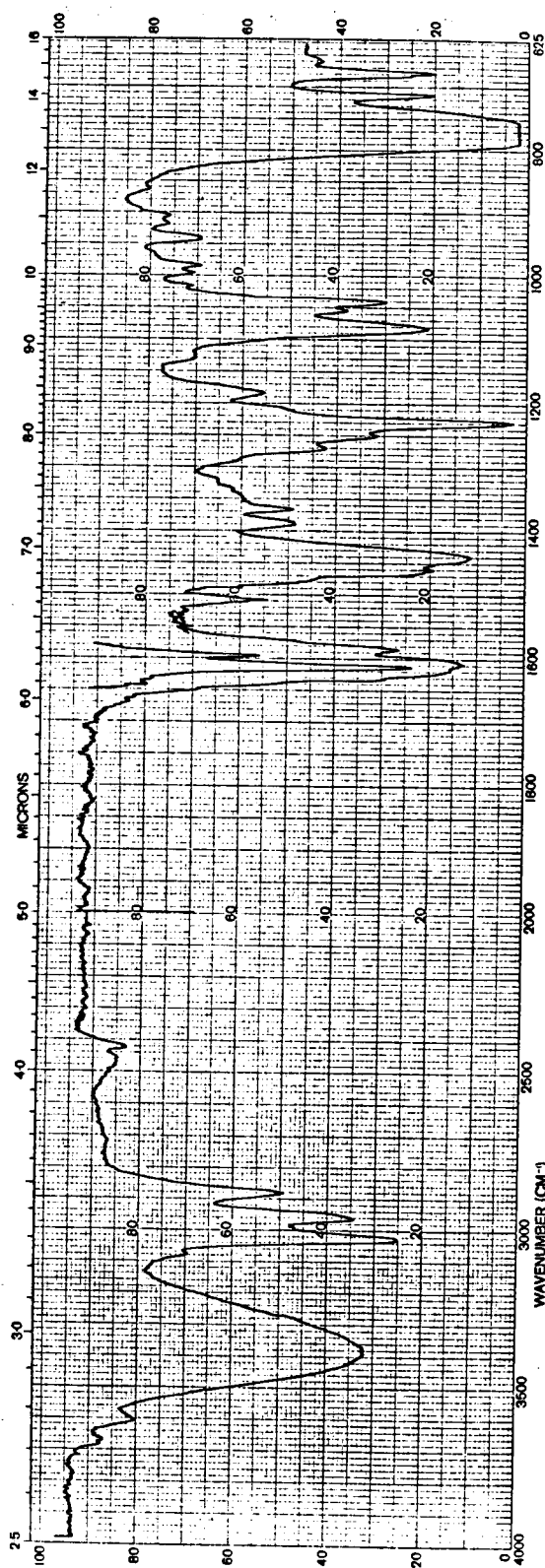


Figure 33. Infrared spectrum of 1,6-cis-8-8-hydroxymethylene-2-(N-benzoyl)azabicyclo[4.2.0]octan-5-ol.

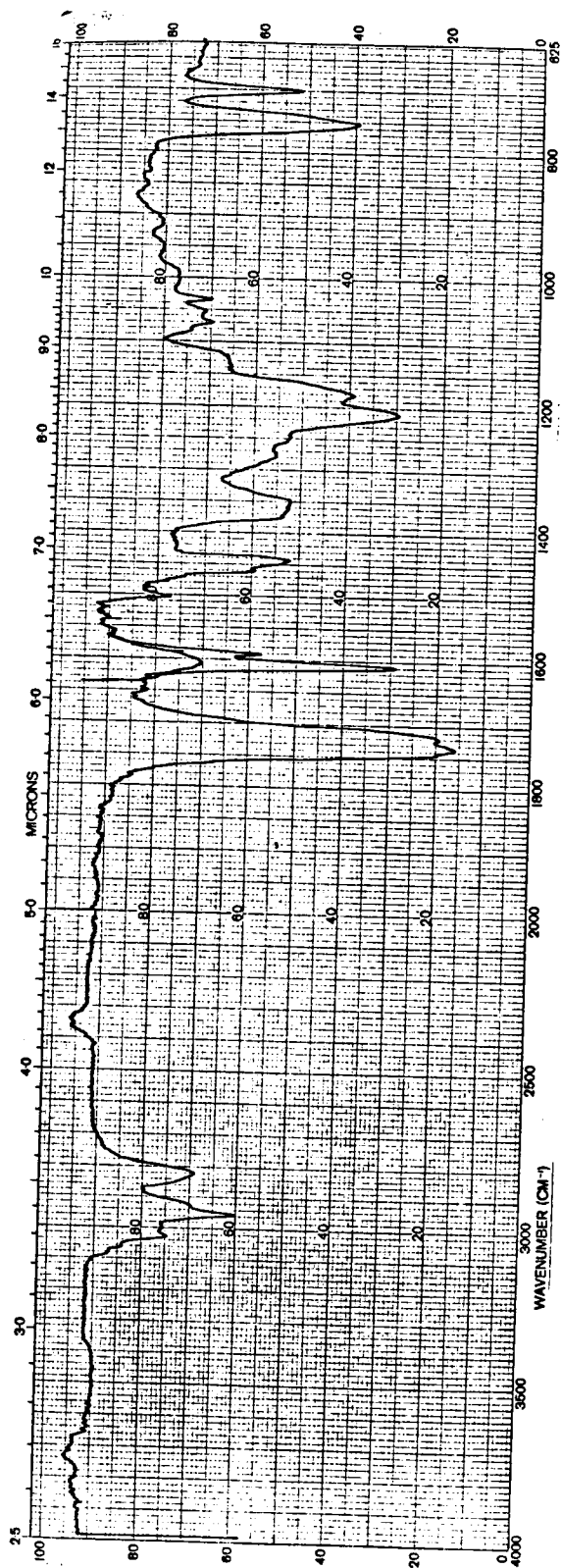


Figure 34. Infrared spectrum of the mixture arising from the photoaddition of vinyllogous amide 212 (p 76) and methyl acrylate, after chromatography.

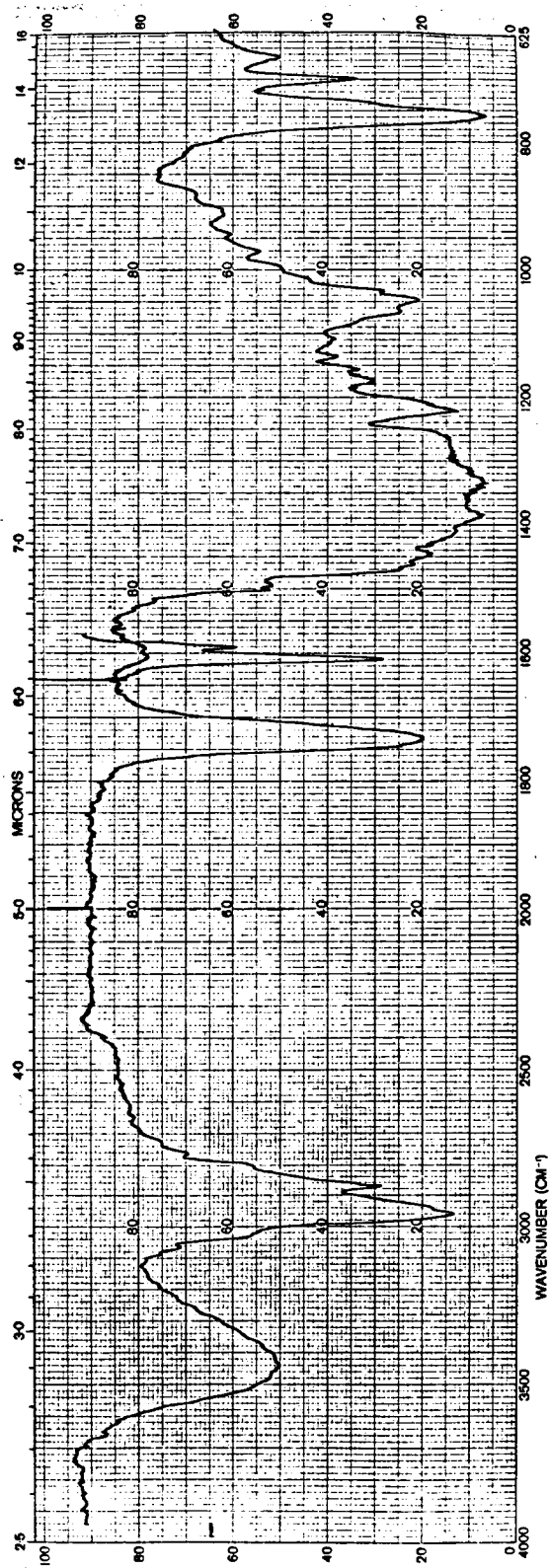


Figure 35. Infrared spectrum of 1,6-cis-7 α -carbomethoxy-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol.

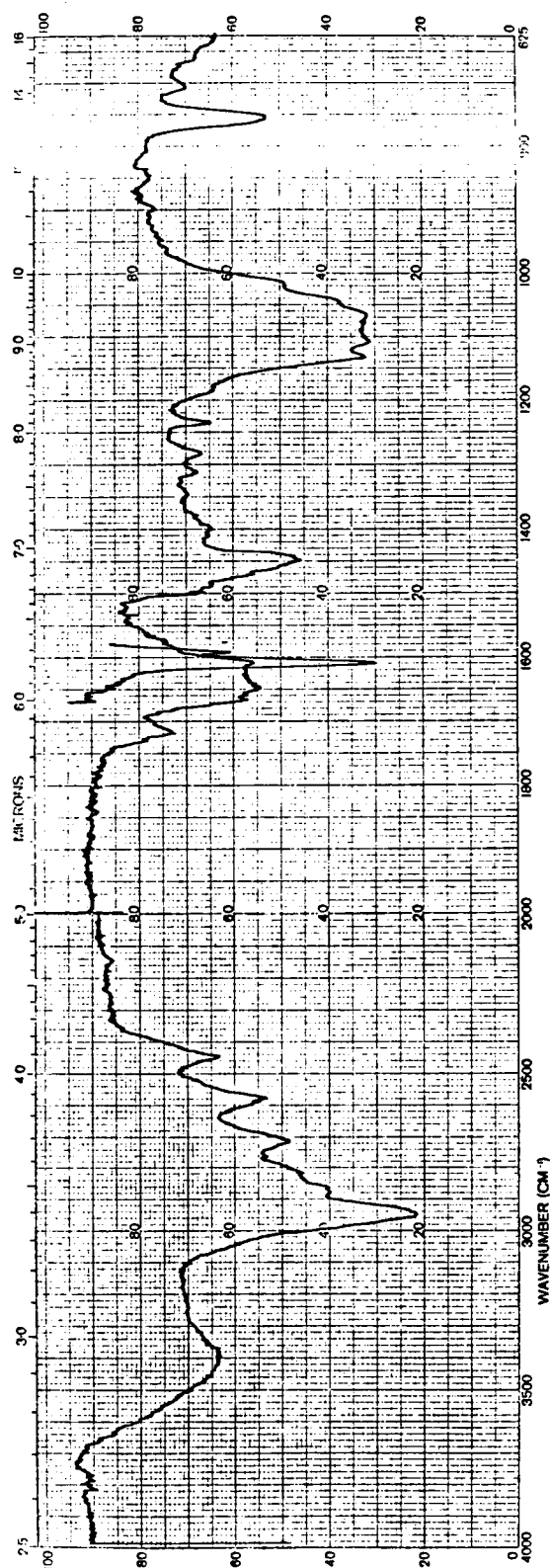


Figure 36. Infrared spectrum of 1,6-cis-7 α -hydroxymethylene-2-(N-benzyl)azabicyclo[4.2.0]octan-5 β -ol.

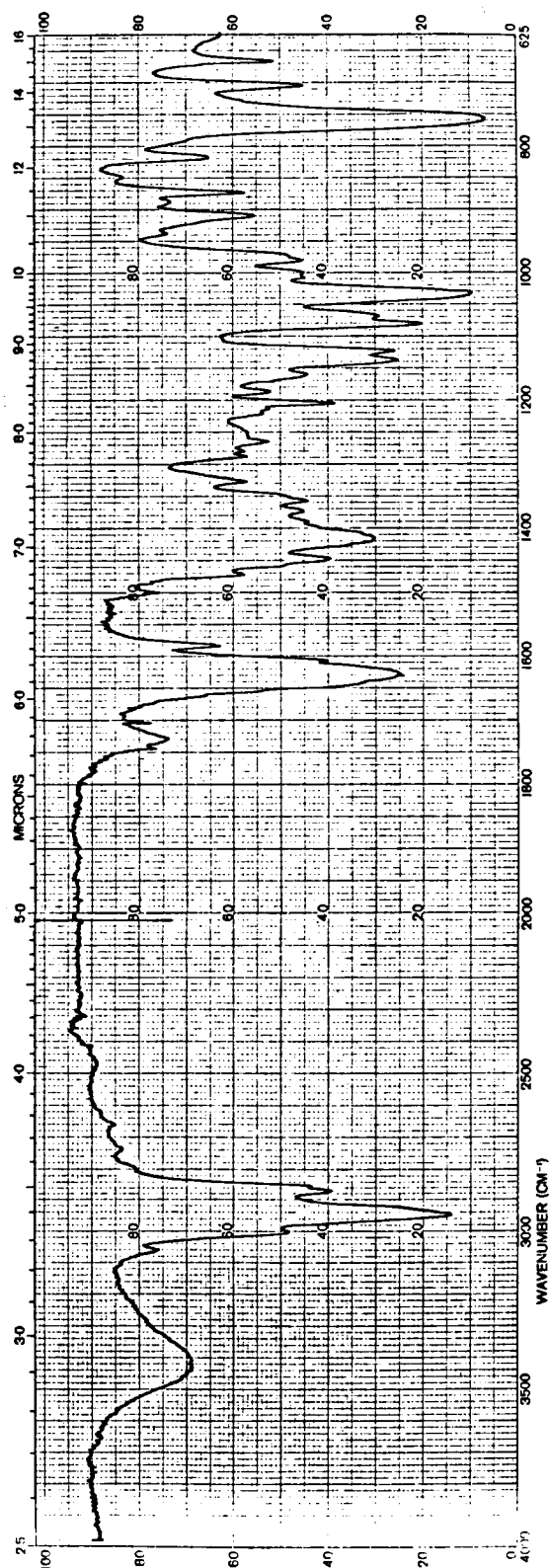


Figure 37. Infrared spectrum of 1,6-cis-8 β -hydroxymethylene-2-(N-benzoyl)azabicyclo-[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

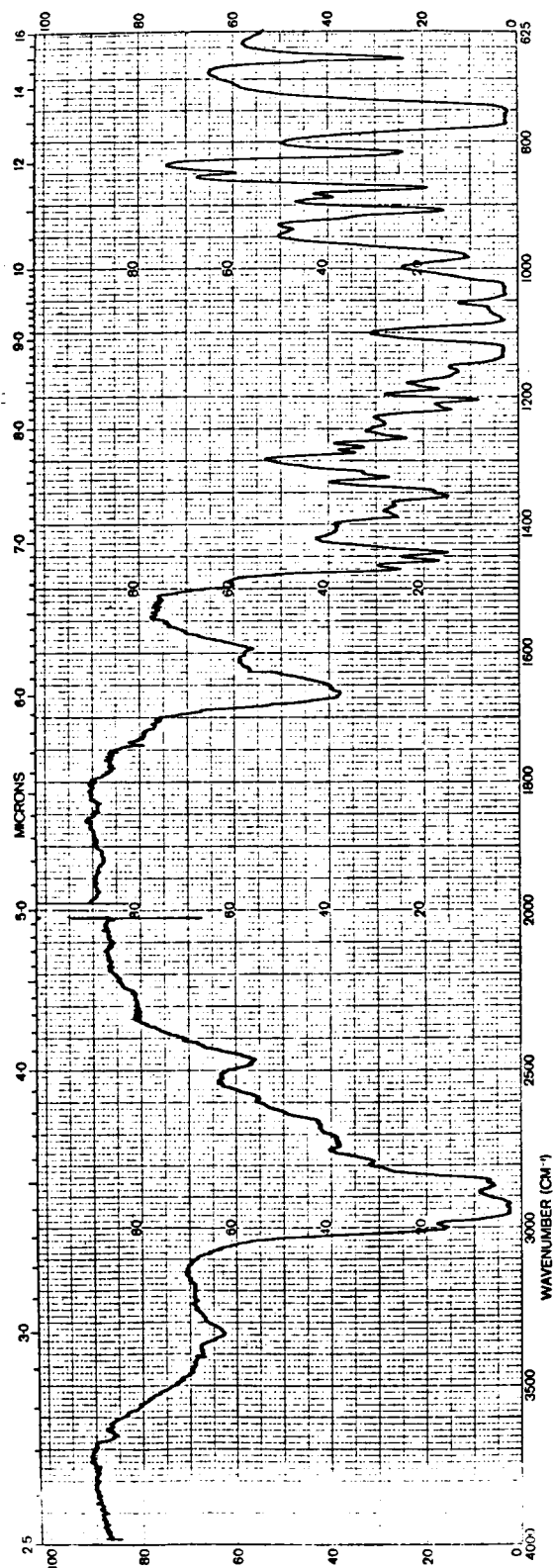


Figure 38. Infrared spectrum of 1,6-cis-8 β -hydroxymethylene-2-azabicyclo-[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

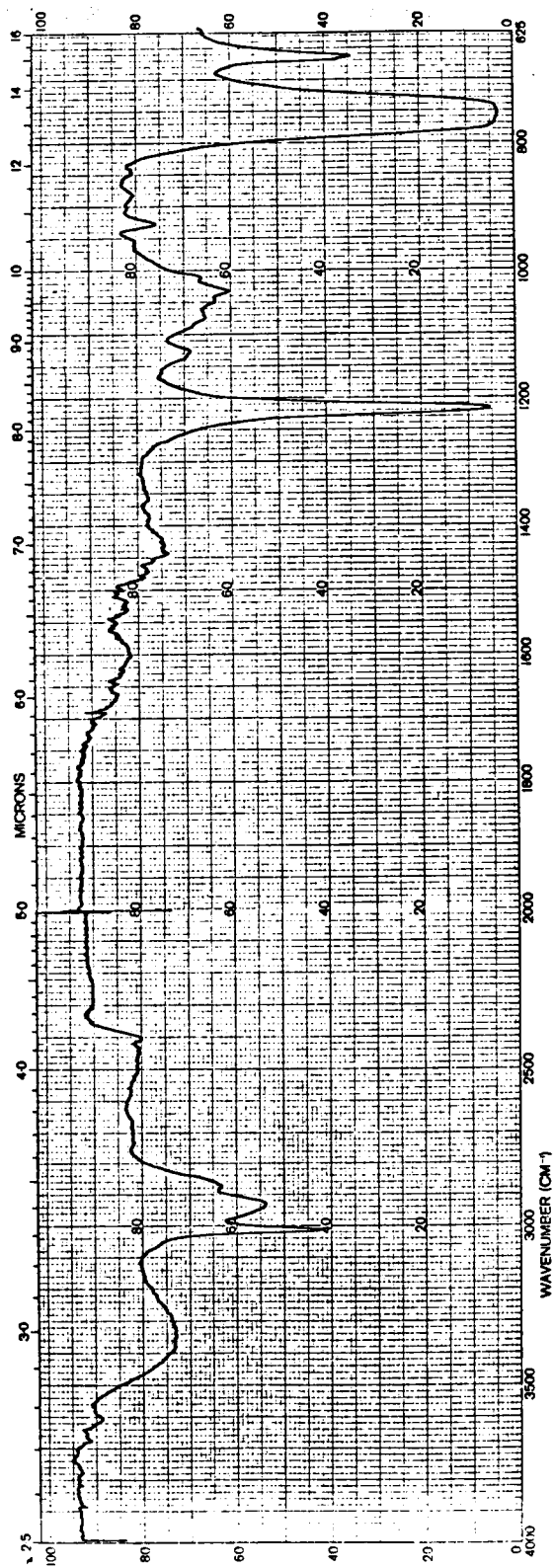


Figure 39. Infrared spectrum of 2β-hydroxymethylene-7β-hydroxy-8α-pyrrolizidine.

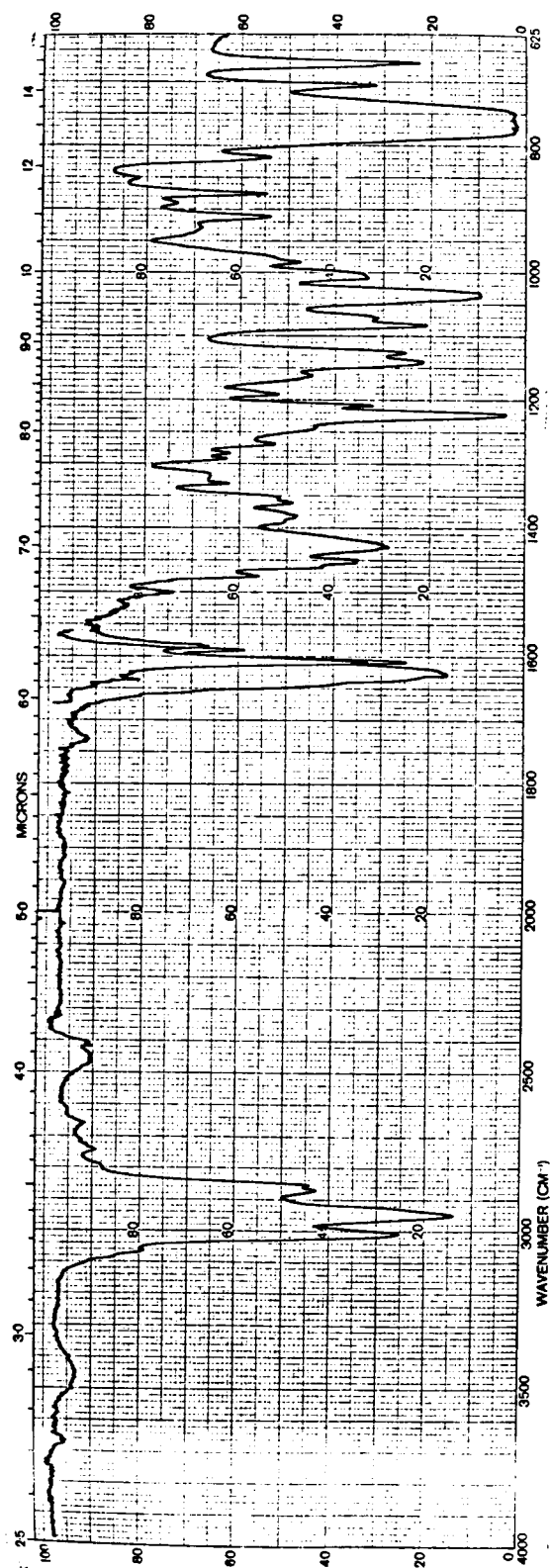


Figure 40. Infrared spectrum of 1,6-cis-8 α -hydroxymethylene-2-(N-benzoyl)-azabicyclo[4.2.0]octan-5 β -ol-5,9-bistetrahydropyranyl ether.

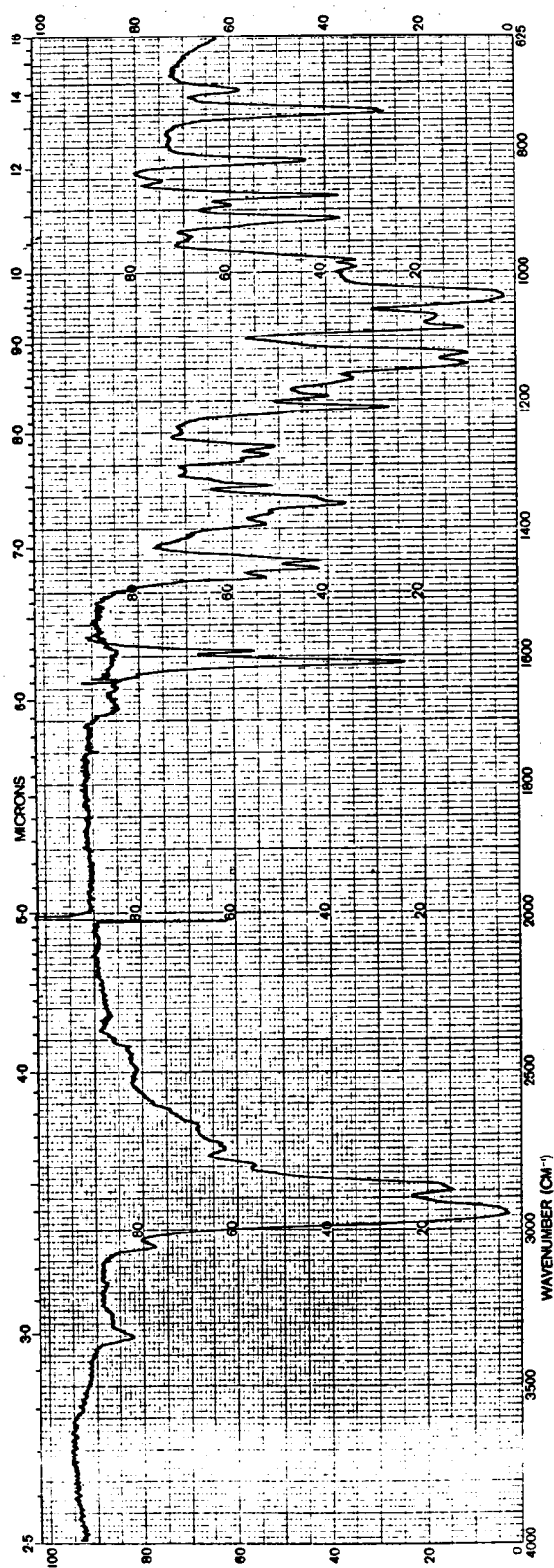


Figure 41. Infrared spectrum of 1,6-cis-8-hydroxymethylene-2-azabicyclo-
[4.2.0]octan-5-ol-5,9-bistetrahydroxyranylether.

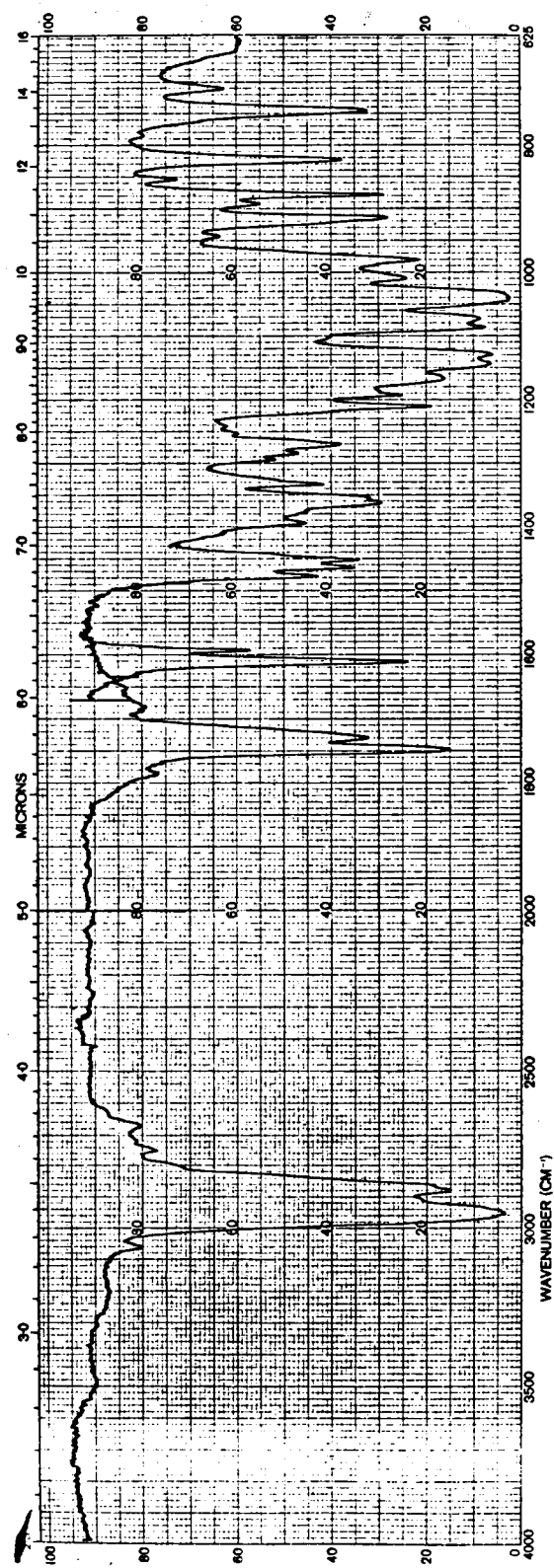


Figure 42. Infrared spectrum of N-chloroamine 209 (p 72).

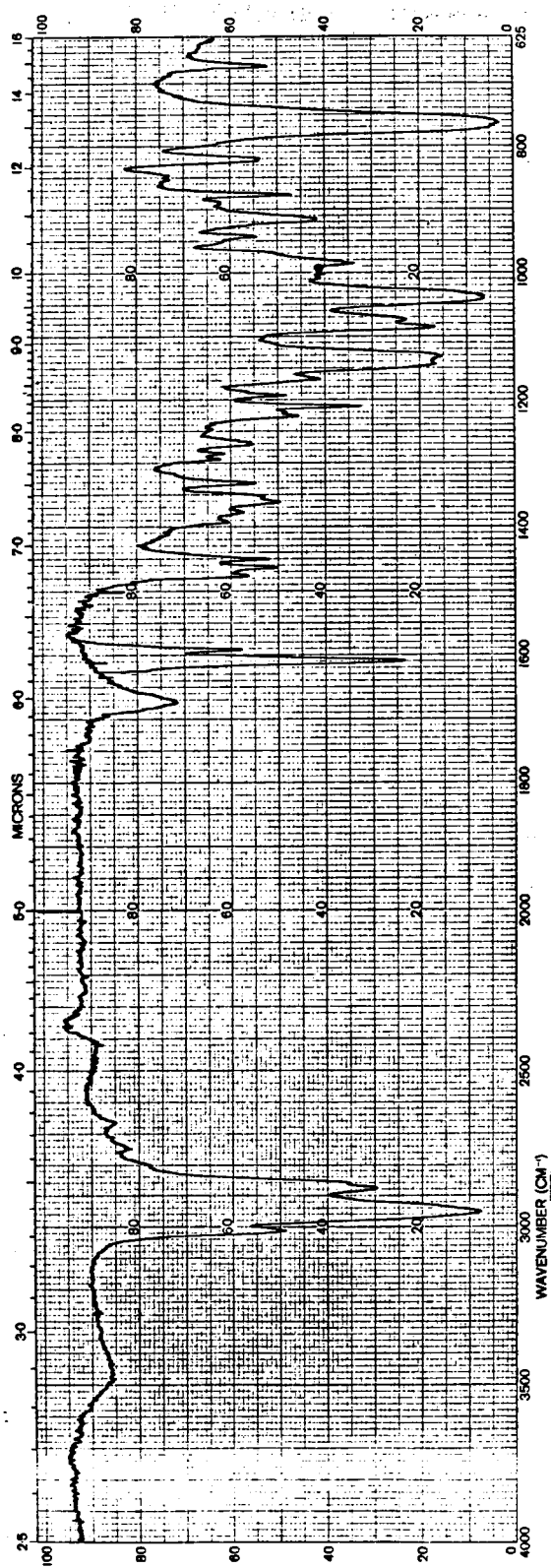


Figure 43. Infrared spectrum of the upper rf material obtained upon rearrangement and reduction of N-chloroamine 209 (p 72).

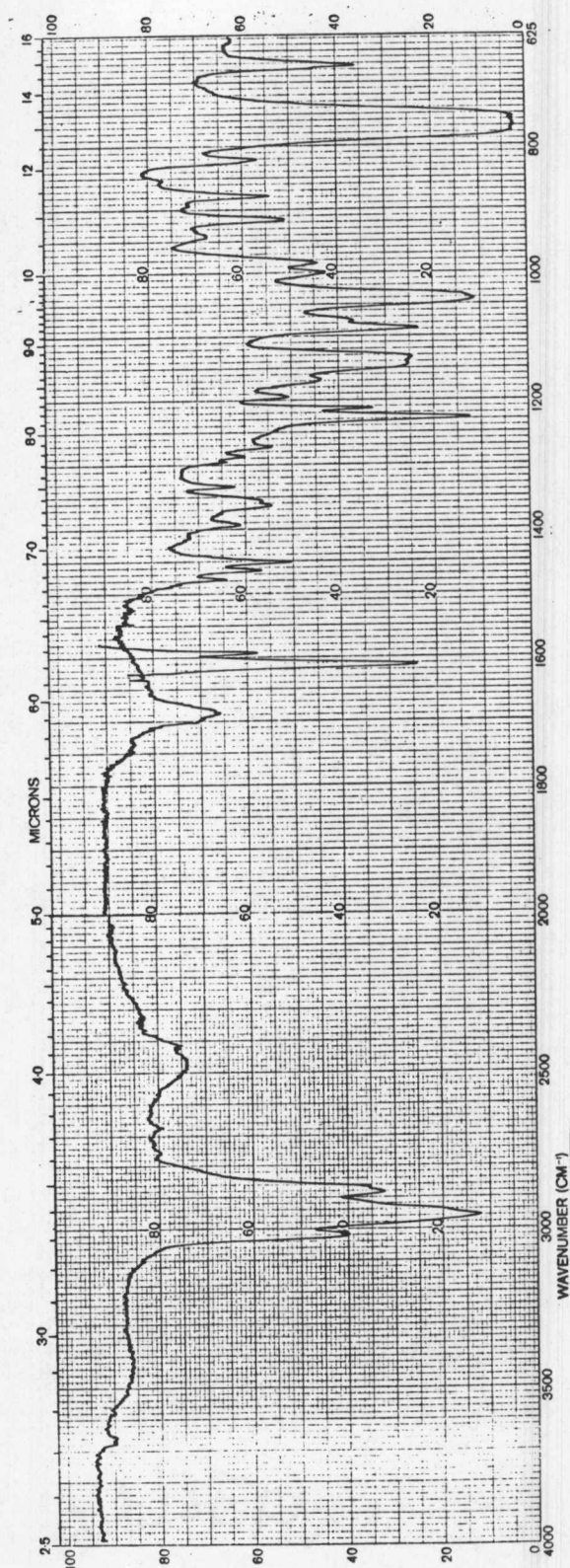


Figure 44. Infrared spectrum of the lower rf material obtained upon rearrangement and reduction of N-chloroamine 209 (p 72).

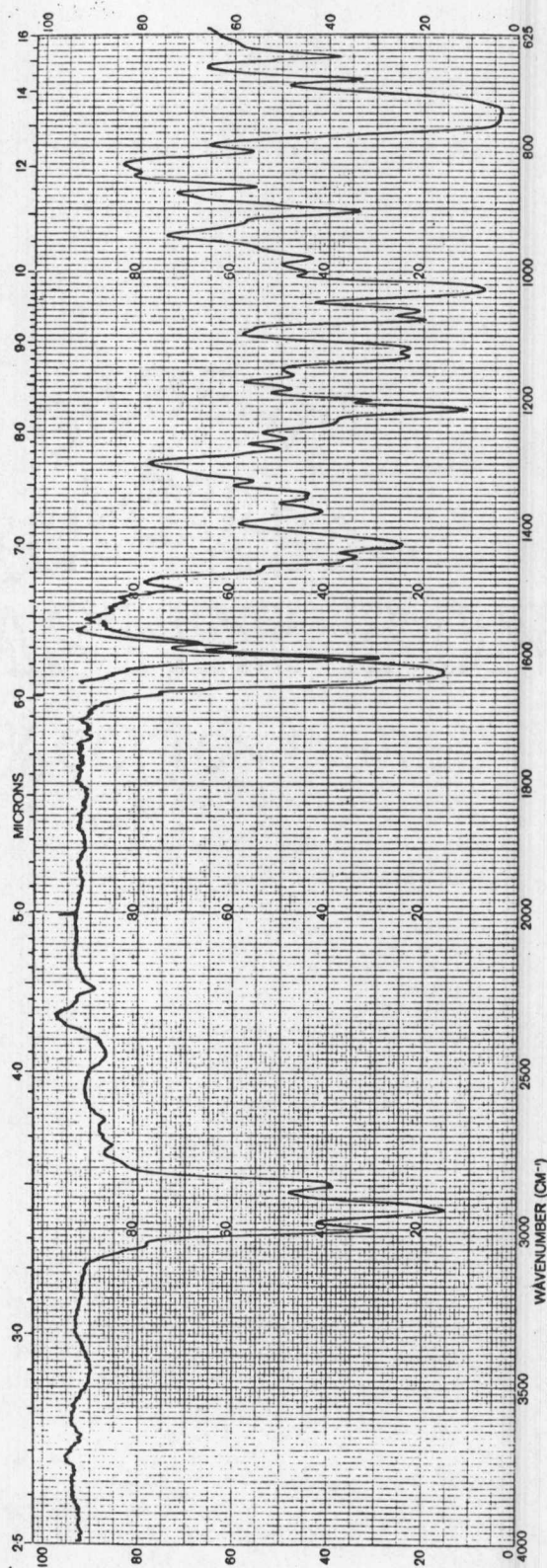


Figure 45. Infrared spectrum of 1,6-cis-8a-hydroxymethylene-2-(N-benzoyl)-azabicyclo[4.2.0]octan-5a-ol-5,9-bistetrahydropranyl ether.

VITA

Paul Randall Williams, Jr. was born on October 1, 1954 in Baltimore, Maryland. He was graduated from Towson Senior High School in June of 1972. The autumn of that year he enrolled at Milligan College and received the Bachelor of Science degree in May of 1976. Two months later he married the former Janice L. Jones from Gahanna, Ohio. In September of 1976, he began his graduate studies in chemistry at The University of Tennessee, Knoxville and was awarded the Master of Science degree in 1980, and Doctor of Philosophy degree in 1982. He and his wife currently reside in Louisville, Kentucky.