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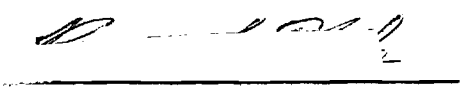

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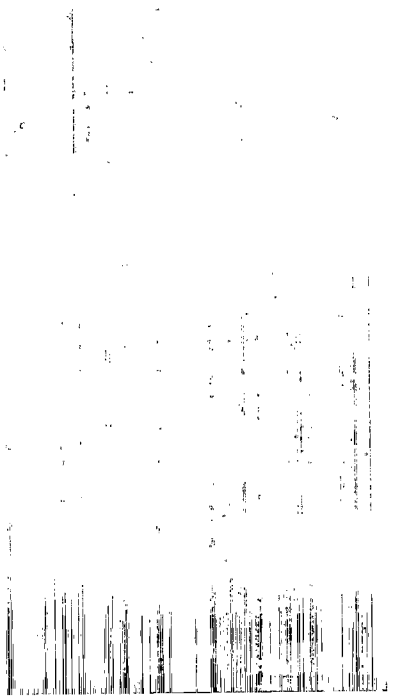

PART I

THE AZIDE-OLEFIN REACTION

PART II

STUDIES IN THE SYNTHESES OF EREMOPHILANE SESQUITERPENES

A THESIS

Presented to

The Faculty of the Graduate Division

by

Ronnie Lee Hale

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

October, 1968

PART I

THE AZIDE-OLEFIN REACTION

PART II

STUDIES IN THE SYNTHESES OF

EREMOPHILANE SESQUITERPENES

Approved:

Chairman

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TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

PART II

TABLE OF CONTENTS (Continued)

LIST OF CHARTS

PART II

LIST OF TABLE

PART I

LIST OF FIGURES

PART I

PART II

GLOSSARY OF ABBREVIATIONS

cps	Cycles per second.
glc	Gas-liquid chromatography.
amu	Atomic mass units.
M^+	Molecular ion in mass spectrum.
ppm	Parts per million.
R_T	Retention time (glc).
tms	Tetramethylsilane.
DMSO	Dimethylsulfoxide.
e.u.	Entropy units.
s	Singlet.
d	Doublet.
q	Quartet.
m	Multiplet.
DNPH	2,4-Dinitrophenylhydrazide.
DNP	2,4-Dinitrophenylhydrazone.
ord	Optical rotatory dispersion.
cd	Circular dichroism.

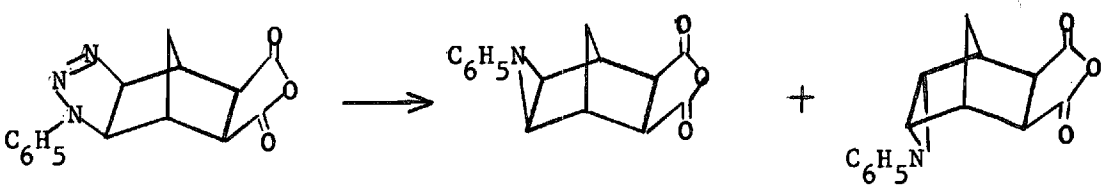
SUMMARY

PART I

Previous reports[30g,i] from this laboratory have described the thermal reactions of benzenesulfonyl azide with bicyclo{2.2.1}-5-heptene-endo-cis (XIXa) and exo-cis (XXIIa)-2,3-dicarboxylic anhydrides which in apparent violation of Alder and Stein's "exo addition rule" yield predominantly endo aziridines. The results of a more thorough investigation[32] of the reaction of benzenesulfonyl azides with these anhydrides and their corresponding dimethyl esters under both thermal and photolytic conditions are now presented. The results of the photolytic reactions are readily explained by initial decomposition of the azide to form the nitrene which adds preferentially to the double bond from the less hindered exo side. The results of the thermal reactions are interpreted in terms of unstable intermediate exo triazolines which give rise to the endo aziridines by a novel carbon-carbon bond fission followed by reclosure to regenerate the norbornyl ring system.

To obtain support for this mechanism the reactions of several azides with these olefins have been investigated with the object of obtaining a stable exo triazoline which could be pyrolyzed to give both exo and endo aziridines. This was accomplished in the pyrolysis of the exo triazoline i in decalin at 160±5°which led to the formation of exo aziridine ii and the previously unreported endo aziridine iii in the ratio 46:54. No additional products were observed by glc. Pyrolyses

of i and the corresponding endo anhydride exo triazoline in diethylene glycol diethyl ether gave complex mixtures. The endo aziridine iii and its dimethyl ester showed characteristic aziridine absorption in the infrared and the nmr spectrum of the dimethyl ester was characteristic of an endo aziridine.



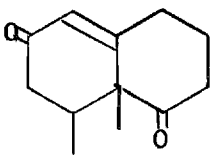
i ii iii

Additional evidence was provided by a preliminary investigation of the temperature dependence of the endo:exo aziridine ratio in the reaction of benzenesulfonyl azide with the exo dimethyl ester and with norbornene. The endo aziridine had not previously[30e,50,18] been detected in the latter reaction.

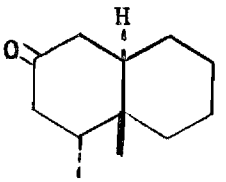
PART II

The Robinson annelation reaction of 2-methyl-1,3-cyclohexanedione with trans-3-penten-2-one has been investigated as a means of obtaining the bicyclic diketone iv. The structural features of this important intermediate would be suitable for its conversion to a number of the eremophilane sesquiterpenes. The major product of the reaction however, was the isomer which possessed trans methyl groups rather than the cis configuration common to all of the eremophilane sesquiterpenes. A number of chemical transformations have been carried out on iv. The trans configuration was indicated by chemical and physical evidence[54] and was estab-

lished[75] in the present study by conversion of racemic iv to the racemic ketone v which was partially resolved by means of its l-menthydrazone derivative[63]. The relative and absolute stereochemistry of the regenerated ketone was established by means of optical rotatory dispersion. An important by-product of the ord studies, the question of ketal vs. hemiketal formation on treatment of a methanol solution of 3-cholestanone with hydrochloric acid has been settled.



iv



v

In addition the correlation of hydroxydihydroeremophilone and dihydroeremophilone has been investigated.

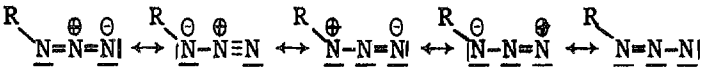
PART I

CHAPTER I

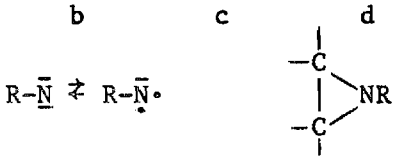
INTRODUCTION

The preparation of the first organic azide (I) over 100 years ago[1] marked the beginning of investigations into the fascinating chemistry of these relatively stable systems of three adjoining nitrogen atoms. The stability of the azides is due to their considerable resonance energy as depicted by contributing structures Ia-e. The Curtius degradation of acyl azides is representative of the interesting reactions discovered in the rapid early development of azide chemistry. More recently, the activity in carbene chemistry has led to renewed interest in the analogous monovalent nitrogen species (II) known variously as nitrenes[2], imidogens, imido intermediates, etc.[3] The chemistry of the nitrenes was thoroughly reviewed by Abramovitch and Davis[3] in 1964. Lwowski[2] has subsequently studied the chemistry of carboethoxynitrene produced by photolytic and thermal decomposition of ethylazidoformate or produced by α-elimination from the N-p-nitrobenzenesulfonate of ethyl carbamate. This author found that the photolytic process produced the nitrene in both singlet (IIa) and triplet (IIb) states in a ratio of approximately 2:1 while the latter two processes produced only singlet nitrene which, rapidly decayed to the triplet ground state. Of particular interest was the observation that both triplet and singlet states added to double bonds to produce aziridines (III); the triplet added non-stereospecifically while the singlet added in a stereospecific manner. It was also observed that the singlet nitrene inserted into carbon-hydrogen bonds

while the triplet did not. Also of interest to the present study, as will be discussed later, are the recent results of Abramovitch and co-workers[4] which illustrate similar properties for sulfonyl nitrenes.



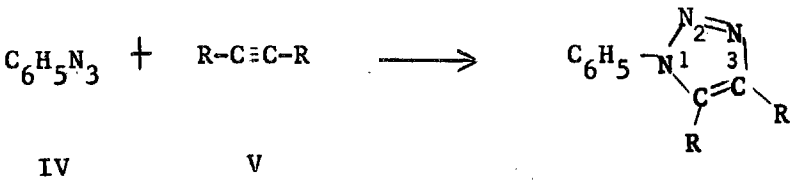
Ia b c d e



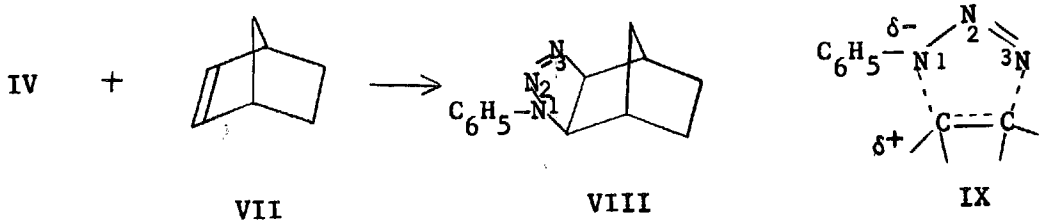
IIa IIb III

A reaction of azides which has received much attention because of its synthetic utility is the addition to unsaturated compounds. This property was first noted by Michael[5] who in 1893 reacted phenyl azide (IV) with acetylene derivatives (V) and isolated the corresponding 1-phenyl-1,2,3-triazoles (VI). Addition of azides to olefinic linkages was introduced later by Wolff[6] who obtained a mono- and two bis- adducts upon reaction of phenyl azide with p-benzoquinone. Alder and Stein[7] later found that the strained double bonds of bicyclo{2.2.1}heptene (VII) and its derivatives reacted rapidly with phenyl azide to yield crystalline Δ^2-1,2,3-triazolines (VIII) and these workers developed the reaction as a diagonostic test for such strained bonds. The strained double bond of trans-cyclooctene also adds phenyl azide exothermically while the cis isomer and the higher trans cyclic olefins react more slowly[8]. Alder and Stein[9] were unable to obtain an adduct with cyclohexene and until recently the reaction of unstrained olefins with azides has received little attention. In 1965, Logothetis[10] synthesized alicyclic organic azides with unstrained double bonds three and four carbons removed from the azide

function and found that thermal decomposition gave intramolecular addition. More recently Scheiner[11] has shown that addition of azides to unstrained olefins under the proper conditions provides a convenient route to alkyl substituted triazolines. Conjugated olefins[12] and the electron-rich double bonds of vinyl ethers[12,13] and enamines[14] also react readily with azides. The addition of electronegatively substituted azides to allenes was reported very recently.[15]



IV V VI

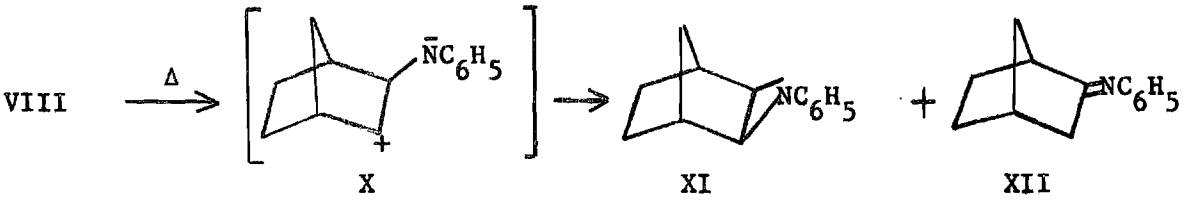


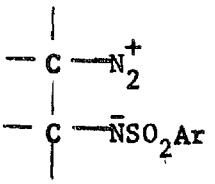
VII VIII IX

In recent reveiws[12,16] Huisgen and his associates have found that the azide-olefin reaction falls within the reaction type which they refer to as "1,3-dipolar cycloaddition". Because of the small dependence of rate on solvent polarity, these workers suggested a concerted addition of the azide to the olefin. Scheiner and coworkers[18] later made a kinetic investigation of the reaction of substituted phenyl azides with norbornene and found large negative entropies of activation ($\Delta S^* = -29$ to -32 e.u.) as expected for the highly ordered transition state (IX) of a concerted addition. These workers also observed a sizable substituent effect ($\rho = +0.84$) which they attributed to the development of a partial negative charge on N-1 in the transition state since electron-withdrawing substituents enhanced the rate of reaction. Thus, they proposed that bond formation proceeds unevenly with the transition state (IX) having the

terminal nitrogen (N-3) more completely bound to the olefin. The orientational effects observed in the reactions of enamines[14] and enol ethers[12,13] are in accord with a Markownikoff addition involving an initial electrophilic attack by the terminal nitrogen (N-3).

There has been considerable interest recently in the decomposition of Δ^2-1,2,3-triazolines as a synthetic route to substituted aziridines. By far the most desirable mode is photodecomposition[18,19,20] which in most cases leads to quantitative formation of aziridines. This reaction has been described[19b] as proceeding through 1,3 diradical intermediates. The triazolines formed from phenyl azide and the bicycloheptene series are relatively stable to heat but decompose above about 150°C to give mixtures of aziridines (XI) and imines (XII). These products were presumed to arise via the zwitterionic intermediate X[12,16] which could stabilize itself through closure to an aziridine or by hydride shift. A slightly different but analogous diazonium-betaine intermediate of the type XIII was proposed by Fusco[21] et al. to account for the formation of diazomethane in the decomposition of triazolines derived from certain enamines.





XIII

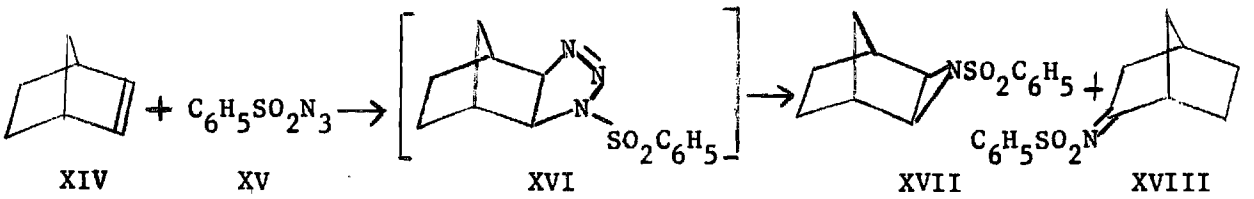
Kinetic data recently reported[10,22-24] offer support for an intermediate of the type XIII in the thermal decomposition of isolable triazolines. Thus, Logothetis[10] found that the rate of nitrogen evolution from triazolines formed by intramolecular reaction of olefinic azides increased 10-fold when nitromethane and 20-fold when aqueous diglyme were substituted for toluene as solvents. Zalkow and coworkers[22,23] observed similar results in the pyrolysis of the triazoline formed by addition of methyl azidoformate to norbornene. Thus, the relative rates of decomposition in 1,1-diphenylethane, triglyme and dimethyl sulfoxide were found to be 1:3:20, respectively. These authors also pointed out that a hydride shift should be a slow[25] process compared to Wagner-Meerwein rearrangement for stabilization of XIII and proposed[23] the alternative proton transfer from C-1 to the nitrogen anion followed by isomerization of the resulting enamine to the imine. Berlin et al.[24] recently studied the decomposition of the triazoline formed from diethyl phosphorazidate and norbornene and interpreted their results in terms of a reaction scheme involving two consecutive first order reactions with accumulation of an intermediate of type XIII in the early stages of the reaction.

The addition of azides to olefins generally leads to formation of stable triazolines, however, when the azides contain strongly electron-withdrawing groups aziridines and imines are usually isolated directly from the reaction even at room temperature or below. This observation was first noted by Bruner[26] in his study of the reactions of p-toluenesulfonyl azide with various bicyclic alkenes. While different mechanisms may be proposed[27] for these reactions the accumulated evidence favors the

usual 1,3-dipolar addition to form Δ^2-1,2,3-triazolines which are unstable because the electron-withdrawing power of the group at N-1 stabilizes the diazonium-betaine intermediate XIII. Thus, Bailey and White[28] found entropies of activation (ΔS^*=-27 to -36e.u.) for a number of reactions where triazolines could and could not be isolated which were all indicative of a highly ordered transition state. In addition, these workers found that while phenyl azide and norbornene gave a triazoline which was stable to above 150°C, attachment of nitro groups to the aromatic ring led to decreased stability of the product, and picryl azide gave no triazoline but led directly to the aziridine. Similarly, while benzyl azide gave a stable triazoline with norbornene,[18] benzoyl azide formed an unstable triazoline which decomposed at 40°C.[12] The very reactive cyanogen azide reacted with even simple olefins at room temperature or below to give alkylidene cyanamides and/or N-cyanoaziridines.[29] The kinetics of these reactions also indicated that the rate-determining step was concerted addition of the azide to the double bond to give an unstable triazoline, the decomposition of which was interpreted in terms of a diazonium-betaine type intermediate. Huisgen[20] has recently presented evidence which shows that arylsulfonyl azides react with norbornene by a cycloaddition reaction.

Previous work in this laboratory has been concerned with the reaction of benzenesulfonyl azide (XV) with norbornene (XIV) and its derivatives.[18,22,23,30] Kinetic evidence[22,30i] supports a mechanism involving formation of an intermediate unstable triazoline in these reactions. Thus, the entropy of activation (ΔS^* = -29 e.u.) for this reaction with norbornene (XIV - XVIII) is in good agreement with that reported by Scheiner[17]

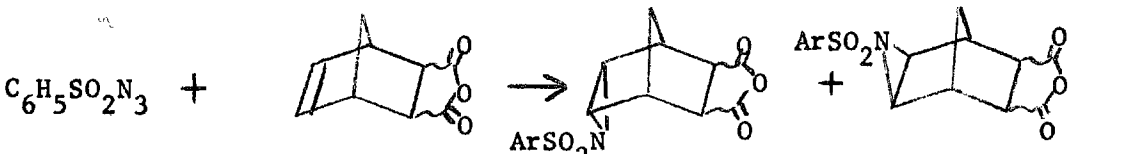
for the reaction of phenyl azides with norbornene where stable triazolines are isolated. The aziridine XVII was formed in almost quantitative yield at room temperature[30e] but a considerable amount of imine XVIII was formed at higher reaction temperatures.[18] The formation of a third product in this reaction will be described later.



XIV XV XVI XVII XVIII

Zalkow and Kennedy[30g] studied the reaction of benzenesulfonyl azide (XV) with the endo anhydride XIX and found that the major product of the reaction was the endo aziridine XX. This result was surprising since it appeared that attack had occurred from the more sterically hindered endo direction in violation of Alder and Steins[31] "exo addition" rule. These authors first suggested a mechanism involving formation of an electrophilic nitrene which was attracted to the endo side of XIX by the electron-rich anhydride ring leading to formation of XX. Evidence against such a mechanism was later provided by the observation[30i] that the endo aziridine XXIII was the major product in the reaction of XV with the exo anhydride XXII. In addition, XV was found not to evolve nitrogen on heating under the reaction conditions in carbon tetrachloride either alone or in the presence of dihydro-XIX or dihydro-XXII. Thus, a mechanism involving intermediate nitrenes or induced decomposition of the azide by the anhydride was not indicated. A careful study[30i] of the reaction products

showed that smaller amounts of the corresponding exo aziridines were also formed in the reactions. Thus, the reaction of XV with endo anhydride XIX gave 60 per cent endo aziridine XX and 19 per cent exo aziridine XXI while reaction with exo anhydride XXII gave 74 per cent endo aziridine XXIII and 22 percent exo aziridine XXIV.



XV

XIX
endo anhydride

XX
endo anhydride

XXI
endo anhydride

XXII
exo anhydride

XXIII
exo anhydride

XXIV
exo anhydride

The purpose of the present study[32] was to seek an answer to the questions of why and how endo aziridines are formed in these cases. This study includes a reinvestigation of the reactions above, as well as the thermal reaction of XV with the corresponding dimethyl esters of XIX and XXII. The reaction of benzenesulfonyl azide with the anhydrides and dimethyl esters under photolytic conditions was also studied. In addition, the reactions of several other azides with these olefins have been investigated in order to provide evidence for a mechanism proposed to explain the formation of endo aziridines.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B spectrophotometer with solids in the form of potassium bromide pellets and liquids as thin films on sodium chloride plates. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer using deuteriochloroform as the solvent unless otherwise specified. Chemical shifts are reported in ppm downfield from the internal standard tetramethylsilane. The abbreviations s, d, t, q and m, respectively refer to singlet, doublet, triplet, quartet and multiplet; coupling constants are reported in cps. Gas-liquid chromatography (glc) was performed using an F & M Biomedical Gas Chromatograph, Model 400, with glass column and a hydrogen flame detector. Preparative glc was performed using the same instrument employing a stream splitter attachment. Mass spectra were recorded using a Varian M-66 mass spectrometer. Photolyses were performed in jacketed cells flushed with dry nitrogen. Pyrex filters were used with a Hanovia 200 watt lamp. Carbon and hydrogen microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mülheim, West Germany.

CHAPTER III

EXPERIMENTAL

Photolytic Reaction of Benzenesulfonyl Azide with Bicyclo-{2.2.1}-5-heptene-endo-cis (XIXa) and exo-cis (XXIIa)-2,3-dicarboxylic Anhydrides and Dimethyl Esters (XIXb and XXIIb)

The four reactions were run simultaneously by dissolving the reactants (6.1 millimoles of olefin and 8.2 millimoles of azide) in 50 ml of carbon tetrachloride, cooling the solutions to -5°C (whereupon the olefins partially precipitated), and irradiating for 3 hours with a Pyrex-filtered 200 watt Hanovia lamp. The reaction mixtures, in the case of the anhydrides after treatment with methanol and ethereal diazomethane, were analyzed on a 6 foot by 1/8 inch glass column of 2 percent SE-30 on 60/80 mesh Gas-Chrom Q at 238°C and a helium flow rate of 80 ml/min. The ratios of endo to exo aziridine products are reported in Table 1. In each case the exo aziridine was formed almost exclusive of the endo aziridine. In the reactions of the olefins containing endo carbonyl functions (i.e. XIXa and XIXb) the major product was not the exo aziridine but XXVI formed from the exo aziridine XXIb as in the thermal reaction of XIXb. In the reaction of XXIIa a considerable amount of insertion product XXV was also formed. The isolation of XXV is described below.

Photolysis of Benzenesulfonyl Azide with Anhydride XXIIa in Ethyl Acetate; Isolation of the Insertion Product XXV

The azide (18.3 g, 0.1 mole) was added to a solution of 16.4 g (0.1 mole) of XXIIa in 500 ml of ethyl acetate. The resulting solution was

cooled to 0°C, deoxygenated by bubbling dry nitrogen through it, and irradiated for six hours with a Hanovia 200 watt lamp during which time a considerable amount of black tarry material precipitated. The solvent was removed on the rotary evaporator to give 33.6 g of a dark syrup which was dissolved in methanol and esterified with ethereal diazomethane. After evaporation of solvent, the residue was chromatographed on Merck acid-washed alumina. Elution with 200 ml of benzene gave about 10 mg of a yellow oil which showed no carbonyl or azide absorptions in the infrared. Elution with an additional 500 ml of benzene and 500 ml of 1:1 benzene:chloroform gave 12.54 g of a solid which was recrystallized from ether to give 10.3 g of <u>exo</u> aziridine XXIVb (m.p. 148-49°C) identical with that previously reported.[30g,i] Analysis of the mother liquor by glc showed the presence of <u>endo</u> aziridine XXIIIb (46 percent) and the insertion product XXV (13 percent) in addition to XXIVb (20 percent) and XXIIb (10 percent). Elution with 1200 ml of chloroform gave 4.36 g of material. Rechromatography of this material on silica gel and crystallization from acetone of the chloroform eluate gave 290 mg of XXV. The analytical sample was obtained by recrystallization from acetone and gave m.p. 142-43°C. (Found: C, 55.68; H, 5.40. Calc. for $C_{17}H_{19}O_6NS$: C, 55.94; H, 5.25 percent); ν_{max}^{KBr} 3280, 1740, 1715 cm^{-1}; Nmr ($CDCl_3$) δ2.97 (s, $W_{\frac{1}{2}h}$ 6 cps, 2H), δ3.25 (s, $W_{\frac{1}{2}h}$ 5.5 cps, 2H), δ3.50 (d, J=9 cps, 1H, collapses to broad singlet on addition of D_2O), δ3.54 (s, 3H), δ5.42 (d, J=9.5 cps, 1H, disappears on addition of D_2O), δ6.12 (s, 2H) δ7.4-7.9 (m, 5H).

Photolysis of Benzenesulfonyl Azide

A solution of the azide (3.0 g) in carbon tetrachloride (100 ml) was deoxygenated with nitrogen, cooled to -12°C and irradiated for three hours with a 200 watt Hanovia lamp using a Pyrex filter. Filtration of the reaction mixture removed a small amount (0.07 g) of a tarry precipitate formed in the reaction and left a clear light yellow solution which was evaporated to give 3.1 g of a light yellow oil. An acetone solution of this oil was analyzed by glc using a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 260°C and a helium flow rate of 100 ml/min and showed a number of peaks of retention times less than two minutes as well as a number of very small peaks from 2.2 to 5.6 minutes. The same peaks were obtained when benzenesulfonyl azide was simply injected onto the column. Analysis of an acetone solution of the tarry precipitate showed no peaks between 0.5 and 10 minutes. Under the same conditons XXIVb had a retention time of 5.0 minutes.

Thermal Reaction of Benzenesulfonyl Azide with Bicyclo{2.2.1}-5-heptene-endo-cis (XIXa) and exo-cis (XXIIa)-1,3-dicarboxylic Anhydrides and Dimethyl Esters (XIXb and XXIIb)

Benzenesulfonyl azide was prepared as previously described[30e] by the reaction of benzenesulfonyl chloride with aqueous sodium azide. The endo anhydride XIXa (m.p. 142-44°C) was prepared by the method of Craig.[33] The corresponding dimethyl esters XIXb and XXIIb were prepared by treatment of methanol solutions of the anhydrides with ethereal diazomethane. The four reactions were run simultaneously under identical conditions (6.1 millimoles of olefin and 8.2 millimoles of benzenesulfonyl azide in 20 ml of carbon tetrachloride refluxed on the steam bath). After addition of

chloroform to dissolve precipitated products, samples were analyzed by gas chromatography using a 4 foot by 1/8 inch glass column of 3.8 percent SE-30 on 80/100 mesh Diatoport S at a column temperature of 238°C and a helium flow rate of 80 cc/min. The anhydride reaction mixtures were treated with methanol and ethereal diazomethane prior to analysis to convert the anhydrides to dimethyl esters. Authentic samples for comparisons were obtained as previously described[30g,i] and gave the following retention times under the conditons specified above: XXb, 3.7 min.; XXIIIb, 4.3 min.; XXIb, 5.1 min.; XXIVb, 5.9 min. The ratios were determined by measuring glc peak areas with a planimeter and the results are given in Table 1.

While XIXa, XXIIa and XXIIb gave only endo and exo aziridines in a ratio of between 2 and 3:1, XIXb gave almost exclusively exo aziridine XXIb in the early stages of the reaction. In addition, a third product (XXVI) was observed, with a glc retention time of 7.2 min., which increased as the reaction proceeded. At 42 hours the ratio XXVI:XXIb was 0.46 and after 63 hours the ratio had increased to 1.25, i.e., XXVI was the major product. After 24 months at room temperature, the conversion of XXIb to XXVI was complete; crystallization of this solid product from acetone gave pure XXVI in essentially quantative yield. The analytical sample was obtained after recrystallization from acetone and gave m.p. 167-69°C. (Found: C, 54.44; H, 4.63. Calc. for $C_{16}H_{17}O_6NS$: C, 54.68; H, 4.88 percent); ν_{max}^{KBr} 3230, 1780, 1730 cm^{-1}; Nmr (d_6-acetone) δ1.70 (d, J=12 cps, 1H), δ2.10 (d, J=12 cps, 1H), δ3.54 (s, 3H), δ3.93 (m, 1H), δ4.60 (d, J=5 cps, 1H), δ7.5-8.03 (m, 5H).

Attempted Reaction[41] of Sodium Iodide with Aziridine XXIb

The aziridine XXIb (3.65 g) and sodium iodide (7.5 g) were dissolved in acetonitrile (125 ml) and the solution was refluxed and periodically checked by gas chromatography. After 30 days, no apparent reaction had occurred. The solvent was evaporated and the solid residue was washed with methylene chloride. The mixture was filtered and the methylene chloride evaporated to give unreacted starting material XXIb in quantitative yield.

Preparation of Benzoyl Azide and Attempted Reaction with Bicyclo-{2.2.1}-5-heptene-endo-cis-2,3-dicarboxylic Anhydride (XIXa)

Benzoyl chloride (59 ml, Eastman) was added dropwise over a period of two hours to a stirred solution of sodium azide (50 g) in water (180 ml) and 95 percent ethanol (100 ml) at room temperature. The solution was then transferred to a one liter separatory funnel and water (200 ml) was added and the mixture extracted with ether. The ether extract was washed first with 5 percent aqueous sodium hydroxide and then with water and finally dried over magnesium sulfate, filtered and evaporated to give a pale yellow liquid which crystallized as colorless needles (m.p. 29-30°C, lit.[34a] 32°C) when cooled in ice water. Filtration gave 44.8 g (62 percent) of benzoyl azide, ν_{max}^{KBr} 2190, 1692, 1599 cm^{-1}. Another product formed in the reaction was insoluble in ether and slowly crystallized from the aqueous layer as fine needles. Filtration and air drying gave 1.1 g of a solid which was indicated to be sym-diphenylurea by the melting point (239-41°C, lit.[34b] 238-39°C) and infrared spectrum (ν_{max}^{KBr} 3316, 3278, 1646, 1597, 1553 cm^{-1}).

The azide (6.1 g) and the anhydride (6.5 g) were dissolved in 50 ml of ethyl acetate and refluxed for one week. The solution was then concentrated to about two-thirds of its volume and allowed to crystallize. Filtration gave 1.18 g of a solid, m.p. 241-41.5°C, which gave an infrared spectrum identical to that of the sym-diphenylurea above. Further concentration and fractional crystallization gave 3.78 g of starting anhydride XIXa, m.p. 163-64°C, identified by its infrared spectrum, and then an additional 0.26 g of sym-diphenylurea, m.p. 239-41°C. The next fraction (2.43 g) was a mixture which was analyzed by glc (4 foot by 1/8 inch column of 3.8 percent SE-30 on 80/100 mesh Diatoport S at 200°C and a helium flow rate of 80 ml/min.) and found to be 77 percent XIXa (R_T 0.4 min), 15 percent sym-diphenylurea (R_T 3.5 min), and 8 percent of an unidentified peak at R_T 1.4 min. The tarry residue following evaporation of the remaining solvent weighed 2.20 g and showed only XIXa in glc.

Preparation and Pyrolysis of the Phenyl Azide Adduct XL of endo Anhydride XIXa

Phenyl azide (11.9 g, 0.1 mole) was added to a solution of 16.4 g (0.1 mole) of XIXa in 200 ml of ethyl acetate and stirred at room temperature. The exo triazoline XL precipitated as the reaction proceeded and was filtered after 19 days to give 17.9 g of XL, m.p. 232-34°C dec. (lit.[7] 225°C dec.); ν_{max}^{KBr} 1860, 1780, 1600 cm^{-1}.

Triazoline XL (10 g) was added to 250 ml of dry, freshly distilled diethylene glycol diethyl ether (Eastman) and the resulting mixture was degassed with dry oxygen-free nitrogen for five minutes and then heated over 30 minutes to 160°C under a nitrogen atmosphere. The triazoline first dissolved and then the solution began to bubble at about 155°C. The solution

was maintained at 160±5°C for two hours and then allowed to cool to room temperature overnight, during which time 1.8 g of a brownish solid crystallized. This material was filtered, dissolved in about 100 ml acetone: methanol (1:1) and concentrated to about one-half this volume, whereupon 1.2 g (15 percent) of LXII crystallized. Recrystallization from acetone gave the analytical sample, m.p. 208-10°C (lit.[9] 204°C). (Found: C, 66.09; H, 5.72. Calc. for $C_{16}H_{17}O_4N$: C, 66.90; H, 5.92 percent); M^+ 287.134, Calc. 287.116; ν_{max}^{KBr} 3394, 1776, 1727 cm^{-1}; Nmr (d_6-DMSO) δ1.50 (d, J=11 cps, 1H), δ1.92 (d, J=11 cps, 1H), δ3.37 (sharp singlet on broad base, 4H), δ4.10 (d, J=5 cps, 1H), δ5.9-6.7 (multiplet, 5H). Further concentration of the solution led to the crystallization of 0.6 g (7.5 percent) of XLI. The analytical sample was obtained by recrystallization from acetone and gave m.p. 233-35°C (lit.[9] 236°C). Found: C, 66.16; H, 5.70. Calc. for $C_{15}H_{15}O_4N$: C, 65.93; H, 5.49 percent) ν_{max}^{KBr} 3400, 2800-3650 (broad), 1780, 1700 cm^{-1}; Nmr (d_6-DMSO) δ1.48 (d, J=11 cps, 1H), δ1.90 (d, J=11 cps, 1H), δ3.40 (broad singlet, $W_{\frac{1}{2}h}$ 3 cps, 1H), δ4.07 (doublet, J=5 cps, 1H), δ5.9-6.7 (m, 5H) Treatment of XLI with diazomethane in ether methanol gave XLII which was found to be identical with XLII obtained above by comparison of melting points and infrared spectra.

The reaction solution, after filtration of the 1.8 g of XLI and XLII, was evaporated <u>in vacuo</u> at about 100°C leaving 8.0 g of a brown gum which was chromatographed on 250 g of Merck acid-washed alumina (activity I) with ten fractions being collected. The first fraction (0.07 g) was a light yellow oil eluted with 250 ml of benzene which gave a band in the infrared at 1730 cm^{-1} but did not have the strong aromatic band at 1600 cm^{-1}

characteristic of all the N-substituted anilines in this study. For this reason, as well as because of the small amount of material available and its noncrystalline nature, this fraction was not further investigated. Elution with an additional 1000 ml of benzene gave the second fraction (1.46 g) as a brown viscous gum which on glc analysis (10 foot by 3/8 inch glass column of 10 percent SE-30 on 80/100 mesh Gas Chrom Q at 267°C and helium flow rate of 125 ml/min) gave the following peaks: retention time, minutes (percentage), 1.1 (28 percent), 1.5 (3 percent), 1.9 (2 percent, 2.1 (12 percent), 3.1 (51 percent). Crystallization of the material from ether gave 62 mg of a solid which was fractionally crystallized from ether to give 50 mg of solid A and 12 mg of solid B. Product A had a retention time of 1.1 min and recrystallization from ether gave the analytical sample, m.p. 176-78°C. (Found: C, 79.35; H, 6.32. Calc. for $C_{14}H_{13}ON$: C, 79.62; H, 6.16 percent); M^+ 211, Calc. 211; ν_{max}^{KBr} 1661, 1600 cm^{-1}; Nmr ($CDCl_3$), δ2.18 (d, J=1.5 cps, 3H), δ3.13 (triplet of doublets, J=1.3 cps, 2H), δ4.45 (triplet, J=3 cps, 2H), δ6.28 (m, 1H), δ6.8-7.35 (m, 5H). Product B had a retention time of 1.5 min and recrystallization from petroleum ether gave the analytical sample, m.p. 100-01°C, (Found C, 79.79; H, 6.35. Calc. for $C_{14}H_{13}ON$: C, 79.62, H, 6.16 percent); ν_{max}^{KBr} 1686, 1600 cm^{-1}.

The third, fourth and fifth fractions (0.94 g total) were eluted with benzene and chloroform mixtures and could not be crystallized. Analysis by glc showed these fractions to be complex mixtures containing a total of 8 percent of A and 1.2 percent of C described below.

The sixth fraction (0.44 g) was eluted with 50 percent $CHCl_3$: C_6H_6 (750 ml) and crystallized from acetone to give 0.27 g of C. Recrystallization from acetone gave the analytical sample, m.p. 212-214°C.

(Found: C, 70.65; H, 5.44. Calc. for $C_{15}H_{13}O_3N$: C, 70.59; H, 5.10 percent); M^+ 255, Calc. 255; ν_{max}^{KBr} 3540, 3390, 1785, 1700, 1600 cm^{-1}. The mother liquor contained 42 percent C and about 1 percent A by glc analysis.

The seventh fraction (0.48 g) was eluted with 75 percent $CHCl_3$: C_6H_6 (2000 ml) and crystallized from ethyl acetate to give 0.19 g of D. The analytical sample was recrystallized from ethyl acetate and gave m.p. 287-88°C. (Found: C, 70.84; H, 5.32. Calc. for $C_{15}H_{13}O_3N$: C, 70.59; H, 5.10 percent); ν_{max}^{KBr} 3420, 3315, 1757, 1676, 1600 cm^{-1}. The mother liquor analyzed by glc to be 14 percent D, 13 percent C and 7 percent A.

The eighth, ninth and tenth fractions (4.5 g total) were eluted with chloroform and methanol mixtures. Analysis by glc showed about 2 percent D, 65 percent C and 17 percent A.

Reaction of p-Methoxybenzenesulfonyl Azide with Anhydride XIXa

The azide was prepared by addition of an acetone solution of p-methoxybenzenesulfonyl chloride (Aldrich) to aqueous sodium azide according to the published procedure for m-nitrobenzoyl azide[35]. The azide was purified by recrystallization from methanol and gave m.p. 50-2°C (lit.[36] 49-51°C); ν_{max}^{KBr} 2340, 2130, 1580 cm^{-1}; Nmr (CCl_4), δ7.42 (d, J=8.5 cps, 2H), δ6.60 (d, J=8.5 cps, 2H), δ3.52 (s, 3H). The azide (4 g, 18.8 millimoles) and anhydride XIXa (3 g, 18.3 millimoles) were dissolved in 100 ml of methylene chloride and stirred at room temperature. After 60 hours no apparent reaction had occurred (no decrease in intensity of azide band in infrared) and the solution was then refluxed on the steam bath 56 hours. Upon cooling to room temperature, 3.61 g of LI (m.p.

200-10°C) crystallized. Concentration of the filtrate to about one-half its volume led to crystallization of an additional 1.39 g (m.p. 220-24°C). The combined solids were recrystallized from methylene chloride to give the analytical sample of LI, m.p. 226-28°C. (Found: C, 55.04; H, 4.46. Calc. for $C_{16}H_{15}O_6NS$: C, 55.01; H, 4.30 percent); ν_{max}^{KBr} 1845, 1775, 1155, 1310, 1325 cm^{-1}; Nmr (d_6-DMSO) δ1.71 (d, J=9 cps, 1H), δ2.07 (d, J=9 cps, 1H), δ2.72 (s, $W_{½h}$ 7 cps, 2H), δ3.23 (s, $W_{½h}$ 6 cps, 2H), δ3.43 (s, $W_{½h}$ 6 cps, 2H), δ3.58 (s, 3H), δ6.59 (d, J=8 cps, 2H), δ7.17 (d, J=8 cps, 2H). The filtrate was evaporated and the residue dissolved in methanol and treated with ethereal diazomethane. After evaporation of the solvents, 3.0 g of a yellow gum was obtained which was then chromatographed on Merck acid-washed alumina (activity III). Elution with 0.25 liters of benzene gave 0.2 g of oil which could not be crystallized. Further elution with 1.25 liters gave a fraction (0.5 g) which was crystallized from ether to give 0.35 g of diester LII (m.p. 191-92°C) identical (m.p., infrared spectra) to LII obtained by treatment of a methanol solution of LI with ethereal diazomethane. The analytical sample was obtained by recrystallization from acetone and gave m.p. 191-92°. (Found: C, 54.73; H, 5.37. Calc. for $C_{18}H_{21}O_7NS$: C, 54.50; H, 5.72 percent); ν_{max}^{KBr} 1738, 1595, 1165, 1175 cm^{-1}; Nmr ($CDCl_3$) δ1.44 (d, J=10cps,1H), δ1.85 (d, J=10 cps, 1H), δ2.59 (s, $W_{½h}$ 4 cps, 2H), δ2.70 (s, $W_{½h}$ 4 cps, 2H), δ3.25 (s, 6H) overlapping δ3.28 (s, $W_{½h}$ 6 cps, 2H), δ3.58 (s, 3H), δ6.44 (d, J=8 cps, 2H), δ7.17 (d, J=8 cps, 2H). After elution with 4000 ml of benzene-chloroform mixture, a fraction was eluted with $CHCl_3$:C_6H_6(3:1) through CH_3OH:$CHCl_3$ (1:4) and crystallized from acetone to give 0.34 g of LIII. The analytical sample

was obtained by recrystallization from acetone and gave m.p. 210-12°C. (Found: C, 53.33; H, 5.15. Calc. for $C_{17}H_{19}O_7NS$: C, 53.33; H, 5.36 percent); ν_{max}^{KBr} 3222, 1760, 1727, 1157 cm^{-1}; Nmr (d_6-acetone) δ1.67 (d, J=12 cps, 1H), δ2.12 (d, J=12 cps, 1H), δ3.59 (s, 3H), δ3.91 (s, 3H), δ4.59 (d, J=5 cps, 1H) δ7.13 (d, J=9 cps, 2H), δ7.83 (d, J=9 cps, 2H).

Preparation of endo-5-Hydroxy-endo-6-(p-methoxybenzenesulfonamido)-endo-cis-2,3-dicarboxybicyclo{2.2.1}heptane γ-Lactone (LIX)

A mixture of 0.88 g of aziridine LI and 2 ml of 1.35 N sodium hydroxide solution was heated on the steam bath for 6 hours during which time the solid LI dissolved. After cooling, the solution was extracted with chloroform. Drying over magnesium sulfate and evaporation of the chloroform extract gave no residue. Upon the addition of concentrated hydrochloric acid (5 ml) to the aqueous solution a colorless oil separated. The aqueous solution was then extracted with chloroform and the extract was combined with the oil. Drying over magnesium sulfate and evaporation of the chloroform gave 0.83 g of oil which crystallized to give LIX, m.p. 219-22°C dec. (vigorous bubbling). Recrystallization from acetone gave the analytical sample, m.p. 223-25°C (dec). (Found: C, 52.55; H, 4.74. Calc. for $C_{16}H_{17}O_7NS$: C, 52.32; H, 4.63 percent); ν_{max}^{KBr} 3225, 1777, 1767, 1705 cm^{-1}; Nmr (d_6-DMSO) δ1.55 (m, $W_{\frac{1}{2}h}$ 8 cps, 2H), δ3.87 (s, 3H), δ5.38 (s, $W_{\frac{1}{2}h}$ 12 cps, 1H), δ7.15 (d, J=9 cps, 2H), δ7.83 (d, J=9 cps, 2H).

Preparation of endo-5-Hydroxy-endo-6-(p-methoxybenzene-sulfonamido)-endo-cis-2,3-dicarboxybicyclo[2.2.1]heptane γ-Lactone-γ-Lactam (LXI)

The lactone LIX (0.14 g, m.p. 223-25°C) was heated at 225°C until vigorous bubbling had ceased and then the flask was evacuated to 0.5 mm and heated an additional 5 min. The resulting glassy solid (0.13 g) was recrystallized from acetone to give the analytical sample of LXI, m.p. 204-05°C. (Found: C, 55.16; H, 4.41. Calc. for $C_{16}H_{15}O_6NS$: C, 55.06; H, 4.33 percent). ν_{max}^{KBr} 1730, 1780 cm^{-1}; Nmr (d_6-DMSO) δ1.78 (m, $W_{\frac{1}{2}h}$ 5 cps, 2H), δ3.88 (s, 3H), δ4.45-5.0 (complex multiplet, 2H), δ7.19 (d, J=9 cps, 2H), δ7.95 (d, J=9 cps, 2H).

Attempted Preparation of Benzenesulfinyl Azide

Sodium benzenesulfinate (Eastman, 16.4 g) was dissolved in water (200 ml) and acidified with concentrated hydrochloric acid (10 ml). The product crystallized and was filtered, dried and weighed to give 9.9 g of benzenesulfinic acid, m.p. 82-4°C (lit.[37] 84°C). The acid was dissolved in ether (200 ml) and thionyl chloride (Fisher, 10 g) was added dropwise over 30 minutes in the hood. The solution was then warmed on the steam bath for 30 minutes and then the ether was evaporated to give 10.4 g of benzenesulfinyl chloride, ν_{max}^{film} 1442, 1150, 750 cm^{-1}. The acid chloride was added dropwise over one hour to a solution of sodium azide (7.2 g) in water (50 ml) and then stirred an additional one hour, diluted with 50 ml of water and the oil which separated was removed. The aqueous layer remaining was extracted with ether and the extract combined with the oil. After washing with 5 percent aqueous sodium hydroxide and water

and drying over magnesium sulfate, the ether was evaporated to give 1.3 g of a yellow oil which was distilled at 76°C (0.3 mm Hg); ν_{max}^{film} 1135, 1005, 885 cm^{-1}. The oily distillate showed no azide band in the infrared and was not further investigated.

Reaction of Hydrazoic Acid with endo Anhydride XIXa

The hydrazoic acid was prepared in ether solution according to the method of Frost and coworkers.[38] An ether solution containing approximately 10 g of hydrazoic acid was added to 8.2 g of XIXa in 250 ml of ether and the resulting solution was stirred at room temperature for one week during which time the azide band in the infrared was observed not to decrease in intensity. The solution was then refluxed for two weeks causing the azide band to steadily decrease and a white solid to precipitate. The reaction was discontinued when the mixture bumped violently expelling most of the material. The material remaining in the flask was filtered to give 2.71 g of a solid, m.p. 130-34°C; ν_{max}^{KBr} 3420 (broad), 1776, 1719 cm^{-1}; which showed olefinic protons in the nmr (d_6-DMSO) at δ6.23 and was therefore not further investigated.

Preparation of Methanesulfonyl Azide and Reaction with endo Anhydride XIXa

Methanesulfonyl azide was prepared according to the published procedure[39] by dropwise addition, over 30 minutes, of a solution of sodium azide (14.3 g) in water (50 ml) to a stirred solution of methanesulfonyl chloride (Eastman, 22.9 g) in 95 percent ethanol (50 ml). The solution was stirred an additional 30 minutes and then 250 ml of water was added causing separation of a heavier-than-water organic layer. This layer

was removed and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give a yellow oil which was distilled at 36.5°C (0.08 mm) to give 16.0 g (66 percent) of methanesulfonyl azide as a colorless oil; ν_{max}^{film} 2360, 2160 1200, 1170 cm^{-1}. The azide (3.0 g) and endo anhydride XIXa (4.1 g) were dissolved in methylene chloride (50 ml) and refluxed for one week. Evaporation of the solvent to about one-half of the original volume led to the crystallization of 3.4 g of LXIII (m.p. 180-90°C) which was removed by filtration. Recrystallization from acetone gave the analytical sample, m.p. 195-96°C. (Found: C, 46.73; H, 4.31. Calc. for $C_{10}H_{11}O_5NS$: C, 46.55; H, 4.13 percent); ν_{max}^{KBr} 1832, 1768, 1320, 1245, 1191, 1158 cm^{-1}; Nmr (d_6-DMSO), δ1.87 (d, J=10 cps, 1H), δ2.28 (d, J=10 cps, 1H), δ2.98 (singlet on broad base, 5H), δ3.67 (m, $W_{\frac{1}{2}h}$ 10 cps, 4H). Evaporation of the filtrate left 2.6 g of a gummy residue which was not further investigated.

Treatment of a methanol solution of LXIII with ethereal diazomethane gave the dimethyl ester LXIV in quantitative yield. Recrystallization from acetone gave the analytical sample, m.p. 171-72°C. (Found: C, 47.39; H, 5.47. Calc. for $C_{12}H_{17}O_6NS$; C, 47.56; H, 5.66 percent); ν_{max}^{KBr} 1735, 1297, 1215, 1199, 1139 cm^{-1}.

Preparation of Methylazidoformate and Reaction with endo Anhydride XIXa

Methylchloroformate (Eastman, 47.3 g) was added dropwise over 30 minutes to a stirred solution of sodium azide (50 g) in water (150 ml). After stirring an additional 30 minutes, the solution was extracted with ether. The ether extract was washed with 20 percent aqueous sodium hy-

droxide and water, dried over magnesium sulfate and evaporated in vacuo at room temperature to give a yellow oil which was distilled through the rotary evaporator at about 35°C to give 31.6 g (63 percent) of methyl-azidoformate as a colorless oil ν_{max}^{film} 2165, 1743, 1240 cm^{-1}. The azide (20 g) and the endo anhydride XIXa (16.4 g) were dissolved in methylene chloride (100 ml) and stirred at room temperature for two weeks. The reaction mixture was then opened to the atmosphere and allowed to evaporate slowly. After one week, the yellow, gummy residue which was left was found to bubble vigorously when shaken or scratched. This gummy material was placed in the freezer for two days during which time partial crystallization occurred. Methylene chloride (50 ml) was added to dissolve the gum leaving the crystals. Filtration gave 1.08 g of LXV (m.p. 220-40°C). Recrystallization from methylene chloride gave the analytical sample, m.p. 242-44°C. (Found: C, 55.68; H, 4.72. Calc. for $C_{11}H_{11}O_5N$: C, 55.74: H. 4.68 percent); ν_{max}^{KBr} 1858, 1771, 1713, 1197 cm^{-1}. Treatment of a methanol solution of LXV with ethereal diazomethane gave the dimethyl ester LXVI; Nmr ($CDCl_3$), δ0.94 (d, J=10 cps, 1H), δ1.63 (d, J=10 cps, 1H), δ2.87 (m, $W_{\frac{1}{2}h}$ 5 cps, 2H), δ3.11 (m, $W_{\frac{1}{2}h}$ 4 cps, 2H), δ3.18 (m, $W_{\frac{1}{2}h}$ 2.5 cps, 2H), δ3.68 (s, 6H), δ3.70 (s, 3H). After standing in a capped vial for 18 months this solid melted at 178-80°C and had apparently undergone a reaction since the infrared spectrum showed bands at 3310, 1782, 1735 and 1686 cm^{-1}.

The filtrate from LXV was returned to the freezer and filtered after 8 weeks to give 0.8 g of a new solid, m.p. 122-23°C; ν_{max}^{KBr} 3337, 1787, 1721, 1689 cm^{-1}. The nmr (d_6-acetone) however, indicates that this solid is a mixture since it exhibits methyl singlets at δ3.61 and δ3.67 in a 2:1 ratio.

Preparation and Pyrolysis of the Phenyl Azide Adduct of exo Anhydride XXIIa

Phenyl azide was prepared from phenylhydrazine and nitrous acid as described in the literature.[40] The azide (6 g) was added to a solution of XXIIa (8.2 g) in 250 ml of carbon tetrachloride and the mixture was refluxed on the steam bath for 3 hours during which time the triazoline LXVIII (11 g, 79 percent) precipitated as a white powder, m.p. 195-96° (lit.[9] 220°C dec.); ν_{max}^{KBr} 1850, 1770, 1600 cm^{-1}. Triazoline LXVIII (14.2 g) was added to 500 ml of dry, freshly distilled diethylene glycol diethyl ether (Eastman) and the mixture was placed in an oil bath at 160±5°C. As the mixture warmed, the solid dissolved and vigorous evolution of nitrogen occurred. After 30 minutes, the rate of gas evolution was very low and heating was discontinued. The solution was evaporated on the steam bath at 0.05 mm to a volume of about 150 ml and cooled to room temperature, whereupon 4.12 g of the exo aziridine LXIXa crystallized. Recrystallization from acetone gave a sample melting at 217-19°C (lit.[31] 219°C) which was shown by infrared spectra and glc to be identical with LXIXa obtained by pyrolysis of LXVIII in decalin as described below. The mother liquor was examined by glc and found to be a very complex mixture and was not further investigated.

Triazoline LXVIII (11 g) was added to 500 ml of freshly distilled decalin (Eastman) and heated in an oil bath at 160±5°C for 3.3 hours. The mixture had not become homogeneous and 3.2 g of starting material was filtered from the hot reaction mixture. The filtrate was analyzed by glc using a 6 foot by 1/8 inch glass column of 10 percent SE-30 on 100/120 mesh Gas-Chrom Q at 173°C and a helium flow rate of 93 cc/min. Under

these conditions, two peaks only were observed at retention times of 12.3 min. (54 percent) and 13.4 min. (46 percent). After standing in the refrigerator 48 hours a solid (6.83 g) had crystallized and was collected by filtration. The filtrate was evaporated at 32°C and 0.025 mm to give an additional 0.46 g of solid. A portion (2.4 g) of the combined solids was fractionally crystallized from acetone. The first crystals were pure exo aziridine LXIXa which had a retention time of 13.4 min. under the conditions described above. The analytical sample was obtained by recrystallization from acetone and gave m.p. 218-20°C (Found: C, 70.59; H, 5.09. Calc. for $C_{15}H_{13}O_3N$: C, 70.65; H, 5.14 percent); ν_{max}^{KBr} 1848, 1775, 1231 cm^{-1}. After several fractions were crystallized as mixtures, the residue left upon evaporation of the mother liquor was endo aziridine LXXa with a glc retention time of 12.3 min. The analytical sample was obtained by recrystallization from acetone and gave m.p. 165-67°C. (Found: C, 69.75; H, 5.00. Calc. for $C_{13}H_{15}O_3N$: C, 70.65; H, 5.14 percent); ν_{max}^{KBr} 1860, 1785, 1200 cm^{-1}. Treatment of a methanol solution of 4.4 g of the solid reaction product with ethereal diazomethane followed by fractional crystallization from hexane resulted in the isolation of the dimethyl esters LXIXb and LXXb. Esterification of the pure anhydrides LXIXa and LXXa also gave LXIXb and LXXb, respectively. The analytical sample of LXIXb was obtained by recrystallization from hexane and gave m.p. 134-36°C (lit.[31] 138°C) (Found: C, 67.61; H, 6.35. Calc. for $C_{17}H_{19}O_4N$: C, 67.83; H, 6.36 percent); ν_{max}^{KBr} 1733, 1208 cm^{-1}; Nmr ($CDCl_3$), δ1.73 (s, $W_{\frac{1}{2}h}$ 5 cps, 2H), δ2.34 (s, $W_{\frac{1}{2}h}$ 2.5 cps, 2H), δ2.73 (s, $W_{\frac{1}{2}h}$ 3 cps, 2H), δ2.91 (s, $W_{\frac{1}{2}h}$ 4 cps, 2H), δ3.67 (s, 6H), δ6.7-7.4 (m, 5H).

The analytical sample of LXXb was obtained by recrystallization from hexane and gave m.p. 87-89°C. (Found: C, 67.66, H. 6.42. Calc. for $C_{17}H_{19}O_4N$: C, 67.83; H, 6.36 percent); ν_{max}^{KBr} 1744, 1195 cm^{-1}; Nmr ($CDCl_3$), δ1.83 (d, J=10 cps, 1H), δ2.27 (d, J=10 cps, 1H), δ2.78 (s, 2H) overlapping half of triplet (J=2 cps, 2H) at δ2.81, δ3.12 (d, J=1.6 cps, 2H), δ3.60 (s, 6H), δ6.8-7.4, 5H); Nmr (C_6H_6)δ2.42 (m, $W_{½h}$ 6.5 cps), δ2.58 (m, $W_{½h}$ 4.5 cps).

Photolysis of the Phenyl Azide Adduct XL of endo Anhydride XIXa; Preparation of Dimethyl Ester LXXIb and Lactone XLII

In order to prepare the exo aziridine LXXIb, 4.2 g of the triazoline XL was suspended in 500 ml of ethyl acetate and irradiated at 16°C for 2.5 hours with a Hanovia 200 watt lamp fitted with a quartz filter. The solution was then concentrated, whereupon, 2.04 g (84 percent) of LXXIa crystallized as fine white platelets, m.p. 160-62°C; ν_{max}^{KBr} 1860, 1780, 1220 cm^{-1}. Treatment of LXXIa with ethereal diazomethane and methanol followed by evaporation of the solvent and recrystallization of the residue from ether gave the dimethyl ester LXXIb, m.p. 83-84°C (lit.[9] 86°C); Nmr (CCl_4), δ0.84 (d, J=11 cps, 1H), δ1.92 (d, J=11 cps, 1H), δ2.78 (s, $W_{½h}$ 2.5 cps, 2H), δ2.87 (s, $W_{½h}$ 5 cps, 2H), δ2.98 (s, $W_{½h}$ 3.5 cps, 2H), δ3.62 (s, 6H), δ6.7-7.3 (m, 5H). After standing 27 months this solid material was analyzed by glc and found to have undergone a significant (40 percent) change to XLII. Recrystallization from methylene chloride gave crystalline XLII, m.p. 208-10°C (no depression on admixture with XLII obtained in the pyrolysis of XL). These compounds also showed identical retention times by glc (6.7 min on a 6 foot by 1/8 inch column of 3 percent SE-30 on Gas Chrom Q

at 210°C and a helium flow of 95 ml/min) and gave identical infrared spectra. Analysis by glc of the mother liquor after four days at room temperature gave only one peak corresponding to XLII. The nmr (d_6-acetone) of XLII was very similar to that of XXXVI showing peaks at δ1.76 (d, J=11 cps, 1H), δ2.26 (d, J=11 cps, 1H), δ3.69 (s, 3H), δ4.00 (m, 1H), δ4.52 (d, J=5 cps, 1H), δ6.5-7.4 (m, 5H).

Reaction of Benzenesulfonyl Azide with exo-Dimethyl Ester XXIIb at Room Temperature

Dimethyl ester XXIIb (1.28 g) and the azide (1.5 g) were dissolved in 20 ml of carbon tetrachloride in a flask protected from light by aluminum foil. The reaction was left standing at room temperature and nitrogen was slowly evolved. After four weeks, a considerable amount of crystalline solid had formed and filtration gave 0.4 g of exo aziridine XXIVb, m.p. 147-49°C. The solvent was then removed in vacuo at room temperature to give 2.1 g of a gummy residue. Chromatography on alumina of 1.6 g of this material gave in the benzene eluate (850 ml), 0.21 g of a mixture of the starting materials and in the chloroform:benzene (1:1) eluate (125 ml) 0.31 g of solid material which was found by glc analysis (6 foot by 1/8 inch column of 10 percent SE-30 on 100/120 mesh Gas-Chrom Q at 250°C and a helium flow rate of 110 ml/min.) to contain 36 percent exo aziridine XXIVb and 63 percent endo aziridine XXIIIb. Elution with 125 ml chloroform gave 0.15 g of solid consisting of 73 percent XXIVb and 24 percent XXIIIb. Elution with an additional 375 ml of chloroform gave 0.02 g of pure XXIVb. Calculation then gives an endo:exo aziridine ratio of 30:70.

Reaction of Benzenesulfonyl Azide with Norbornene in Refluxing Ether

Norbornene (184 g) and benzenesulfonyl azide (366 g) were dissolved in 3 liters of ether and refluxed on the steam bath 3 hours. The solution was evaporated to about one-third volume and allowed to crystallize. Filtration gave 160 g of aziridine LXXII, m.p. 105°C. Evaporation of the filtrate left 228 g of a gummy residue. A portion (1.95 g) of this material was placed in a flask with 75 ml of water and steam distilled in an oil bath at 135°C for two hours adding more water as necessary. The distillate was collected in a receiver containing a solution of 1.60 g of 2,4-dinitrophenylhydrazine (DNPH) in 100 ml of methanol; concentrated hydrochloric acid (9:1) and distillation was stopped after the distillate no longer gave a precipitate with fresh DNPH solution. The distillate (ca. 200 ml) was then diluted with 500 ml of water and filtered to give 2.36 g of orange solid. Chromatography on 130 g of alumina gave, on elution with two liters of benzene, 1.39 g of norbornanone DNP, m.p. 133-35°C (lit.[55] 131.5-32.5°C). Calculation thus gives a value of 41 percent for aziridine LXXII and 38 percent for imine LXXIII in the reaction product.

Reaction of Benzenesulfonyl Azide with Norbornene in Carbon Tetrachloride at Room Temperature

A solution of norbornene (4.3 g) in carbon tetrachloride (15 ml) and a solution of azide (4.6 g) in carbon tetrachloride were mixed and stirred at room temperature and analyzed by glc after one, 48 and 120 hours reaction time using a 6 foot by 1/8 inch glass column of 10 percent SE-30 on 100/120 Gas-Chrom Q at 210°C and a helium flow rate of

95 ml/min. Three peaks were observed at retention times of 5.0, 5.8 and 6.7 min. Standard samples of the endo aziridine LXXIV[30i] and LXXII[30e] showed retention times of 5.0 and 5.8 min, respectively, and mixed injections of each with the reaction mixture gave enhancement of the first and second peak. The third peak was assigned to LXXIII because of the known[18] occurrence of this product in the reaction described described above. The following relative percentages were obtained

	1 Hour	48 Hours	120 Hours
LXXIV	3	3	2
LXXII	77	76	73
LXXIII	20	21	25

Reaction of Norbornene with Benzenesulfonyl Azide in Refluxing Carbon Tetrachloride

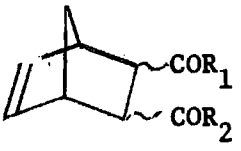
A solution of the azide (4.6 g) in carbon tetrachloride (75 ml) was heated to reflux and a solution of norbornene (9.4 g) in carbon tetrachloride (50 ml) was added dropwise over 60 min. The reaction solution was then analyzed by glc as described above the following relative percentages were obtained.

	1 Hour	48 Hours	120 Hours
LXXIV	13	11	13
LXXII	51	44	42
LXXIII	37	45	45

CHAPTER IV

DISCUSSION OF RESULTS

In Chapter I, we described the thermal reactions[30g,i] of benzenesulfonyl azide (XV) with bicyclo{2.2.1}-5-heptene-endo-cis (XIXa) and exo-cis (XXIIa)-1,3-dicarboxylic anhydrides which, in apparent violation of Alder and Stein's[31] "exo addition rule", gave predominantly endo aziridines XXa and XXIIIa, respectively. These results were in contrast with the almost quantitative formation of exo aziridine in the reaction of XV with norbornene at room temperature.[22,18] As previously stated, the purpose of the present study was to obtain information which might lead to an understanding of how and why endo aziridines are formed in these cases.

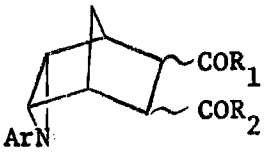


XIXa. endo-anhydride
$R_1 \equiv R_2 = O$

XIXb. endo-dimethyl ester
$R_1 = R_2 = OCH_3$

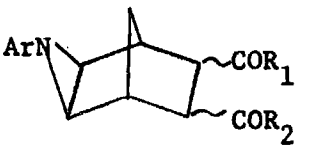
XXIIa. exo-anhydride
$R_1 \equiv R_2 = O$

XXIIb. exo-dimethyl ester
$R_1 = R_2 = OCH_3$



XX. $Ar = C_6H_5SO_2$
a. endo-anhydride
b. endo-dimethyl ester

XXIII $Ar = C_6H_5SO_2$
a. exo-anhydride
b. exo-dimethyl ester



XXI $Ar = C_6H_5SO_2$
a. endo-anhydride
b. endo-dimethyl ester

XXIV $Ar = C_6H_5SO_2$
a. exo-anhydride
b. exo-dimethyl ester

As a first step, the thermal reactions of anhydrides XIXa and XXIIa were reinvestigated. The thermal reactions of the corresponding dimethyl esters XIXb and XXIIb, respectively, were also studied. In addition, the photolytic reactions of XV with XIXa, b and XXIIa, b were also investigated. The results of these studies are summarized in Table 1. The ratio of endo to exo aziridines was determined by gas-liquid chromatographic (glc) analysis of the product mixtures. In the case of the anhydrides, the reaction mixtures were treated with diazomethane in ether-methanol prior to analysis. Pure standard samples of the aziridine dimethyl ester products were obtained as previously described[30g,i] and used for determination of retention time (R_T).

Table 1. $\frac{\text{endo}}{\text{exo}}$ Aziridine Ratio

Reaction	Aziridine Products		Thermal Reaction $\frac{\text{endo}}{\text{exo}}$ Aziridine Ratio	Photolytic Reaction $\frac{\text{endo}}{\text{exo}}$ Aziridine Ratio
	endo	exo		
$C_6H_5SO_2N_3$ + XIXa	XXa +	XXIa	68/32	6/94
XIXb	XXb +	XXIb	<1/>99	<1/>99
XXIIa	XXIIIa +	XXIVa	76/24	5/95
XXIIb	XXIIIb +	XXIVb	70/30	10/90

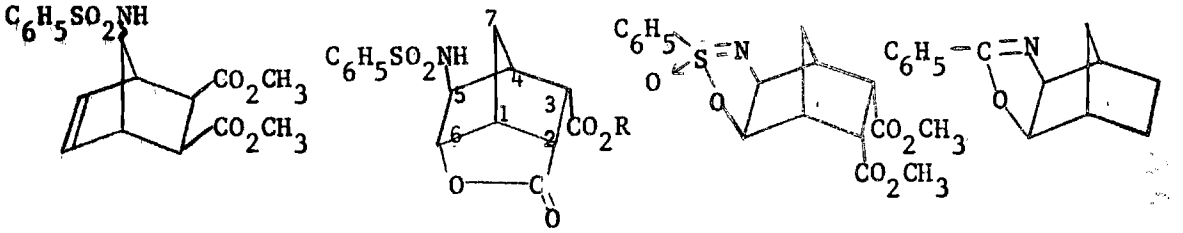
The photolytic reactions were carried out by irradiating carbon tetrachloride solutions of the azide and olefin (1.3:1 molar ratio) at -5°C for three hours using a 200 watt Hanovia lamp with a Pyrex filter. As shown in Table 1, formation of the exo aziridine was in each case overwhelmingly favored over endo aziridine formation. The photolytic

reaction may be visualized as occurring by one of three pathways: (1) an initial thermal addition of azide to give preferentially exo triazoline, followed by photochemical decomposition to yield exo aziridine; (2) photochemical addition of azide to give exo triazoline followed by photochemical decomposition to yield exo aziridine; (3) photochemical generation of nitrene followed by addition to the less hindered exo side of the alkene to give exo aziridine. While photochemical decomposition of triazolines is known[18-20] to be an efficient method of synthesizing aziridines without accompanying rearrangement, the first possibility is eliminated because thermal reaction of benzenesulfonyl azide with the anhydrides is too slow under the reaction conditions. Thus, while norbornene reacts with XV rapidly and exothermically at room temperature[30e] the anhydrides require prolonged heating to effect reaction. The relative rates of nitrogen evolution were found[30i] to be norbornene (100), XXIIa (10) and XIXa (1). With the evidence available at present, it is not possible to state with certainty whether the photochemical reaction proceeds by pathway (2) or (3). However, Lwowski[2] has shown that production of nitrenes by photolysis of azides is a very efficient process and thus pathway (3) is favored. Additional support for pathway (3) is offered by the detection of a product XXV formed in the photolysis of XXIIa with XV. This product is assumed to arise by insertion into the carbon-hydrogen bond, a reaction characteristic of singlet nitrenes.[2,3] Compound XXV was isolated by repeating the photolysis of XV and XXIIa on a large scale. Thus, irradiation of an ethyl acetate solution of 0.1 moles each of XV and XXIIa at 0° for six hours followed by esterification with diazomethane and careful column chroma-

tography gave a small amount of a white crystalline solid, m.p. 142-43°C, which analyzed correctly for $C_{17}H_{19}O_6NS$. This material showed N-H absorption in the infrared at 3280 cm^{-1}. The compound showed two distinct carbonyl bands at 1740 and 1715 cm^{-1}. The nmr spectrum was consistent with structure XXV. Thus, the C-1, 4 and C-2,3 protons appeared as broad singlets at δ2.97 and δ 3.25, respectively, while the C-5,6 olefinic protons appeared as broad signal at δ5.12. The C-7 proton gave a doublet (J=9.5 cps) at δ3.50 which collapsed to a broad singlet. The N-H doublet (J=9.5 cps) at δ5.42 disappeared upon addition of deuterium oxide. While these properties are consistent with structure XXV they do not allow an unambiguous assignment of stereochemistry. The sulfonamide group is considered most likely to be syn to the double bond since the high yield of exo aziridine XXIVb indicates that the nitrene is attracted to this side of XXIIa.

Another observation made with regard to the photolytic reactions was that in the reactions of the olefins containing endo carbonyl functions (i.e., XIXa and XIXb) the major product was not the exo aziridine but rather a compound which has been identified as XXVI by comparison with XXVI formed in the thermal reactions. Originally it was suspected that this major component in the photolytic reaction mixtures might be a compound formed by coupling of benzenesulfonyl nitrenes but photolysis of the azide in the absense of any olefin failed to produce a compound having the same glc retention time. This photolysis produced a number of products having relatively short retention times but the same components were produced by simply injecting pure benzenesulfonyl azide directly onto

the glc column. Under these conditions the aziridines had considerably longer retention times.



XXV XXVI R=CH_3 XXVII XXVIII

XXVIa R=H

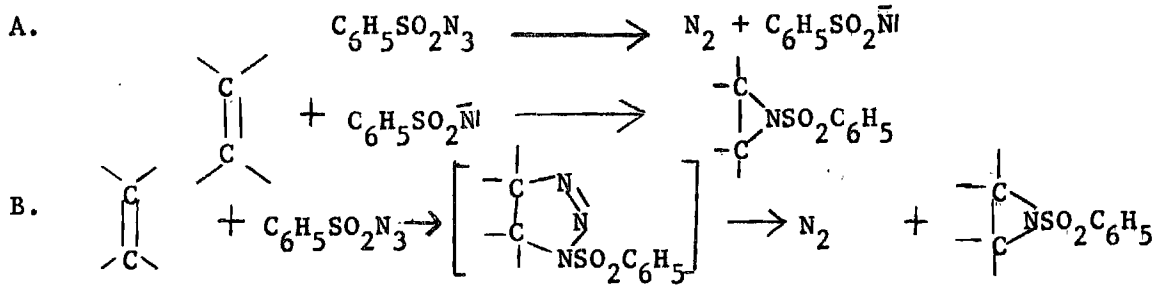
The thermal reactions were carried out by refluxing carbon tetrachloride solutions of the azide and olefin (1.3:1 molar ratio) for 42 hours. The endo/exo aziridine ratio was essentially invariant from 14 to 63 hours. As shown in Table 1, the results obtained in the reactions of the anhydrides XIXa and XXIIa are in excellent agreement with previous[30g,i] findings. Similarly, the exo dimethyl ester XXIIb also gives predominantly endo aziridine in its reaction with benzenesulfonyl azide (XV). However, the endo dimethyl ester XIXb is clearly different in its behavior upon reaction with XV. Thus, while XIXa, XXIIa and XXIIb gave endo and exo aziridines in a ratio of between two and three to one, XIXb gave almost exclusively exo aziridine XXIb in the early stages of the reaction. An explanation of this divergent behavior will be presented later. In addition, the formation of a third product was observed, the amount of which increased as the reaction proceeded indicating conversion of XXIb to this product. Thus, after 42 hours reaction time the ratio of the third product to XXIb was 0.46. After 63 hours reaction time this ratio had increased to 1.25, i.e., the unknown was the major product. The structure XXVII was considered as a possibility for this product by

analogy to the formation of oxazoline XXVIII in the reaction of benzoyl azide with norbornene.[12,18] An attempt to prepare XXVII by refluxing XXIb with sodium iodide, a process known to isomerize acyl aziridines to oxazolines[41], led only to the recovered starting material.

After the thermal reaction mixture above had stood at room temperature for two years the conversion of XXIb to the unknown was complete and crystallization of the reaction mixture gave the lactone XXVI in almost quantitative yield. The assignment of structure XXVI is based on the spectral properties of the product, particularly the similarity of its nmr spectrum to that of the known[42] acid XXVIa. Thus, while XXVIa gave signals for the C-7 protons at δ1.84 and δ2.18 (doublet, J=12 cps), the C-5 proton at δ3.88 (multiplet), and the C-6 proton at δ4.83 (doublet, J= cps) the corresponding protons of XXVI appeared at δ1.70 and δ2.10 (doublets, J=12 cps), δ3.93 (multiplet) and δ4.60 (doublet, J=5 cps). The conversion of exo aziridines possessing endo dimethyl ester functions into lactone amines appears to be a very facile reaction which can occur even when the aziridine is in crystalline form. Several examples of this reaction have been observed during the course of the present studies and are described later.

In any consideration of the mechanism of the thermal reaction, one immediately wishes to determine whether the reaction involves nitrene intermediates (Scheme 1-A) or whether the reaction proceeds via a 1,3-dipolar cycloaddition mechanism involving unstable Δ^2-1,2,3-triazoline intermediates (Scheme 1-B). As stated previously, benzenesulfonyl azide was found not to evolve nitrogen on heating under the thermal reaction conditions in carbon tetrachloride either alone or in the presence

Scheme 1

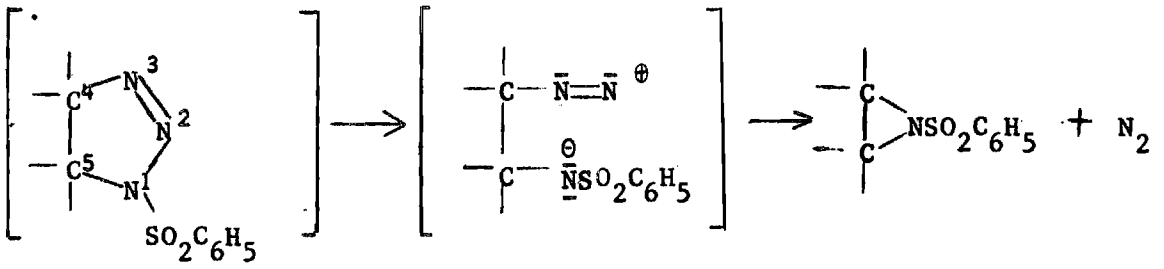


of dihydro-XIXa or dihydro-XXIIa.[8] Thus, a mechanism involving intermediate nitrenes or induced decomposition of the azide by the anhydride moiety is not indicated. Likewise, the fact that dimethyl ester XXIIb gives essentially the same ratio of endo:exo aziridine products as anhydrides XIXa and XXIIa suggests that the anhydride ring plays no unique role as previously thought[30g]. In addition, thermal decomposition of the azide to form nitrenes might be expected to occur only at temperatures considerably higher than those employed here.[43,2-4] Furthermore, a thermally produced nitrene would be expected to undergo reactions not unlike those of a photochemically produced nitrene.[2-4] Thus, the fact that photolysis gives almost exclusively exo aziridines further suggests that mechanism A (Scheme 1) is not operable in the thermal reaction.

In Chapter I evidence[22,23] was discussed which indicates that the reaction of norbornene with benzenesulfonyl azide proceeds by the now ubiquitous 1,3-dipolar cycloaddition mechanism to give an unstable and as yet unisolable Δ^2-1,2,3-triazoline intermediate. Also discussed was Huisgen's[20] recently presented evidence which shows that arylsulfonyl azides react with norbornene by a cycloaddition reaction and Bailey and White's[28] similar results with picryl azides. The instability of the Δ^2-1,2,3-triazoline ring arises because of the electron withdrawing power

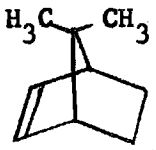
of the benzenesulfonyl group which stabilizes the well established diazonium-betaine intermediate (Scheme 2).[22,23,20,28,10] There is no reason to assume a change in mechanism for the compounds listed in Table 1. As previously pointed out, the relative rates of nitrogen evolution in the thermal reactions of benzenesulfonyl azide are norbornene (100), XXIIa (10), and XIXa (1).[30i] A similar relative order of reactivity of XXIIa and XIXa has been reported in their epoxidation[44] and is ascribed to a field effect which is greater for the endo anhydride because of the closer proximity of the endo anhydride to the double bond. A field effect has also been reported in the reaction of XIXa with picryl azide.[28] It is interesting that evidence has recently been presented which suggests a 1,3-dipolar cycloaddition mechanism for preacid epoxidation also.[45]

Scheme 2

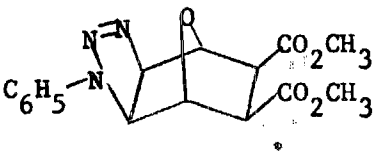


If one accepts that the aziridines produced in the thermal reactions of the olefins listed in Table 1 with benzenesulfonyl azide arise via the unstable Δ^2-1,2,3-triazoline, then the next question is whether the endo aziridines arise from endo triazolines. This does not seem likely. Alder and Stein[9] first pointed out that azide additions to norbornene systems take place with exclusive exo orientation.[9,16,30g,i] These authors also found that what is today referred to as cycloaddition fails if exo attack

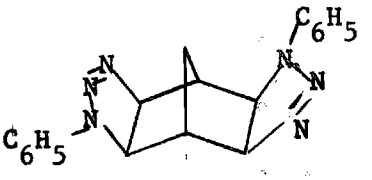
is sterically hindered by substituents at the methylene bridge as in apobornylene (XXIX). It was this work that led to the postulation of the "exo addition rule" and Huisgen[16] has reported conclusive proof of this selectivity in the reaction of phenyl azide with norbornene. In spite of the fact that thorough investigations have recently been made of the reaction of norbornene with aryl azides[17] and of 7-oxabicyclo{2.2.1}heptene derivatives[46] with phenyl azide no endo triazolines have been detected. Thus, pure crystalline XXX was isolated in 97 percent yield.[46] Even in the case of norbornadiene, a 96 percent yield of the exo-exo bis-adduct XXXI was obtained.[20] It should be noted that in the reaction of norbornadiene with the first molar equivalent of phenyl azide there are no endo hydrogens at C-5 and C-6 which could offer steric hindrance to endo attack by the azide. Therefore, there seems to be no reason to expect arylsulfonyl azides to react with XXIIa or XXIIb from the endo side and certainly the endo side of XIXa and XIXb should be extremely hindered. We therefore, are led to the conclusion that both endo and exo aziridines arise from exo triazolines in the cases under consideration.



XXIX



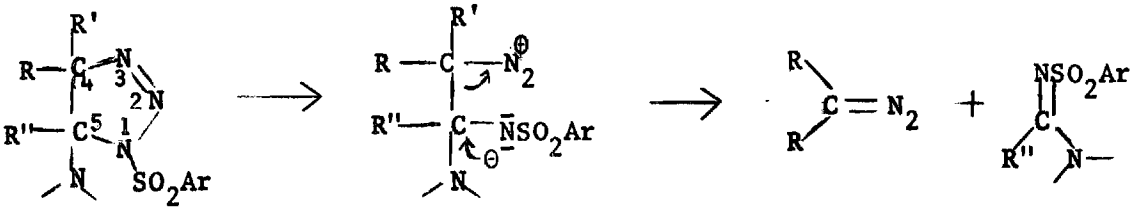
XXX



XXXI

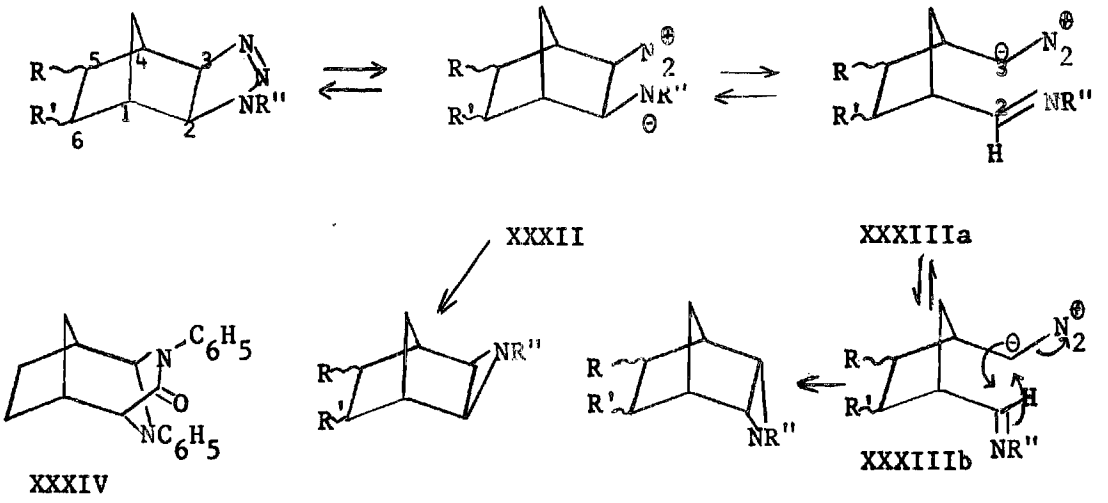
A consideration of the requirement for conversion of a Δ^2-1,2,3-triazoline to an endo aziridine immediately leads to the conclusion that cleavage of the C-2, C-3 bond of the bicyclic ring must occur, followed at some stage by regeneration of this carbon-carbon bond. There is precedence for carbon-carbon bond cleavage in the decomposition of Δ^2-1,2,3-triazolines. Thus, Fusco et al.[21] report that the reaction of certain enamines with aryl-sulfonyl azides results in cleavage of the C-4, C-5 bond of the Δ^2-1,2,3-triazoline ring via the diazonium-betaine intermediate as indicated in Scheme 3. This fragmentation is particularly facile when R contains a carbonyl group attached directly to C-4. This reaction was the basis of the synthesis of α-diazobutyraldehyde (R=CHO, R'=C_2H_5), the first reported aliphatic α-diazoaldehyde.[47] When R and R'' are part of the same molecular ring system the diazo and imino groups,

Scheme 3



because of their close proximity, can react with each other. Thus, the formation of the endo aziridines observed in this study could be explained as outlined in Scheme 4. Baldwin et al.[48] first proposed the existence of an intermediate such as XXXIII in order to explain the formation of XXXIV from the pyrolysis of the norbornene-phenyl azide adduct in the presence of phenyl isocyanate. McDaniel and Oehlschlager[49]

Scheme 4



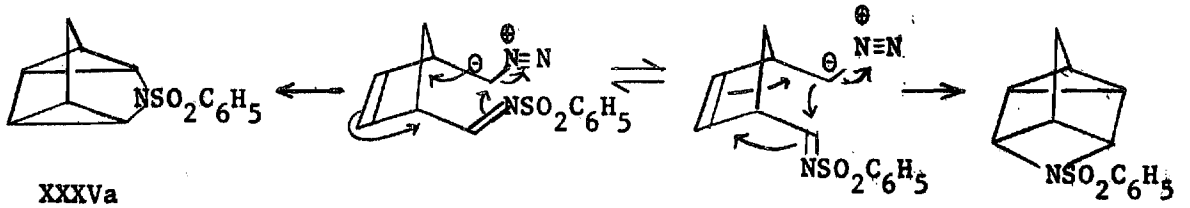
independently arrived at a similar explanation for their observations on decomposition of the phenyl azide-norbornene adduct and observed a positive deviation in the rate of nitrogen evolution, i.e., the rate of evolution was slower than expected at the first of the reaction and faster at the end. This is consistent with the formation of an intermediate such as XXXII or XXXIII and offers strong support for the mechanism in Scheme 4.

The test of any hypothesis such as the mechanism proposed in Scheme 4 is how well it explains the existing data and how well it predicts the outcome of future reactions. With regard to the former, the mechanism shown in Scheme 4, of course, explains how the endo aziridines could arise from exo triazolines by cleavage of the C-2, C-3 bond of the diazonium-betaine intermediate to give the diazoimine XXXIIIa. Rotation about the C-1, C-2 bond of XXXIIIa would then give XXXIIIb in which the imine and diazo groups are ideally situated for ring closure and loss of nitrogen

leading to the endo aziridine. The anomalous behavior of XIXb which gives a very low endo:exo aziridine ratio is readily understandable in terms of steric hindrance by the endo carbomethoxy and unfavorable entropy which results in a low population of the conformer XXXIIIb, the intermediate for endo aziridine formation. A priori, it does not appear likely that the formation of endo aziridine from XXXIIIb should be substantially faster than exo aziridine formation from XXXIIIa or XXXII hence this is not a violation of the Curtin-Hammett principle.[56]

The question of why the endo aziridines are the predominant products from XIXa, XXIIa and XXIIb is more difficult to explain. Most likely the preference for formation of endo aziridines in these cases as compared to the previously observed[30e] preference for formation of exo aziridine in the reaction of norbornene is due to a combination of several factors. Thus, the higher temperatures employed in the reactions of the anhydrides, the effect of the electron withdrawing capacity of the sulfonyl group on the imino nitrogen and the carbonyl groups on C-5 and C-6, and the eclipsing of the groups at C-2 and C-3 in XXXIIIa would all be expected to favor formation of intermediate XXXIIIb which leads to the endo aziridines.

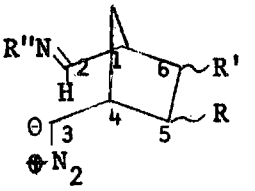
The mechanism proposed in Scheme 5 also readily accounts for the minor product reported by Franz and Osuch[50] in the reaction of norbornadiene with benzenesulfonyl azide regardless of whether this product possesses structure XXXVa or XXXVb.



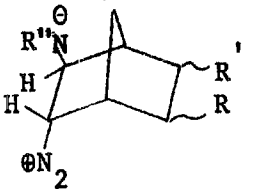
XXXVa

XXXVb

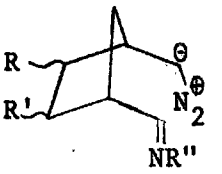
Scheme 4 represents a simplified version of the possible processes which could conceivably be involved in a system such as the triazoline-diazoimine pathway suggested. Thus, the possibility must be considered that rotation about the C-3, C-4 bond could give XXXIIIc which could be in equilibrium with a diazonium-betaine such as XXXVI. Examination of molecular models, however, indicates that the linear diazo group of XXXIIIa would encounter considerably greater steric interactions with the <u>endo</u> functions at C-5, 6 upon rotation to an <u>endo</u> conformation than would the nonlinear imine. For similar steric reasons the conformation XXXIIId, and the diazonium-betaine XXXVII and the <u>endo</u> triazoline XXXVIII which might be in equilibrium, are considered unlikely to play a significant role in these reactions. The intermediacy of a diazonium-betaine such as XXXIX in equilibrium with XXXIIIb is possible but not required by the data now available.



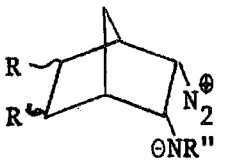
XXXIIIc



XXXVI

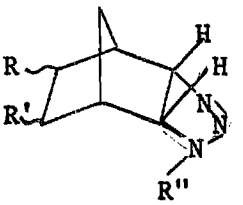


XXXIIId

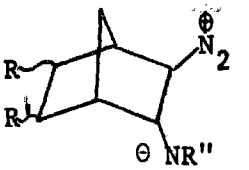


XXXVII

XXXVII



XXXVIII



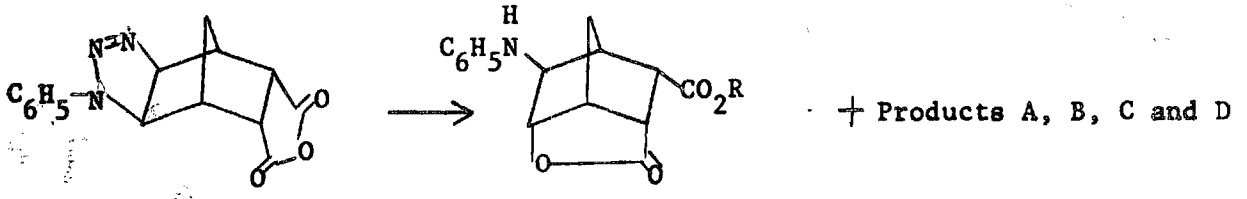
XXXIX

Consideration of the factors suggested previously as possible reasons for the preferred formation of endo aziridines in the thermal reactions of XIXa, XXIIa and XXIIb leads to the following predictions based on the mechanism outlined in Scheme 4. (1) Theoretically, the pyrolysis of any exo Δ^2-1,2,3-triazoline should lead to formation of at least some endo aziridine if performed under the proper conditions. (2) Nonpolar solvents should favor conversion of the diazonium-betaine XXXII to the diazoimine XXXIIIb since less charge separation occurs in the latter. Thus, a higher endo:exo aziridine ratio would be expected when triazoline decomposition is carried out in nonpolar solvents. Since exo aziridine may be formed from XXXII as well as XXXIIIa, polar solvents, which could stabilize the charge separation in XXXII, would be expected to give a lower endo:exo aziridine ratio. Also polar solvents could promote loss of nitrogen from XXXII leading to norbornyl cations and thus give more complex reaction mixtures. (3) Electron-releasing substituents on the aromatic ring should destabilize the negative charge on the imino nitrogen in XXXII and hence promote cleavage of the C-2, C-3 bond leading to a higher endo:exo aziridine ratio. (4) Since carbon-carbon bond cleavage would be an energy-requiring process the endo:exo aziridine ratio should increase with temperature. (5) Electron-withdrawing substituents at C-5 and C-6 should stabilize the partial negative charge developed at C-3 during conversion of XXXII to XXXIIIa by the operation of inductive and field effects. This should in turn lead to a higher endo:exo aziridine ratio. A study was begun to test the five predictions listed above and to provide evidence for the operation of the mechanism of Scheme 4 in the reactions of benzenesulfonyl azide with bicyclic olefins. The central postulate of the proposed mechanism is that exo triazolines could give rise to endo

aziridines. Thus, the obvious approach was to pyrolyze a stable exo triazoline in hopes of obtaining endo aziridines. The reaction of benzoyl azide ($C_6H_5CON_3$) with endo anhydride XIXa was first studied because it was felt that the lower electron-withdrawing power of the carbonyl group as compared to that of the sulfonyl group in benzenesulfonyl azide would lead to increased stabilization of the exo triazoline product. Refluxing benzoyl azide and XIXa in ethyl acetate for one week, however, led only to recovered anhydride and sym-diphenylurea formed form the azide.

The pyrolysis of the known exo triazoline XL, formed by addition of phenyl azide to XIXa, was next studied. Pyrolysis of XL in diethylene glycol diethyl ether at 160±5°C gave a complex mixture of products. Material which crystallized directly from the reaction solution was fractionally crystallized from methanol to give the known[9] lactones XLI and XLII which most likely are formed from the exo aziridine XLIII although the latter was not detected as a product of this reaction. The nmr spectrum of XLII, which must have formed from XLI during the methanol crystallization, is very similar to that of lactone XXVI previously described. Thus, the C-7 protons appear at doublets (J=11 cps) δ1.50 and δ1.92 while the C-5 proton is a multiplet at δ3.37 and the C-6 proton appears as a doublet (J=5 cps) at δ4.10. The nmr spectrum of XLI is almost superimposable on that of XLII with the exception of the methyl ester signal at δ3.37 in the latter. Careful column chromatography of that portion of the reaction mixture which did not crystallize led to the isolation of four crystalline solids (products A-D) for which no structures have been deduced. Product A, m.p. 176-78°C, analyzed for $C_{14}H_{13}ON$ corresponding to the loss of one mole of nitrogen and one mole of carbon dioxide from XL. The base peak in mass spectrum is the molecular ion (M^+) at 211 amu. Of almost equal intensity is the

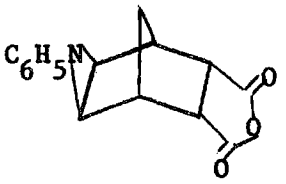
ion mass 92 which may be assigned to $(C_6H_5NH)^+$. The ion $(C_6H_5N)^+$ with mass 91 occurs to the extent of about 10 percent of the base peak while $(C_6H_5)^+$ with mass 77 appears with a relative intensity of approximately 70 percent. The ion of mass 119 (relative abundance 30 percent) may be $(M-C_6H_5NH)^+$ or $(C_6H_5NCO)^+$.



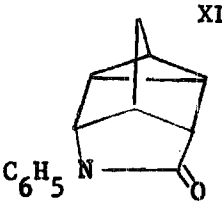
XL

XLI. R=H
XLII. R=CH_3

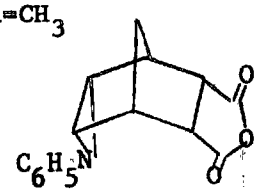
+ Products A, B, C and D



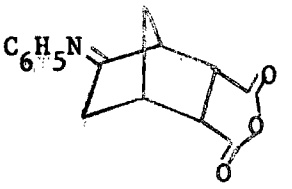
XLIII



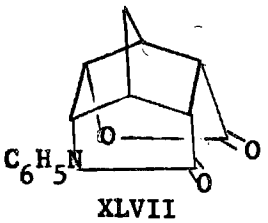
XLIV



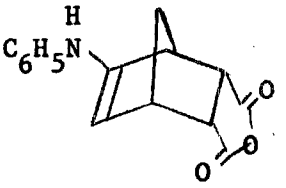
XLV



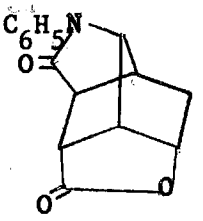
XLVI



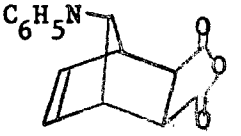
XLVII



XLVIII



XLIX



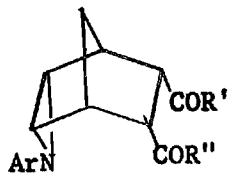
L

Other ions of interest occur at masses of 28 (CO^+ or $C_2H_4^+$), 39 ($C_3H_3^+$), 51 ($C_4H_3^+$), 182 (M^+-29), 183(M^+-28), 196 (M^+-15) with relative abundances of approximately 10, 10, 20, 30, 15 and one percent, respectively. The infrared spectrum of A shows bands at 1661 and 1600 cm^{-1}. The former may be due to an amide carbonyl while the latter is undoubtedly due to the aromatic ring. The nmr spectrum of A showed signals at δ2.18 (d, J=1.5 cps, 3H), δ3.13 {triplet (J=3 cps) of doublets (J=1 cps, 2H)}, δ4.45 (triplet, J=3 cps, 2H), δ6.28 (m, 1H), δ6.8-7.85(m, 5H) accounting for all thirteen

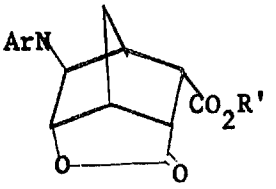
protons. Mechanistic considerations have led to only one structure, XLIV, for $C_{14}H_{13}ON$ which might be expected to be formed in the pyrolysis of XL. This structure is consistent with the infrared data and the formation of the major ions observed in the mass spectrum. The formation of the relatively large abundance of the M^+-29 peak in the latter and the nmr spectrum of A are, however, clearly not reconcilable with structure XLIV. Even more confusing is the isolation of product B, m.p. 100-01°C, an isomer of A which also analyzes for $C_{14}H_{13}ON$ and has a similar infrared spectrum showing bands at 1686 and 1600 cm^{-1}. No additional data has been obtained for product B. Product C, m.p. 212-14°C, analyzed for $C_{15}H_{13}O_3N$ and gave a parent ion (M^+=255 amu) in agreement with this analysis. The base peak appeared at a mass of 198 (M^+-57) and other ions were observed at masses 227 (M^+-28), 170 (M^+-85), 158 (M^+-97), 104 (M^+-151), 77 ($C_6H_5^+$), 51 ($C_4H_3^+$), 39 ($C_3H_3^+$) and 28 (CO^+ or $C_2H_4^+$) with relative abundances of 3, 20, 8, 50, 35, 10, 5 and 5 percent, respectively. The infrared spectrum of C showed bands at 3540, 3390, 1785, 1700 and 1600 cm^{-1}. Product D, m.p. 287-88°C, was an isomer of C and showed infrared absorptions at 3420, 3315, 1757, 1676 and 1600 cm^{-1}. No suitable solvents could be found for obtaining the nmr spectra of C and D. The $C_{15}H_{13}NO_3$ isomers XLIII and XLV-L are all reasonable products for the pyrolysis of XL but none are in complete agreement with the infrared data obtained for C and D. It is somewhat surprising that neither the <u>exo</u> aziridine XLIII nor the <u>endo</u> aziridine XLV were detected in this reaction. Thus, the results described above are in agreement with the predicted complicating effects expected for pyrolysis of triazolines in polar solvents.

It was felt that the attachment of electron-releasing groups to the aromatic ring of benzenesulfonyl azide would partially counteract the electron-withdrawing effect of the sulfonyl gorup and thus stabilize the intermediate triazoline. Therefore, the reaction of p-methoxybenzenesulfonyl azide with the endo anhydride XIXa was next studied. The major product obtained by refluxing the azide and anhydride in methylene chloride was not the triazoline but rather the endo aziridine LI which crystallized directly from the reaction mixture upon cooling. The physical properties of LI are in agreement with the proposed structure. The assignment of the endo configuration to the aziridine ring is based on the chemical reactions described below and the nmr spectrum of LI and its dimethyl ester LII. The assignment of aziridine stereochemistry by nmr will be discussed later. In addition to LII, there was obtained on chromatography of the methylated portion of the product, five percent yield of LIII, which undoubtedly arises from the exo aziridine which was not isolated. The nmr spectrum of LIII was completely analogous to that of lactone XXVI described earlier. The total yield of endo aziridine as both LI and LII was 81 percent. Since the yield of LIII may be considered to reflect the amount of exo aziridine formation, an endo:exo aziridine ratio of 94:6 is observed for the reaction of p-methoxybenzenesulfonyl azide with XIXa. This is to be compared to the 68:32 ratio obtained for the reaction of benzenesulfonyl azide with XIXa. Thus, as was predicted earlier, electron-releasing substituents on the aromatic ring lead to an increase in the endo:exo aziridine ratio in support of the mechanism proposed in Scheme 4.

Chemical evidence for the endo configuration of the aziridine ring in LI was obtained by conversion of LI to LIX in the manner used previously[30g] in converting XXa to LX. The nmr spectra of LIX and LXI (formed by heating LIX) were analogous to those of the previously[30g] prepared compounds LX and LXII.



Ar = p-$RC_6H_4SO_2$



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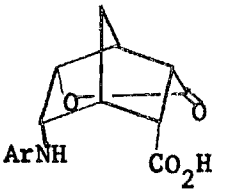
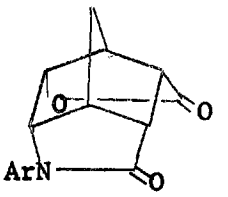


Ar = p-$RC_6H_4SO_2$



Ar = p-$RC_6H_4SO_2$

LI. R=CH_3O, R'≡R"=O

LII. R=CH_3O, R'=R"=OCH_3

XXa. R=H, R'≡R"=O

LIII. R=CH_3O, R'CH_3

LIX. R=CH_3O

LX. R=H

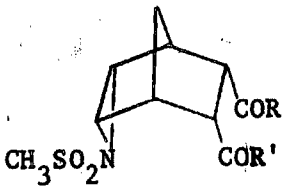
LXI. R=CH_3O

LXII. R=H

In yet another attempt to provide support for the mechanism shown in Scheme 4, it was proposed to prepare benzenesulfinyl azide and react it with XIXa. The decreased electron-withdrawing power of the sulfinyl group as compared to the sulfonyl group might be expected to lead to formation of an isolable exo triazoline. Oxidation of this triazoline would then produce the unstable exo triazoline proposed as an intermediate in the reaction of benzenesulfonyl azide. However, an attempt to prepare the unknown benzenesulfinyl azide by the usual method led only to products showing no azide absorption in the infrared. Sulfinyl azides are known[37a] to disproportionate to compounds of the type RSO_2SR and R_2S_2 and this is most likely the course taken in the present case.

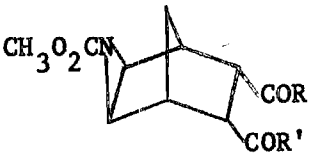
The reaction of hydrazoic acid[38] with XIXa was also investigated but the product obtained showed olefinic protons in the nmr spectrum indicating addition of HN_3 to the double bond had not occurred.

The reaction of methanesulfonyl azide with XIXa was undertaken in hopes that the replacement of the aryl group of the sulfonyl azides with an alkyl group would stabilize the intermediate triazoline. However, the product isolated when XIXa and methanesulfonyl azide were refluxed in methylene chloride was identified as the <u>endo</u> aziridine LXIII. Treatment of LXIII with ethereal diazomethane gave the dimethyl ester LXIV. The product crystallized directly from the reaction mixture in 53 percent yield. Although the gummy residue left upon evaporation of the solvent after removal of LXIII, has not been investigated to see if any <u>exo</u> aziridine was formed, it is obvious that this is another case in which the <u>endo</u> aziridine is the major product. The assignment of the <u>endo</u> configuration of the aziridine ring was made by examination of the nmr spectrum as described later.



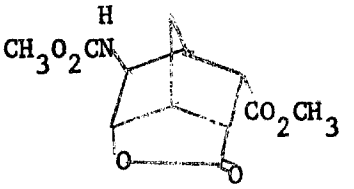
LXIII. R≡R'=O

LXIV. R=R'=OCH_3



LXV. R≡R'=O

LXVI. R=R'=OCH_3

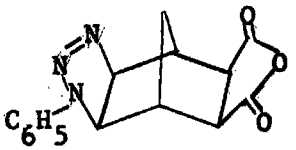


LXVII

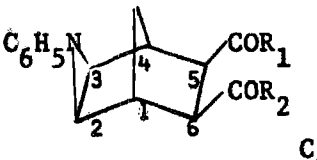
In still another attempt to prepare a stable <u>exo</u> triazoline having electron-withdrawing groups attached to nitrogen the reaction of methyl azidoformate with XIXa was investigated. The reactants in methylene chloride solution were stirred at room temperature for two weeks and the solvent was then allowed to evaporate at room temperature to leave a gummy residue. This material was very unstable and vigorously evolved nitrogen when shaken or scratched indicating the possible presence of an unstable triazoline.

When allowed to stand in the freezer, this material slowly deposited crystals. Filtration gave a four percent yield of a solid, m.p. 242-44°C, to which structure LXV has been assigned on the basis of the nmr spectrum of dimethyl ester LXVI. The latter was prepared by treatment of LXV with ethereal diazomethane. The dimethyl ester, after standing 18 months as a crystalline solid in a vial, apparently underwent a change. The infrared spectrum of this material indicated that the aziridine ring had opened to form the lactone LXVII. The investigation of this reaction is not complete and, therefore, no conclusions can be made with regard to the relative amounts of endo and exo aziridines formed in this case.

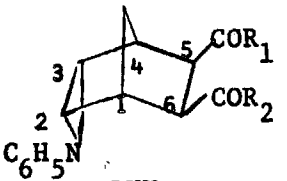
In order to obtain additional evidence in support of this mechanism outlined in Scheme 4, an investigation was made of the pyrolysis of a stable exo Δ^2-1,2,3-triazoline, namely LXVIII, prepared by the reaction of phenyl azide[40] with XXIIa. The pyrolysis of LXVIII was found to be greatly influenced by the nature of the solvent; thus, heating LXVIII in diethylene glycol diethyl ether led to a complex mixture whereas heating in decalin at 160±5°C gave only aziridines LXXa and LXIXa in an endo:exo ratio of 54:46



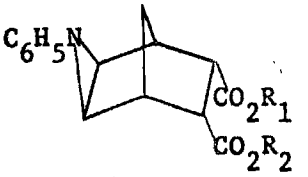
LXVIII



LXIX
a. $R_1 \equiv R_2 = O$
b. $R_1 = R_2 = OCH_3$



LXX
a. $R_1 = R_2 = O$
b. $R_1 = R_2 = OCH_3$



LXXI
a. $R_1 \equiv R_2 = O$
b. $R_1 = R_2 = OCH_3$

These results are in agreement with the prediction made earlier that electron-withdrawing substituents at C-5 and C-6 should lead to a higher endo:exo

aziridine ratio as compared to the unsubstituted case which has recently been reported[49] to give only 9 percent endo aziridine on pyrolysis in decalin at 160°C. Exo aziridine LXIXa and its dimethyl ester LXIXb, prepared by treatment of LXIXa with diazomethane in ether-methanol, showed physical properties identical with those previously reported for these compounds.[51] The previously unreported endo aziridine LXXa showed the characteristic aziridine absorption[52] in the infrared (1200 cm^{-1}) and was readily converted into the corresponding dimethyl ester which showed similar aziridine absorption (1195 cm^{-1}).

That LXXb, and therefore LXXa, contained an endo aziridine ring was apparent from its nmr spectrum. Thus, the exo protons at C-2 (H_2) and C-3 (H_3) gave an ill-defined triplet at δ2.80 with a half-height width ($W_{\frac{1}{2}h}$) of 6 cps which was superimposed on the signal arising from the bridgehead protons ($H_1 + H_4$) in $CDCl_3$. However, in benzene the two signals were clearly separated. The width of the H_2, H_3 signal is clearly indicative of exo protons and therefore, of an endo aziridine ring as shown in Table 2. Thus, endo aziridines XXb and XXIIIb show a similar broad signal for the H_2, H_3 protons (see Table 2). The structure of XXa, and therefore, XXb has been well established[30g] by its conversion to LX. Likewise, the structure of XXIIIa and therefore, XXIIIb, is known since the former has been chemically degraded to the 2-endo benzenesulfonamidobicyclo{2.2.1}-heptane.[30g,i] In the case of the endo aziridine LXIII, the H_2, H_3 and H_5 and H_6 signals overlap to give a single broad signal of half-height width 10 cps. The endo stereochemistry is, however, readily deduced from the relative chemical shifts of the C-7 protons described below.

In contrast to the endo aziridines, the isomeric exo aziridines XXIb. XXIVb and LXIXb show narrow signals for H_2, H_3 with $W_{\frac{1}{2}h}$ 2.5±0.5 cps (Table 2),

which are known to be characteristic of exo aziridines.[30i,18] As an additional example, exo aziridine LXXIb was prepared[53] by addition of phenyl azide to anhydride XIXa to give the known[9] exo triazoline XL which was photolyzed to give exo aziridine LXXIa. In turn, LXXI was treated with diazomethane to give the known[9] LXXIb. It is interesting to note that upon standing for 27 months in a foil-covered flask solid LXXIb was converted to LXII, identical in every manner to the LXII

Table 2. Nmr Spectra of Aziridines

Compound	Half-Height Width of H_2, H_3 signal	δ_7 anti	δ_7 syn
XXIb	2.5±0.5	0.90	1.70
XXIVb	2.5±0.5	1.47	1.75
LXXIb	2.5±0.5	0.84	1.92
LXIXb	2.5±0.5	1.73	1.73
LXVI	2.5±0.5	0.94	1.63
XXb	6.5±0.5	2.00	1.53
XXIIIb	6.5±0.5	2.32	1.92
LXXb	6.5±0.5	2.27	1.83
LI	6.0±0.5	2.07	1.71
LII	6.0±0.5	1.85	1.44
LXIII		2.28	1.87

formed in the pyrolysis of XL in diethyl glycol diethyl ether as previously described. As indicated in Table 2, LXXIb shows the characteristic narrow signal for H_2, H_3 observed in exo aziridines. The

exo configuration was assigned to aziridine LXVI, formed by the reaction of methyl azidoformate with XIXa, since its nmr spectrum showed a similar narrow signal, as may be seen in Table 2.

Tori[52] has shown that an exo aziridine produces an anisotropic shielding effect on the 7-anti proton in a norbornyl system and this effect can be used to assign exo or endo configuration to the aziridine ring. This shielding is illustrated by XXIb and LXXIb in Table 2, where the 7-anti protons appear 0.8 to 1.1 ppm upfield from the 7-syn protons. This method cannot be used with XXIVb and LXIXb since these substances contain C-5 and C-6 exo carbomethoxy groups which deshield the 7-syn protons. However, the method is quite useful in assigning the exo configuration to LXVI as may be seen in Table 2. In contrast, the endo configuration is assigned to LXIII formed in the methanesulfonyl azide reaction since the two C-7 protons occur close together at relatively low field.

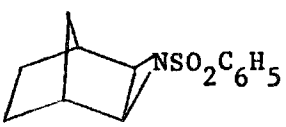
Five predictions based on the mechanism outlined in Scheme 4 were presented earlier. Experimental results substantiating all of these predictions except that concerned with the dependence of the endo:exo aziridine ratio on temperature have now been discussed. Thus, the pyrolysis of LXVIII to LXX has shown that endo aziridines can be formed from exo triazolines and the predicted solvent effects were also observed in this reaction. The high endo:exo aziridine ratio observed in the reaction of p-methoxybenzenesulfonyl azide with XIXa illustrated the predicted effect of electron-releasing substituents on the aromatic ring. Also, the predicted effect of electron-withdrawing substituents at C-5 and C-6 was supported by the larger amount of endo aziridine (54 percent) formed in the pyrolysis of the phenyl azide adduct of XXIIa[32] as compared to the

9 percent formed in the pyrolysis of the phenyl azide adduct of unsubstituted norbornene[49] under the same conditons.

In order to test the temperature dependence of the endo:exo aziridine ratio, the reaction of benzenesulfonyl azide with dimethyl ester XXIIb was reinvestigated. As shown in Table 1, refluxing the azide and olefin in carbon tetrachloride for 42 hours leads to an endo:exo aziridine ratio of 70:30. This reaction was repeated by dissolving the reactants in carbon tetrachloride and allowing the solution to stand in the dark for four weeks. Nitrogen was slowly evolved as a crystalline product formed. Although the extent of reaction was very small, the endo:exo aziridine ratio was found to be 30:70, a complete reversal of the previous results.

In a final test of the proposed mechanism, the reaction of benzenesulfonyl azide with norbornene was reinvestigated. This reaction was previously reported[30e] to give an almost quantitative yield of the exo aziridine LXXII when carried out in nonpolar solvents at room temperature. When the reaction was repeated[18] in refluxing ether the formation of a second product, the imine LXXIII, in 38 percent yield was demonstrated by hydrolysis LXXIII and formation of the dinitrophenylhydrazone of the resulting norbornanone. However, no endo aziridine LXXIV was detected in these reactions. These results caused some doubt about whether a diazoimine intermediate of the type XXXIII (Scheme 4) was involved in this reaction. However, a careful reinvestigation of the reaction in carbon tetrachloride at room temperature employing glc analysis has shown that a small amount (2-3 percent) of the endo aziridine LXXIV is formed under these conditions along with about 75 percent exo aziridine LXXII and 20-25 percent of imine LXXIII.

As would be predicted, when the norbornene in carbon tetrachloride solution is dropped into a refluxing carbon tetrachloride solution of benzenesulfonyl azide, the endo:exo aziridine rate increases. Thus, under these conditions about 12-13 percent of LXXIV is formed along with 45-50 percent of LXXII and about 45 percent of imine LXXIII.



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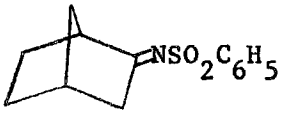
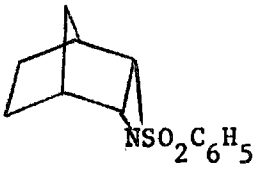
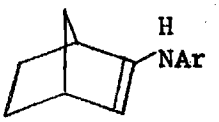


LXXIII



LXXIV



LXXV

It is interesting that in the reactions of the anhydrides and dimethyl esters studied here, no imines analogous to LXXIII were observed. This is to be contrasted with the results of Oehlschlager[49] in the pyrolysis of the triazoline adduct formed in the reaction of norbornene with phenyl azide. The latter workers have observed that the amount of imine increases in more polar solvents. Thus, the imine may be produced by loss of nitrogen from an intermediate such as XXXII (Scheme 4) to give a carbonium ion followed by proton transfer from C-2 to the nitrogen anion of XXXII to give an enamine type structure LXXV which could equilibrate to the imine.[23] Such a process would be more facile in more polar solvents and would be hindered by electron-withdrawing groups such as the anhydride moiety and carbomethoxy groups on the norbornyl ring system. Likewise, Oehlschlager et al. observed rearranged products such as syn-7-N-phenylamino bicyclo{2.2.1}hept-2-ene and 3-N-phenylaminotricyclo{2.2.1.0^{36}}-heptane which were not observed in those examples mentioned in this study and which could arise via the above mentioned carbonium ion mechanism.

The work of Oehlschlager and McDaniel[49], who have independently observed the conversion of exo triazolines to endo aziridines, further supports the mechanism shown in Scheme 4. In their work, which involved the triazoline adduct form norbornene and phenyl azide, the endo aziridine was only a minor product (a maximum of 9 percent yield). These workers noted the 60 percent yield of XXXIV when the same triazoline was pyrolyzed in phenyl isocyanate and compared this to the similar yield of endo aziridine obtained in the reactions of the anhydrides and dimethyl esters with benzenesulfonyl azide. They took this to indicate a similar amount of C-2, C-3 bond cleavage in both reactions and argued against the operation of inductive and field effects by the carbonyl functions. However, the greater electron-withdrawing power of the arylsufonyl group as compared to that of the phenyl group and the lower temperature (ca. 80°C compared to 160°) in which the anhydride reactions were performed have been shown to be factors which oppose carbon-carbon bond cleavage. Thus, on the contrary, if a similar amount of bond cleavage is occurring in the two reactions, the carbonyl functions must be exerting very very powerful inductive and field effects. Also, in support of the operation of such effects is the observation that, while the phenyl azide adduct of norbornene gives only about 9 percent endo aziridine,[49] the phenyl azide adduct of XXIIa, which differs only in the presence of the exo anhydride function at C-5 and C-6, gives 54 percent endo aziridine when pyrolyzed under the same conditions. A similar situation exists with regard to the reaction of benzenesulfonyl azide with norbornene and the anhydrides. Thus, the former gives about 12-13 percent endo aziridine aziridine while the latter gives about 70 percent endo aziridine under similar reaction conditions.

CHAPTER V

CONCLUSIONS

A mechanism has been proposed (Scheme 4) to explain the predominant formation of *endo* aziridines in the reactions of benzenesulfonyl azide with various bicyclic anhydrides and esters. The principle step in this mechanism involves conversion of the diazonium-betaine XXXII to the diazoimine XXXIIIa by carbon-carbon bond cleavage.

Nonpolar solvents favor conversion of XXXII to XXXIIIa since less charge separation occurs in the latter. Polar solvents lead to complex mixtures in the pyrolysis of Δ^2-1,2,3-triazolines.

Electron-releasing substituents on the azide destabilize the negative charge on the imino nitrogen of XXXII and thus promote carbon-carbon bond cleavage and lead to higher *endo*:*exo* aziridine ratios.

The amount of bond cleavage and the resulting formation of *endo* aziridines increases with temperature.

Electron-withdrawing groups at C-5 and C-6 of the bicyclic olefins exert inductive and field effects which favor carbon-carbon bond cleavage and thus lead to higher *endo*:*exo* aziridine ratios.

Stable *exo* Δ^2-1,2,3-triazolines can give rise to *endo* aziridines upon pyrolysis. The conversion of diazonium-betaine intermediates to diazoimines appears to be a general process in the pyrolysis of triazolines, the extent of its operation in a given case being dependent upon the factors mentioned above.

CHAPTER VI

RECOMMENDATIONS

The pyrolysis of the triazolines LXVIII and XL in polar solvents should be reinvestigated. In particular, the unknown products A-D formed in the pyrolysis of XL in diethylene glycol diethyl ether should be further studied with the object of determining their structures.

A study of the effect of substituents on the aromatic ring of arylsulfonyl azides on the endo:exo ratio would provide additional support for the mechanism proposed in Scheme 4.

The investigation of the reactions of methanesulfonyl azide and methyl azidoformate with XIXa should be completed with an effort being made to find exo aziridines in the former and endo aziridines in the latter.

A study of the effects of substitution of different electronegative groups at C-5, C-6 of the bicyclic olefins would provide more data on the operation of inductive and field effects.

An attempt should be made to isolate or obtain spectral evidence for an unstable triazoline in the reaction of benzenesulfonyl azide with XIXa which has been proceeding at low temperature for 30 months.

Attempts should be made to trap the diazoimine intermediate XXXIIIa or ring-opened products derived from it.

Attempts should be made to prepare endo triazolines and study their possible conversion to exo and endo aziridines.

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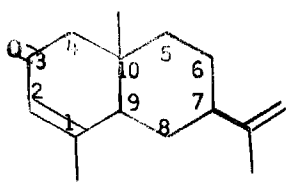
PART II

CHAPTER I

INTRODUCTION

In 1932, while investigating the constituents of the oil from the wood of the Australian shrub Eremophila mitchelli, Simonsen and coworkers[1] isolated three closely related crystalline ketones, eremophilone ($C_{15}H_{22}O$), hydroxyeremophilone ($C_{15}H_{22}O_2$), and hydroxydihydroeremophilone ($C_{15}H_{24}O_2$). Eremophilone was found to be a bicyclic α,β-unsaturated ketone with an isopropenyl side chain. Reaction with amyl formate gave a hydroxymethylene derivative. Dehydrogenation of dihydroeremophilol, formed by sodium and alcohol reduction of eremophilone, gave 1-methyl-7-isopropylnaphthalene (eudalene). Principally on the basis of these reactions, structure I was assigned to eremophilone in accordance with the isoprene rule. Structure II was assigned to hydroxyeremophilone, since ozonolysis of its benzoate gave acetone, and reaction of eremophilone with alkaline hydrogen peroxide gave eremophilone **epoxide** which, on digestion with acetic anhydride and sodium acetate, gave hydroxyeremophilone. Structure III was assigned to hydroxydihydroeremophilone since catalytic hydrogenation followed by sodium amalgam reduction gave tetrahydroeremophilone, which was identical to that obtained by hydrogenation of eremophilone. In addition, ozonolysis of III gave formaldehyde.



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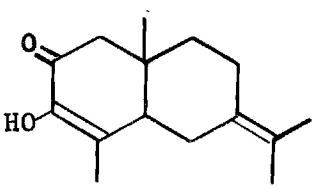

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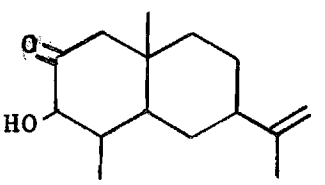
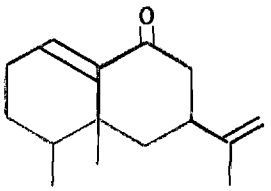


III

Later work[2,3,4] by Simonsen et al. showed that reaction of tetrahydroeremophilone with methylmagnesium iodide followed by selenium dehydrogenation gave 1,5-dimethyl-7-isopropylnaphthalene rather than the expected 1,3-dimethyl-7-isopropylnaphthalene. This established the position of the carbonyl group in eremophilone at C-5 rather than C-3 and necessitated revision of structure I. With the ketone at C-5 the formation of the hydroxymethylene derivative described above clearly requires that the conjugated double bond be placed between C-4 and C-10. This led to difficulty in placement of the remaining methyl group. After considering the data, Sir Robert Robinson in 1939 made the novel suggestion to Simonsen[5] that eremophilone was most probably represented by structure IV. The data which established this structure and led Simonsen in 1941[6] to propose correct structures for hydroxyeremophilone (V) and hydroxydihydroeremophilone (VI) have been summarized elsewhere.[7-10]



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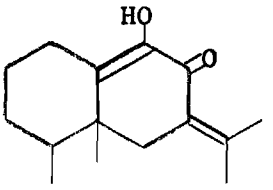

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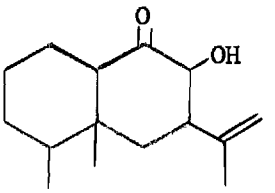
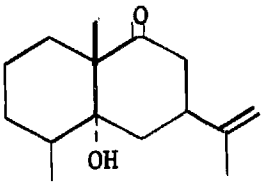


VI

Compounds IV, V and VI were the first members of the rapidly expanding eremophilane group of sesquiterpenes. These compounds do not follow the isoprene rule and their discovery had far-reaching implications in natural product chemistry. It could no longer be assumed that the isoprene rule would apply to the terpenes and structures previously assigned on this basis now required more rigid proof.

Robinson[11] suggested that the biogenetic process by which eremophilone and its congeners were formed might involve methyl migration in a carbonium ion intermediate formed by dehydration of an isoprenoid precursor of the eudalene-type such as VII. Since such a rearrangement would be expected to be stereospecific, the determination of the relative and absolute configurations of IV, V and VI would be of considerable value in deciding the merits of this proposal. In all of the eudalene-type sesquiterpenes known at that time, the angular methyl groups had the β-configuration. Klyne[12] assigned the same configuration to eremophilone on the basis of a comparison of its optical rotation at the sodium-D line with that of Δ^5-cholesten-4-one.

Djerassi[13] assigned the opposite configuration on the basis of a comparison of the optical rotatory dispersion (ord) curves of eremophilone, Δ^5-cholesten-4-one and Δ^4-cholesten-6-one. This conclusion was based on the incorrect assumption of a <u>trans</u> isopropenyl group (relative to the bridgehead methyl group) in eremophilone.



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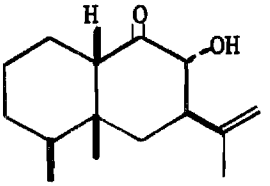
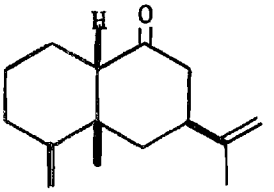
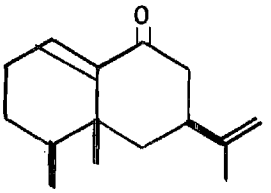


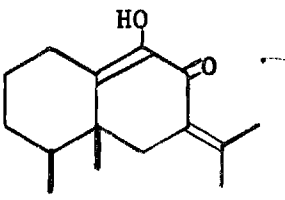
VIII



IX



X

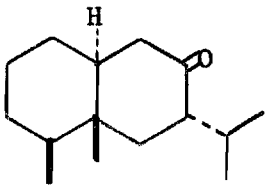


XI

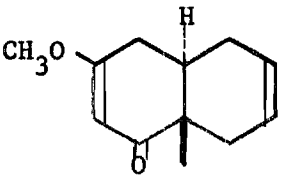
In 1956 Grant and Rogers[14] established the relative configuration VIII for hydroxydihydroeremophilone by means of x-ray analysis. The previous interconversions by Simonsen[1], namely conversion of eremophilone to hydroxyeremophilone by rearrangement of eremophilone epoxide and reduction of hydroxydihydroeremophilone and eremophilone to the same tetrahydroeremophilone, proved only that the three sesquiterpenes possessed the same orientation of the two methyl groups and was stereochemically ambiguous with respect to the isopropenyl group. An unambiguous correlation was provided[15] by conversion of hydroxydihydroeremophilone acetate to cis-dihydroeremophilone IX by calcium-ammonia reduction. The same compound had previously[1,13] been obtained by sodium-alcohol reduction of eremophilone followed by oxidation with chromium trioxide. This correlation thus established that the isopropenyl group of eremophilone was cis to the two methyl groups as had been established[14] for hydroxydihydroeremophilone. Oxidation[16] of the stereochemically defined[14] standard hydroxydihydroeremophilone with bismuth oxide led directly to hydroxyeremophilone thus completing the correlation of the three sesquiterpenes and establishing their relative stereochemistry.

The finding that the isopropenyl group was cis to the methyl groups required a reversal of Djerassi's[13] assignment of absolute configuration so that hydroxydihydroeremophilone, eremophilone and hydroxyeremophilone were now represented by VIII, X and XI, respectively. Zalkow and coworkers[16] provided conclusive proof of this assignment by converting hydroxyeremophilone to the decalone XII which was then synthesized in a stereochemically unambiguous manner from the compound XIII of known[17] absolute configuration. That hydroxyeremophilone is correctly represented

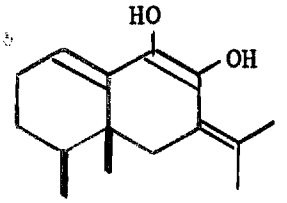
by the tautomeric form XI, rather than the alternative XIV, was recently[18] established by means of nmr.



XII

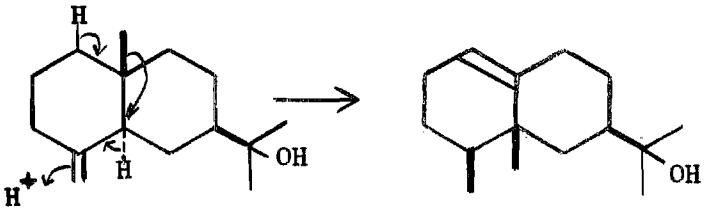


XIII



XIV

The correspondence of the above absolute configurations with that of β-eudesmol (XV) led Zalkow et al.[16] to propose a biogenetic pathway from XV to eremophilone. Support for this proposal was provided several years later by the isolation[19] from Ligularia fischeri Turez. of a key intermediate, eremoligenol (XVI), having a migrated methyl group.



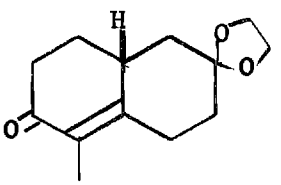
XV XVI

For over twenty years the three ketones from Eremophila mitchelli were the only established examples of the non-isoprenoid eremophilane group of sesquiterpenes. α-Vetivone (isonootkatone, XXXIV, Chart I) was isolated in 1939[20] but was not recognized as an eremophilane-type sesquiterpene until 1967[21]. Calarene (XXXVIII) was isolated in 1953[22] and aristolone (XL) in 1955[23] but their structures were not determined until 1963[24] and 1961[25], respectively. The next eremophilane sesquiterpenes to be isolated and

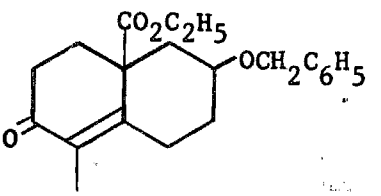
recognized as members of this group were petasine(XX), isopetasine (XXII) and S-petasine (XXI)[26,27] in 1955-56. Since this time, the isolation of eremophilane sesquiterpenes has continued at an ever-increasing rate. A review in 1966[28] listed 31 members of this group while 46 are listed in the present survey constituting a fifty percent increase in only two years! The structures of the eremophilane sesquiterpenes are shown in Chart 1 along with bibliographical references to the isolations and structure determinations which have appeared since the 1966 review.[28]

The synthesis of the eremophilane sesquiterpenes has for many years presented a challenge to organic chemists. The first problem is the synthesis of the carbon skeleton with the correct stereochemistry. Thus, while the eremophilane-type compound XII was synthesized[16] some time ago by a long sequence of reactions it has not been converted into any of the naturally occurring sesquiterpenes.

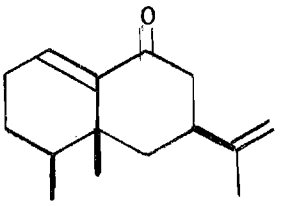
One of the basic synthetic approaches has involved attempts to introduce the angular methyl group by conjugate addition to α,β-unsaturated ketones. A synthetic route proposed by Ireland and coworkers[45] in 1962 in which ketone LXII was reacted with methylmagnesium bromide in the presence of cuprous bromide failed at this step. A similar attempt by Ellis[46] in 1965 to react ketone LXIII with methyl magnesium iodide and cuprous



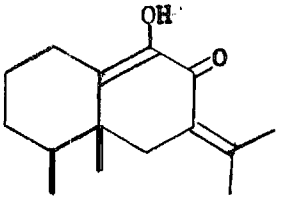
LXII



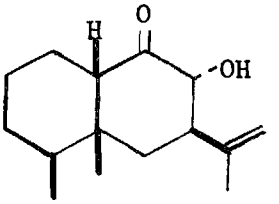
LXIII



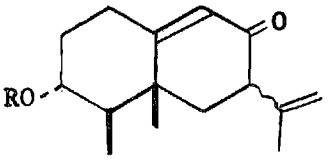
XVII
Eremophilone



XVIII
Hydroxyeremophilone

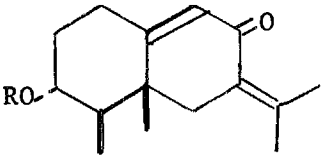


XIX
Hydroxydihydro-
eremophilone



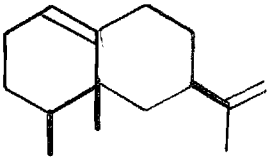
XX Petasine
R=cis-$COC(CH_3)=CHCH_3$

XXI[26,27] S-Petasine
R=cis-$COCH=CHSCH_3$

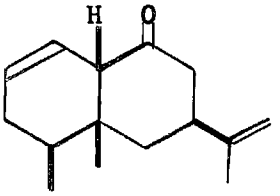


XXII Isopetasine
R=cis-$COC(CH_3)=CHCH_3$

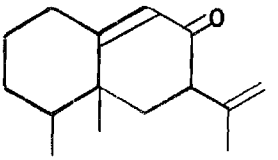
XXIII Isopetasol
R=H



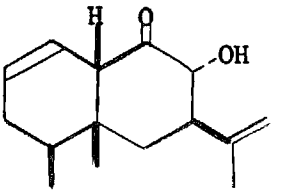
XXIV[29,56]
Eremophilene



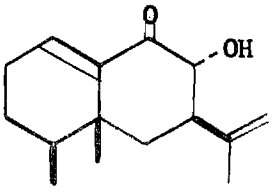
XXV[30]
7α(H)-Eremophila-1,
11-dien-9-one



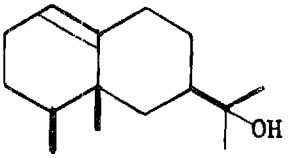
XXVI[31]
Alloeremophilone (?)



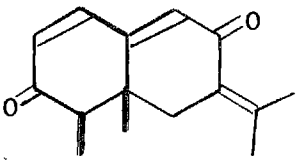
XXVII[32]
8α-Hydroxy-7α(H)-ere-
mophila-1,11-diene-9-one



XXVIII[32]
8α-Hydroxy-7α(H)-eremophila-
10,11-diene-9-one

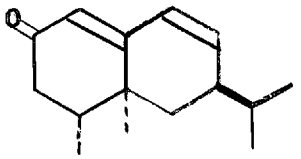


XXIX[19,56]
Eremoligenol



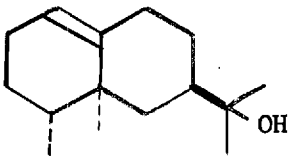
XXX[33]
Warburgiadione

Chart 1. Structures of the Eremophilane Sesquiterpenes



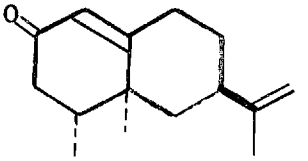
XXXI[34]

Nardostachone



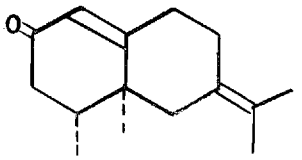
XXXII[35]

Valerianol
(Kusunol)



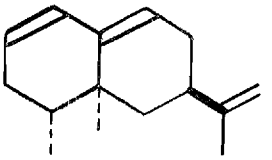
XXXIII

Nootkatone



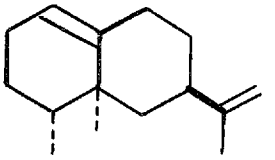
XXXIV[21,36]

α-Vetivone
(Isonootkatone)



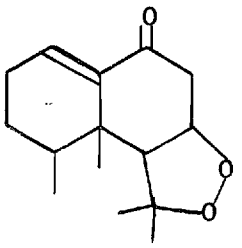
XXXV

Nootkatene



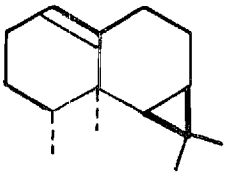
XXXVI

Valencene



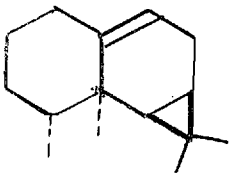
XXXVII[37]

Nardosinons



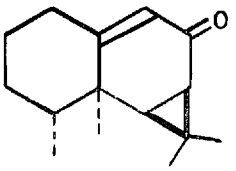
XXXVIII[38]

Calarene
($\Delta^{1(10)}$-Aristolene)



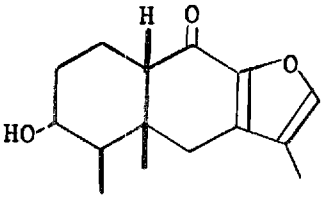
XXXIX

d-Aristolene (α-Ferulene)
l-Aristolene (Aristolene)



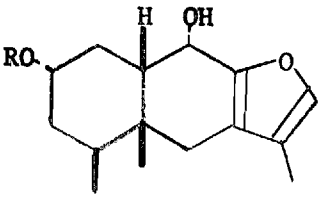
XL[39]

Aristolone



XLI[40]

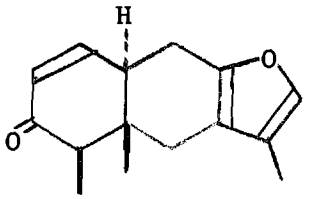
Europsonol



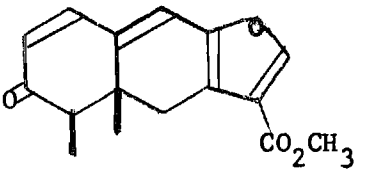
XLII Furanopetasine
R=cis-$COC(CH_3)=CHCH_3$

XLIII Furanopetasol
R=H

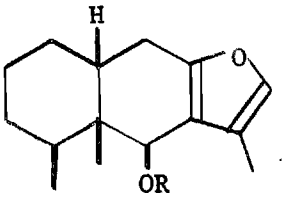
Chart 1. (Continued)



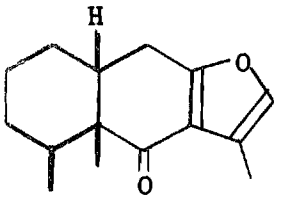
XLIV[41]
Furanoligularenone



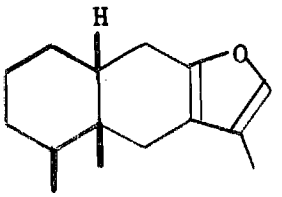
XLV[42]
Warburgin



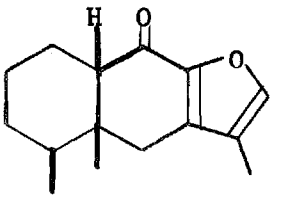
XLVI Petasalbine
R=H
XLVII Albopetasine
R=cis-$COC(CH_3)=CHCH_3$



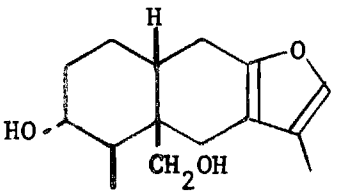
XLVIII
Ligularone



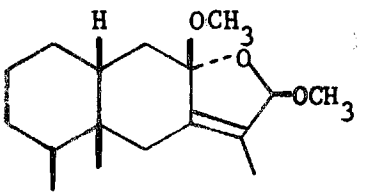
XLIX
Furanoeremophilane



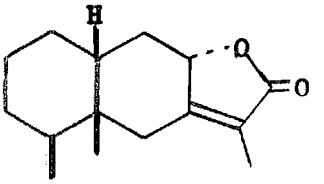
L
Furanoeremophilone



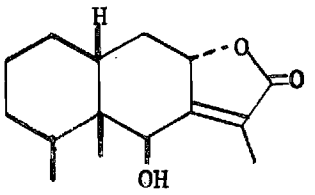
LI
Furanoeremophilandiol



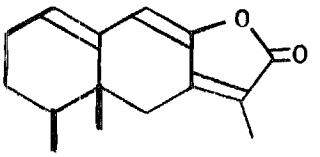
LII[43]
Dimethoxydihydrofuro-
eremophilane



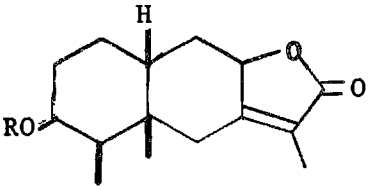
LIII
Eremophilenolide



LIV[19]
6β-Hydroxyeremophilenolide



LV[44]
Ligularenolide



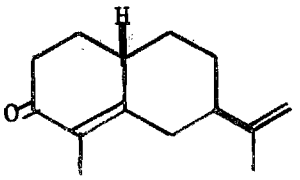
LVI Petasitolide A
R=cis-$COC(CH_3)=CHCH_3$
LVII Petasitolide B
R=trans-$COC(CH_3)CHCH_3$
LVIII S-Petasitolide A
R=cis-$COCH=CHSCH_3$
LIX S-Petasitolide B
R=trans-$COCH=CHSCH_3$

LX
Petasitene (?)

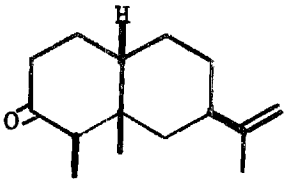
LXI
Albopetasol (?)

Chart 1. (Continued)

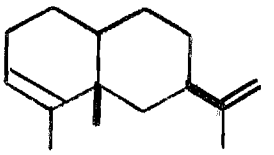
bromide also failed at this step. Piers and Keziere[29a] were recently successful in adding an angular methyl group onto ketone LXIV by use of the reagent lithium dimethylcopper[47] and in two steps converted the resulting product LXV to olefin LXVI. Structure LXVI was orginally proposed for the naturally occurring sesquiterpene eremophilene[48] but the non-identity of LXVI and eremophilene forced revision[29b] of this proposal.



LXIV

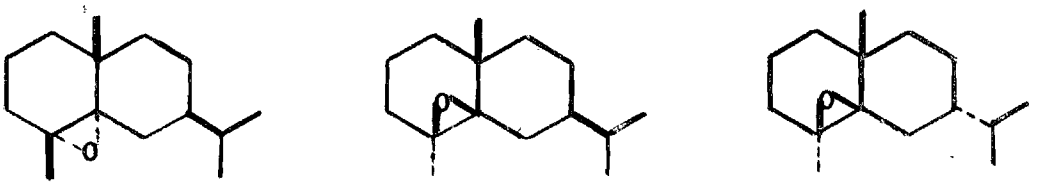


LXV

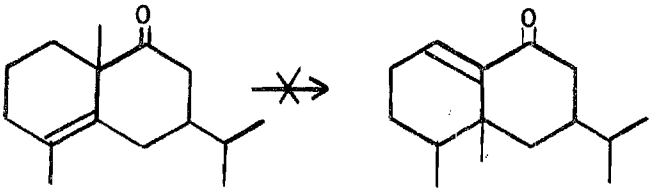


LXVI

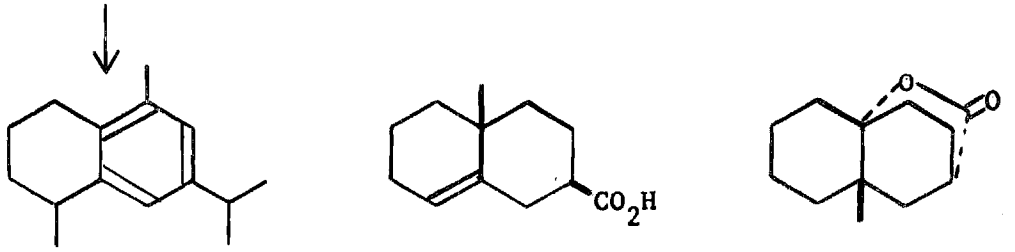
A second approach to the introduction of the angular methyl group has involved attempts to bring about methyl migration in a eudalene-type intermediate in a process not unlike the proposed biogenetic pathway. Treatment[49] of the epoxides LXVII, LXVIII and LXIX with boron trifluoride-etherate, however, gave principally ring-contracted products rather than the desired methyl migration. A similar attempt[50] to rearrange the unsaturated ketone LXX by treatment with boron trifluoride-etherate led to the aromatic compound LXXI rather than the desired dihydroeremophilone LXXII. Heathcock and Kelly[51] were recently successful in converting compound LXXIII to lactone LXXIV by treatment of the former with formic acid. Such a rearrangement in a homologue of LXXIII possessing the other methyl group in ring-A would obviously provide an intermediate quite suitable for conversion to such eremophilane sesquiterpenes as nootkatone (XXXIII), nootkatene (XXXV), valerianol (XXXII), etc.



LXVII LXVIII LXIX



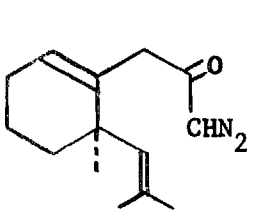
LXX LXXII



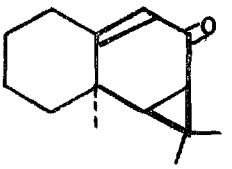
LXXI LXXIII LXXIV

Two unique approaches which resulted in synthesis of a homologue (LXXVI) and a derivative (LXXIX) of natural products deserve comment here. Thus, heating the diazoketone LXXV with cupric sulfate followed by isomerization with methanolic sodium hydroxide gave (±)-4-demethylaristolone LXXVI[52] while formic acid cyclization of the triene LXXVII gave the ester LXXVIII which was converted to (±)-tetrahydroeremophilone[15](LXXIX) in seven steps.[53]

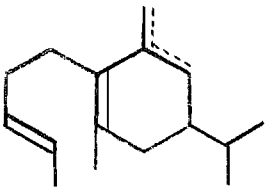
It is interesting to note that Brown et al.[53] could not dehydrate LXXX, the intermediate which gave LXXIX on calcium-ammonia reduction of the corresponding acetate, to achieve a synthesis of LXXII. In contrast, isomer LXXXI was readily dehydrated.



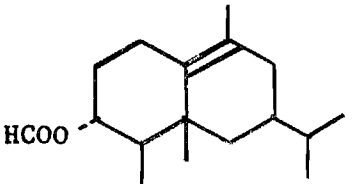
LXXV



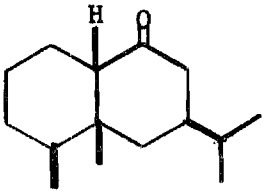
LXXVI



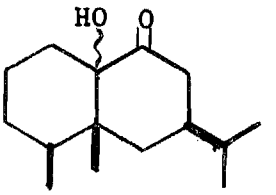
LXXVII



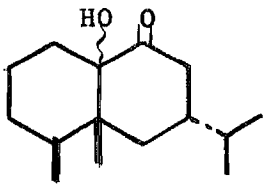
LXXVIII



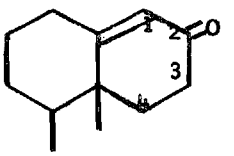
LXXIX



LXXX



LXXXI



LXXXII

The more successful synthetic approaches to the eremophilane sesquiterpenes have involved various Robinson annelation reactions as a means of introducing both methyl groups simultaneously. In 1965 Ellis[46] reacted 2,3-dimethylcyclohexanone with methyl vinyl ketone and thus obtained ketone LXXXII. This approach failed however, when an attempt to introduce an isopropyl group resulted in alkylation at C-1 rather than C-3.

The purpose of the present research was to investigate the Robinson annelation reaction of 2-methyl-1,3-cyclohexanedione (LXXXIV, Chart 2) with trans-3-penten-2-one (LXXXIII) as a means of obtaining the bicyclic diketone LXXXV. The structural features of LXXXV would be suitable for its conversion to a number of the eremophilane sesquiterpenes as illustrated by the examples in Chart 2.

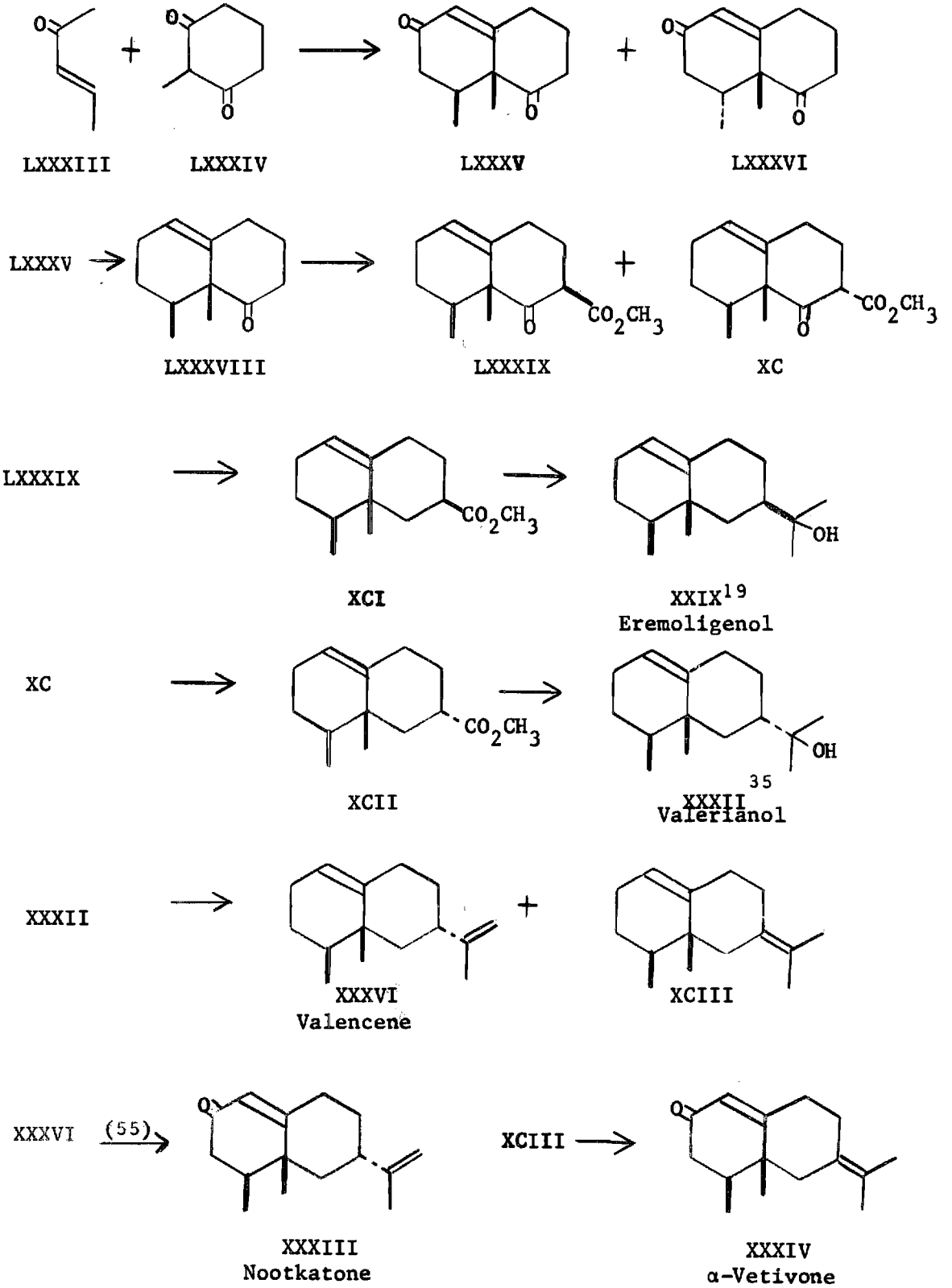
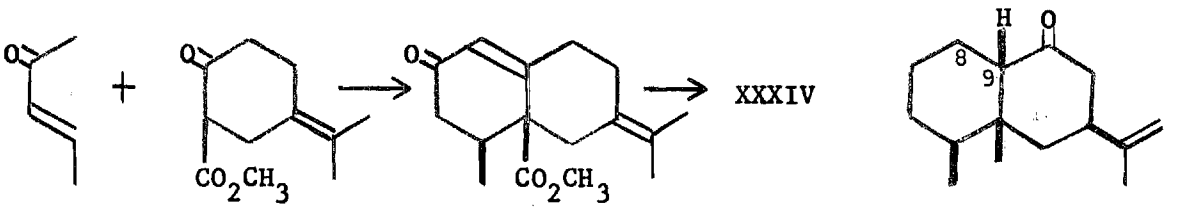


Chart 2. Robinson Annelation Reaction of LXXXIII and LXXXIV.

At the time this research was begun none of the naturally occurring eremophilane sesquiterpenes had been synthesized. Subsequently, however, syntheses of six of these natural products have appeared in the literature. Marshall and coworkers[36] synthesized α-vetivone[21] (isonootkatone, XXXIV) by employing the Robinson annelation reaction of the keto ester XCIV with 3-penten-2-one (LXXXIII) to produce the intermediate XCV. This compound was converted in five steps to (±)-α-vetivone (XXXIV). Ourisson and coworkers[39] converted the α,β-unsaturated ketone LXXXII to (±)-aristolone (XL) in seven steps. Coates and Shaw[54] investigated the Robinson annelation reaction of 2-methyl-1,3-cyclohexanedione (LXXXIV) with 3-penten-2-one (LXXXIII) under slightly different conditions than those employed in the present study and succeeded in obtaining diketone LXXXV. These workers have subsequently used this intermediate in the synthesis of (±)-calarene (XXXVIII)[38], (±)-eremoligenol (XXIX)[56] and (±)-eremophilene (XXIV)[56]. Racemic nootkatone (XXXIII) was recently[74] synthesized in five steps from 4-isopropenylcyclohexanone.



LXXXIII XCIV XCV XCVI

As stated previously, the principal purpose of this investigation was to study the reaction of LXXXIII and LXXXIV as a means of obtaining the diketone LXXXV. It was then necessary to establish the stereochemistry of the two methyl groups in the product of the reaction. Optical rotatory

dispersion was resorted to in order to accomplish this purpose and as a result of observations made during these studies it became of interest to investigate the question of ketal vs. hemiketal formation as discussed in Chapter IV. Another objective developed during this study was the investigation of a possible method of converting cis-8,9-dihydroeremophilone (XCVI) to hydroxydihydroeremophilone (XIX) since a synthesis of XCVI would then constitute a synthesis of the three original eremophilane sesquiterpenes (eremophilone XVII, hydroxyeremophilone XVIII and hydroxydihydroeremophilone XIX) and alloeremophilone (XXVI ?, Chart 2) as discussed in Chapter IV.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Boiling points are also uncorrected. Infrared spectra were recorded with a Perkin-Elmer 237B spectrophotometer with solids in the form of a potassium bromide pellet and liquids as a thin film on sodium chloride plates. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer using deuteriochloroform as a solvent unless otherwise specified. Chemical shifts are reported in ppm downfield from the internal standard tetramethylsilane. The abbreviations s, d, t, q and m respectively refer to singlet, doublet, triplet, quartet and multiplet; coupling constants are reported in cps. Gas-liquid chromatography (glc) was performed using an F & M Biomedical Gas Chromatograph, Model 400,with glass columns and a hydrogen flame detector. Preparative glc was performed on the same instrument employing a stream splitter attachment. Mass spectra were recorded on a Varian M-66 mass spectrometer. Molecular rotations at mercury green line (546.1 mμ) were recorded using a jacketed quartz cell 0.525 decimeters in length at 25.0°C with a Bendix-Ericsson Automatic Polarimeter (No. M5911/1). Optical rotatory dispersion (ord) and circular dichroism (cd) curves were recorded using a 1.0 centimeter strain-free quartz cell with a Jasco ORD-UV5 spectrophotometer with cd attachment (Durrum Instruments). Ultraviolet spectra were recorded on the same instrument using a matched set of 1.0 centimeter quartz cells. Carbon and hydrogen microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mülheim, West Germany.

CHAPTER III

EXPERIMENTAL

Preparation of 3-Penten-2-one (LXXXIII)

This α,β-unsaturated ketone was prepared using the modified procedure of Wilds and Djerassi.[57] A solution of acetone (860 ml) and ether (717 ml) in a five-liter, one-necked, round-bottom flask with magnetic stirrer was cooled to 5°C. To this solution was added 340 ml of a 12 percent aqueous sodium hydroxide solution which had been saturated with salt and cooled to 5°C. A solution of acetaldehyde (656 ml) in acetone (860 ml) was then added through a dropping funnel over a period of about two hours. The resulting double-layered mixture was then vigorously stirred at 5-10°C for 6.5 hours during which time the mixture turned yellow. The organic layer was then separated from the lower aqueous layer and washed with a saturated salt solution. The ether, acetone and approximately 100 ml of water were removed in vacuo at about 60°C on the rotary evaporator and the residue was distilled through a 15-in. Vigreaux fractionating column using the vacuum of a water aspirator. The first fraction obtained was approximately 50 ml of water. This was followed by a fraction (198 g, 17 percent) boiling at 77-81°C (20-25 mm Hg). The reported[57] boiling point of 4-hydroxypentan-2-one is 77-79°C (20 mm Hg). This hydroxy ketone (198 g) and p-toluenesulfonic acid (100 mg) were dissolved in 500 ml of benzene, placed in a Dean-Stark apparatus and the solution was refluxed 12 hours during which time 30 ml of water were obtained (theoretical yield 35 ml). The benzene was then evaporated and

the residue was fractionated through a 15-in. Vigreaux column. The fraction (69.5 g) boiling at 120-23°C was collected as 3-penten-2-one (reported[57] b.p. 121-22.5°C). Analysis by glc using a 6 foot by 1/8 inch column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 85°C and a helium flow rate of 83 ml/min showed peaks at 1.3 (2 percent), 1.5 (83 percent) and 2.0 (15 percent) minutes. Nmr (neat): δ1.85 (doublet of doublets, J_{AX}=6.5 cps, J_{BX}=1.5 cps, 3H), δ2.17 (s, 3H), δ6.05 (doublet of quartets, J_{BX}=1.5 cps, J_{AB}=16 cps, 1H), δ6.82(doublet of quartets, J_{AX}=6.5 cps, J_{AB}=16 cps).

Preparation of 2-Methyl-1,3-cyclohexanedione (LXXXIV)

Following the procedure[58] for hydrogenation of resorcinol, 2-methylresorcinol (Aldrich, 62 g) was dissolved in a solution of sodium hydroxide (24 g) in water (100 ml) and sealed in a high pressure hydrogenation bomb of 200 ml volume with approximately 10 g of Raney nickel catalyst. Hydrogen was introduced at a pressure of 2200 psig, the heater was turned on, and the bomb was shaken. After 30 minutes the temperature had risen to 120°C (a lower temperature would have probably given a better yield) and the pressure had dropped to 500 psig. The heating was discontinued and the bomb recharged to 2200 psig with hydrogen. Four hours later, the pressure had dropped to 1100 psig and the bomb was recharged to 2200 psig and left shaking 12 hours at room temperature during which time the pressure dropped to 1800 psig. The bomb was then opened and the catalyst removed by filtration through a sintered glass filter. The filtrate was then made strongly acidic with concentrated hydrochloric acid whereupon, a large amount of solid precipitated. The solid was removed by filtration and dried overnight at room temperature in a vacuum oven to give 78 g of a product which contained sodium chloride. Separation

was achieved by dissolving the product in acetone (700 ml) and filtering the insoluble sodium chloride. Evaporation of the filtrate gave 48 g (76 percent) of slightly yellow 2-methyl-1,3-cyclohexanedione (m.p.205-207°C) which was recrystallized from acetone to give pinkish-white crystals of LXXXIV, m.p. 208-210°C (lit.[59] m.p. 208-210°C).

Attempted Reaction of 3-Penten-2-one (LXXXIII) and 2-Methyl-1,3-cyclohexanedione (LXXXIV) in Pyridine

The diketone LXXXIV (6.3 g) was added to 150 ml of dry benzene containing 5 g of freshly distilled anhydrous pyridine. The α,β-unsaturated ketone LXXXIII (5 g) was then added and the mixture was refluxed overnight. The diketone did not dissolve so the benzene was evaporated and replaced with pyridine (150 ml) and the resulting homogeneous solution was refluxed overnight. After cooling to room temperature, the brown solution was diluted with ether (200 ml) and washed with 3 percent hydrochloric acid until no more color was extracted and then with 5 percent sodium bicarbonate solution until the extract was colorless. The ether solution was then dried over magnesium sulfate, filtered and evaporated to give 500 mg of dark brown oil. Analysis of the oil by glc (6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 153°C and a helium flow rate of 80 ml/min.) showed mainly diketone LXXXIV and small peaks with retention times of 3.5 and 5.0 minutes. Because of the low yield the reaction was not further investigated.

Attempted Reaction of 3-penten-2-one (LXXXIII) and 2-Methyl-1,3-cyclohexanedione (LXXXIV) in Pyrrolidine

The diketone LXXXIV (1.3 g) and the α,β-unsaturated ketone LXXXIII (2 g) were dissolved in freshly distilled pyrrolidine (50 ml) and refluxed

overnight. The reaction was worked up in the manner described above to give only about 50 mg of a yellow oil which was not further investigated.

Attempted reaction of 3-Penten-2-one (LXXXIII) and 2-Methyl-1,3-cyclohexanedione (LXXXIV) in Methanol/Sodium Methoxide

The diketone LXXXIV (1.3 g) was dissolved in 25 ml of dry methanol (freshly distilled from potassium hydroxide) containing 10 mg of sodium methoxide (Fisher sodium methylate). The α,β-unsaturated ketone LXXXIII (2 g) was added and the solution was refluxed overnight. After cooling, the yellow solution was diluted with ether (100 ml) and washed with 3 percent hydrochloric acid, 5 percent sodium bicarbonate and water, respectively. The ether solution was then dried over magnesium sulfate, filtered and evaporated to give 10 mg of yellow oil. Because of the low yield the reaction was not further investigated.

The Robinson Annelation Reaction of 3-Penten-2-one (LXXXIII) and 2-Methyl-1,3-cyclohexanedione (LXXXIV). Synthesis of 2,5-Dioxo-trans-4,4a-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene (LXXXVI)

Following the method used[6] in the reaction of LXXXIV with methyl vinyl ketone, a mixture of diketone LXXXIV (23 g) and one pellet of potassium hydroxide in dry methanol (125 ml) was heated on the steam bath to effect solution and then refluxed for three hours. About one-half of the methanol was then removed on the rotary evaporator causing the formation of a large quantity of solid which led to bumping, consequently, the evaporation was discontinued. A small portion of the solid was removed and identified as unreacted LXXXIV, m.p. 205-208°C. Although it appeared no

reaction had occurred 75 ml of benzene was added, a Dean-Stark trap was attached, and the remaining methanol was removed by distillation. After about 60 ml of distillate had been collected, two phases began to distill and one milliliter of freshly distilled pyrrollidine was added. The large volume of the lower phase indicated that starting ketone LXXXIII, which is insoluble in benzene, might be forming an azeotrope with benzene and therefore, the contents of the Dean-Stark trap were periodically returned to the reaction pot. After 48 hours reflux, the trap finally contained only about two milliliters of the lower phase and refluxing was discontinued. The purple-black reaction solution was cooled to room temperature and diluted with 100 ml of ether. The resulting solution was washed with 3 percent hydrochloric acid, water and saturated salt solution, respectively, dried over magnesium sulfate, filtered and evaporated to give 18.4 g of a dark purple oil which slowly crystallized. Filtration gave 6.6 g of a light brown solid, LXXXVI. The filtrate was analyzed by glc (6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 170°C and helium flow rate of 72 ml/min.) and gave peaks at retention times of 4.0 minutes (70 percent, LXXXVI) and 4.2 minutes (16 percent, probably LXXXV) along with a number of very small peaks. Evaporation of the solvent from the filtrate gave 11.8 g of dark residue which was chromatographed on 500 g of Merck acid-washed alumina. Elution with 3400 ml of benzene and 250 ml of 10 percent chloroform in benzene gave 9.6 g of LXXXVI which was recrystallized from ether to give 9.2 g of analytically pure LXXXVI, m.p. 81.5-83°C (lit.[54] 82.5-83.5°C), which gave a single symmetrical peak at 61.6 minutes on a 6 foot by 1/8 inch glass column of 5 percent Carbowax 20 M on 90/100 mesh AS at 141°C and a helium flow rate of 79 ml/min. (Found C, 75.21; H,

8.44, Calc for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33 percent); ν_{max}^{KBr} 1703, 1672, 1618 cm^{-1}; Nmr ($CDCl_3$): δ0.80 (d, J=7 cps, 3H), δ1.41 (s, 3H), δ5.74 (s, 1H). Several other noncrystalline fractions (total weight 1.7 g) were collected but were not further investigated.

A simpler modified procedure in which the methanol was replaced with absolute ethanol led to similar results. Thus, diketone LXXXIV (292 g) was dissolved in 2500 ml of hot benzene:ethanol (1:1) and the α,β-unsaturated ketone LXXXIII (246 g), potassium hydroxide (5 g) and pyrrollidine (25 ml) were added. The solution, which turned purple on addition of the pyrrollidine, was heated at or near reflux and the disappearance of LXXXIV was followed by glc. After 9.5 days, very little LXXXIV remained and two liters of solvent were removed by distillation. After cooling overnight, the reaction mixture was diluted with ether (1000 ml) and filtered to give 25.9 g of an unidentified brown solid melting above 360°C. The filtrate was diluted with more ether (1000 ml) and washed with three 200 ml portions of 5 percent hydrochloric acid and five 200 ml portions of water. The aqueous layers were combined and back-extracted with five 200 ml portions of ether. The organic layers were combined, washed with five 200 ml portions of water, dried over magnesium sulfate and evaporated to give 385 g of dark brown viscous oil. Analysis of the product by glc using a 6 foot by 1/8 inch glass column of 3 percent OV-17 on 100/120 mesh Gas-Chrom Q at 145°C and a helium flow rate of 95 ml/min showed LXXXVI (82 percent) at a retention time of 10.3 min along with a peak at 11.2 min (13 percent, probably LXXXV) and three other very small peaks at 1.1, 7.0 and 8.2 minutes. This material was chromatographed on 2700 g of Merck acid-washed alumina. Elution with 2500 ml of benzene gave less than 100 mg of a yellow oil, not further investi-

gated. Elution with 7.5 liters of benzene gave 296 g of a light brown gum which partially crystallized to give 95 g of pure LXXXVI. The mother liquor was rechromatographed on 4400 g of Merck acid-washed alumina. Elution with ten liters of petroleum ether, one liter each of 5 percent and 10 percent benzene in petroleum ether and two liters of 25 percent benzene in petroleum ether gave no material. Elution with nine liters of 50 percent, three liters of 75 percent, and one liter of 80 percent benzene in petroleum ether gave 51 g of pure LXXXVI. A number of other noncrystalline fractions obtained in the two chromatographies described, were not further investigated.

Preparation of Thioketal CIII

The bicyclic diketone LXXXVI (9.2 g) and p-toluenesulfonic acid (1.0 g) were dissolved in glacial acetic acid (200 ml) and a solution of ethanedithiol (4.5 g) in glacial acetic acid (15 ml) was added dropwise over 15 minutes with stirring. After stirring for 36 hours at room temperature, a sample was removed and analyzed by glc using a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 182°C and a helium flow rate of 63 ml/min. This sample showed peaks at retention times of 2.5 min (9 percent),LXXXVI, 15.2 min (55 percent), and 17.1 min (36 percent). Analysis at 18 hours had shown 14 percent LXXXVI and 53 and 33 percent, respectively, of the latter two peaks. The reaction mixture was diluted with water (300 ml) and extracted with three 100 ml portions of chloroform. The organic layer was washed with three 100 ml portions of 0.5 N sodium hydroxide, then 100 ml of water, dried over magnesium sulfate and evaporated to give 13.3 g of a viscous dark yellow oil. Analysis of the oil by glc using the column described above at a slightly lower temperature (179°C) and a helium flow rate of 80 ml/min

showed starting material LXXXVI at 2.8 min (9 percent), the second peak at 16.4 min (88 percent) and the third peak at 18.2 (3 percent). The oil was chromatographed on 650 g of Woelm neutral alumina. Elution with 1.5 liters of hexane and 500 ml each of 10, 20 and 50 percent ether in hexane gave no material. Elution with 3.25 liters of ether and 2.5 liters of one percent and 0.5 liters of 5 percent methanol in ether gave 10.1 g of slightly yellow oil CIII, which gave a single peak at 15.3 min under the conditions first described above. ν_{max}^{film} 1705, 1640 cm^{-1}; Nmr ($CDCl_3$) δ1.07 (d, J=6.5 cps, 3H), δ1.31 (s, 3H), δ3.36 (m, 4H), δ5.67 (s, 1H). On standing at room temperature, CIII begins to turn dark within 24 hours.

Preparation of W-2 Raney Nickel

Following the published[61] procedure, a solution of sodium hydroxide (190 g) in water (750 ml) in a two-liter Erlenmeyer flask was cooled to 0°C in a salt-ice water bath and Raney nickel-aluminum alloy (W. R. Grace, 150 g) was added at such a rate that the temperature did not rise above 25°C and the mixture did not foam over due to the large volume of hydrogen released. During the addition, stirring was accomplished by means of a magnetic stirrer, the use of which greatly speeded the washing process described below by increasing the rate of settling. After addition was complete, the mixture was allowed to come to room temperature and after standing for a period of five hours, was then heated on the steam bath for 12 hours. The flask was removed from the steam bath, the nickel allowed to settle, the liquid decanted and the catalyst washed by decantation with two one-liter portions of water. The catalyst was then transferred to a one-liter Erlenmeyer flask and the water was replaced with a solution of sodium hydroxide (25 g) in water (250 ml). The nickel was

suspended and then allowed to settle and the base decanted. The catalyst was then washed with forty 500 ml portions of water by stirring the catalyst for several minutes with each portion, allowing the nickel to settle and decanting the wash water. The washing process was then repeated with three 100 ml portions of 95 percent ethanol and finally with three 100 ml portions of absolute ethanol to give a very pyrophoric catalyst which could be stored for several months in the freezer in a tightly stoppered flask filled completely with absolute ethanol.

Preparation of Ketone CV

Thioketal CIII (7.7 g) was dissolved in absolute ethanol (250 ml) containing four teaspoons (approximately 16 g) of Raney nickel catalyst (W-2). The mixture was then refluxed 20 hours with more catalyst being added after 12 hours (three teaspoons) and 15 hours (one teaspoon), respectively. The mixture was then allowed to stand at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to give 4.7 g of a yellow oil which on glc analysis using a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 140°C and a helium flow rate of 80 ml/min showed peaks at 3.1 min (≈ 1 percent), 3.8 min (86 percent), 6.9 min (7 percent) and 9.3 min (6 percent). Chromatography on 650 g of Merck acid-washed alumina gave in the first 500 ml of benzene eluent, 200 mg of material which was not further investigated. Elution with an additional 500 ml of benzene gave 2.8 g of light yellow oil, 2.56 g of which was used in the dimethyl carbonate reaction, described on the following page, without further purification. Subsequent nmr analysis of the remainder of the material showed it to be a mixture since methyl singlets were observed at δ1.26

and δ1.08 in a ratio of approximately 2.3:1. Distillation of this material at 51-55°C (0.025 mm Hg) led to extensive decomposition and gave 100 mg of a colorless oil which gave a peak at 6.6 min (>95 percent) and 4.9 min (<5 percent) on a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 120°C and a helium flow rate of 88 ml/min. Analysis on a 6 foot by 1/8 inch glass column of 5 percent Carbowax 20 M on 90/100 mesh AS at 124°C and a helium flow rate of 93 ml/min however, showed peaks at 3.8 min (5 percent), 4.3 min (76 percent), and 5.5 min (19 percent).

The desulfurization reaction was repeated on a large scale by dissolving 180 g of CIII in 500 ml of absolute ethanol containing 850 g of Raney nickel catalyst (W-2) and refluxing the mixture for 24 hours. The solvent was then decanted and replaced with one liter of fresh ethanol and refluxed for 12 hours. This process was repeated four times and the combined solvents were evaporated to give 109.8 g of yellow oil which gave peaks at 4.5 min (9 percent), 5.2 min (69 percent) and 6.7 min (22 percent) on a 6 foot by 1/8 inch glass column of 5 percent Carbowax 20 M on 90/100 mesh AS at 120°C and a helium flow rate of 90 ml/min. This material was chromatographed on 4500 g of Merck acid-washed alumina and a total of 62 fractions of volumes varying from 0.5 to 6 liters were collected using hexane, increasing percentages of benzene in hexane, benzene, increasing percentages of chloroform in benzene and chloroform for elution. The first sixteen fractions were mixtures, the glc's of which showed peaks with retentions times of 4.5 and 5.2 minutes while the other fractions were more complex. The tenth through fifteenth fractions were mixed, dissolved in ether and cooled to Dry Ice-acetone temperature, whereupon, the material partially crystallized. After filtration, the solid melted

on warming to room temperature and was found by glc analysis to be 97 percent of the component with retention time of 5.2 min; ν_{max}^{film} 1705, 1653 cm^{-1}; Nmr (neat) δ0.83 (d, J=6.5 cps, 3H), δ1.26 (s, 3H), δ5.41 (m, 1H). This material was used in the sodium borohydride reduction described below. The sixteenth fraction (1.8 g, 90 percent peak with R_T 5.2 min) was used in the diethyl oxalate reaction below.

Attempted Reaction of Keotne CV with Dimethyl Carbonate[62]

The ketone CV (2.56 g, ca. 2.3:1 mixture) was dissolved in 12 ml of dry dioxane (freshly distilled from sodium aluminum hydride) and the resulting solution was added dropwise under a nitrogen atmosphere over a 30 minute period to a stirred, heated suspension of 1.20 g of a "56.7 percent dispersion of sodium hydride in mineral oil" in dry dioxane (100 ml) containing dry dimethyl carbonate (6.5 g, distilled from sodium). After heating on the steam bath for 6 hours, the mixture was stirred overnight at room temperature and then the solvent was evaporated by passing nitrogen over the mixture. The solid residue was dissolved in 200 ml of 10 percent aqueous acetic acid and extracted with chloroform. The chloroform extract was washed with 5 percent sodium bicarbonate and saturated brine and then dried over magnesium sulfate, filtered and evaporated to give 2.8 g of a dark oil with a distinctive minty odor. Analysis by glc on a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 135°C and a helium flow rate of 80 ml/min showed the starting material with R_T 5.4 min (18 percnet) along with other components with R_T 6.0 min (15 percent); R_T 6.6 min (9 percent) and R_T 7.1 min (50 percent). An infrared spectrum of the product showed very strong hydroxyl absorption at 3400 cm^{-1} and a weak carbonyl band at 1705 cm^{-1}. An unsuccessful attempt was made to separate the mix-

ture by column chromatography on alumina but all fractions were mixtures and showed varying amounts of both hydroxyl and carbonyl absorption in their infrared spectra. The fraction showing the least carbonyl absorption in its chloroform and its nmr spectrum ($CDCl_3$) showed a methyl doublet centered at δ0.98, a methyl singlet at 1.10, several peaks centered at δ3.61, and several peaks in the region δ5.2-6.1 indicating a mixture of isomeric olefinic alcohols.

Attempted Reaction of Ketone CV with Diethyl Oxalate[16]

The ketone CV (180 g, 90 percent one isomer) was dissolved in dry benzene (50 ml), and to this solution 1.66 g of the "sodium hydride" dispersion described above was added, followed by the dropwise addition over ten minutes of 3.80 g of dry diethyl oxalate. The benzene and diethyl oxalate were dried by stirring with "sodium hydride" and filtering just before use. The reaction mixture was stirred under a nitrogen atmosphere for 24 hours at room temperature. Analysis by glc showed only starting material CV and no reaction had apparently occurred. The mixture was then refluxed for 15 min., after which glc analysis showed complete consumption of CV. The mixture was then cooled to room temperature, slowly poured into 100 ml of water and finally extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to give 1.53 g of yellow oil which on glc analysis using a 6 foot by 1/8 inch glass column of 5 percent Carbowax 20 M on 90/100 mesh AS at 123°C and a helium flow rate of 86 ml/min. showed starting material (<1 percent) with R_T 6.4 and other components with R_T 8.6 min (8 percent), R_T 10.5 min (23 percent), R_T 13.0 min (9 percent) and R_T 19.4 min (57 percent) as well as several very minor components (20 percent). The infrared spectrum of the mixture was very simi-

lar to that of the product from the dimethyl carbonate reaction above showing very strong hydroxyl absorption at 3400 cm^{-1} and very weak carbonyl bands at 1730 and 1705 cm^{-1}. A direct comparison by glc of the two reaction products showed that the two major components in each product were identical. The "sodium hydride" may have been mislabeled and might have been lithium aluminum hydride which reduced the ketone to a mixture of alcohols.

Sodium Borohydride Reduction of Ketone CV

Ketone CV (4.13 g, 97 percent one isomer) was dissolved in 95 percent ethanol (50 ml) and a solution of sodium borohydride (1.14 g) in 30 ml of the same solvent was added. After stirring overnight, a white precipitate had formed and the mixture was poured into water (300 ml) and extracted with chloroform. The chloroform extract was washed with water, dried over magnesium sulfate and evaporated to give 4.12 g of a pale yellow viscous oil (CVI). Analysis of the oil by glc on a 6 foot by 1/8 inch glass column of 5 percent Carbowax 20 M on 90/100 AS at 122°C and a helium flow rate of 85 ml/min showed peaks with R_T 9.2 min (1 percent), 11.3 min (29 percent), 13.9 min (2 percent) and 20.6 min (68 percent), respectively. The infrared spectrum showed absorption bands at 3400 and 1655 cm^{-1}. The two major components had the same retention times as the major products of the dimethyl carbonate and diethyl oxalate reactions. When an attempt was made to purify the product by column chromatography on Merck acid-washed alumina, the material could not be eluted from the column even with 20 percent methanol in chloroform.

Dehydration of Alcohol CVI with Phosphorous Oxychloride

The mixture of alcohols CVI (4.12 g) was dissolved in anhydrous pyridine (50 ml) and cooled in an ice bath. Phosphorous oxychloride (9.5 ml) was added dropwise with stirring over a 30 minute period. When about one-half of the reagent had been added, the reaction mixture was analyzed by glc under the conditions described in the previous section. The ratio of the peak area with R_T 20.6 min to that with R_T 11.3 min had decreased from 2.3 to 1.3, i.e., the isomer with R_T 20.6 min was reacting faster. After 5 hours, glc analysis showed disappearance of the orginal peaks and a number of peaks had appeared with R_T 0.5 to 1.2 minutes and one peak at R_T 4.0 minutes. The reaction mixture was then slowly poured into ice water (300 ml) and extracted with ether. The ether extract was washed successively with 5 percent hydrochloric acid, 5 percent sodium bicarbonate and water, then dried over magnesium sulfate and evaporated on the steam bath through a 15 inch Vigreaux column. The residue (0.9 g) was not further investigated.

Acetylation of Alcohol CVI.

Attempted Pyrolysis of CVI Acetate

The mixture of α and β alcohols CVI (1.20 g) was dissolved in anhydrous pyridine (5 ml) and acetic anhydride (2 ml) was added. After stirring overnight, the reaction mixture was poured in water (50 ml) and extracted with chloroform. The extract was washed successively with 5 percent hydrochloric acid, 5 percent sodium bicarbonate and water, dried over magnesium sulfate and evaporated to give 1.35 g of an oily mixture of two acetates with glc retention times of 4.8 and 5.9 minutes on the 6 foot by 1/8 inch column of 5 percent Carbowax 20 M on 90/100 mesh AS at

125°C and helium flow rate of 90 ml/min. The infrared spectrum of this material showed absorptions at 1735, 1658 and 1243 cm^{-1}. The acetate mixture (1.35 g) was dissolved in benzene and slowly dropped through a 12 inch column of glass helices at 537°C under a nitrogen atmosphere. After passing the material through the column five times the eluent was still more than 80 percent starting material.

Preparation and Pyrolysis of the Xanthate Ester of CVI

Potassium (1.37 g) was dispersed in benzene (100 ml) by refluxing and rapid magnetic stirring. The alcohol mixture CVI (4.2 g) in benzene (50 ml) was then added slowly and the mixture turned dark red as it was refluxed for 30 minutes. The mixture was then cooled, carbon disulfide (25 g) was added and refluxing resumed for 30 minutes. The mixture was again cooled, methyl iodide (9.1 g) was added and refluxing continued for 20 hours. The hot mixture was then filtered, the recovered solid material was washed with hot benzene, and the filtrate and washings were combined and washed with water, dried over magnesium sulfate, and evaporated to give 5.6 g of the xanthate as an orange oil. This material was pyrolyzed by heating in an oil bath at 215 ±5°C for 1.5 hours. Large volumes of foul-smelling gases (methyl mercaptan and carbonyl sulfide) were given off leaving 3.8 g of dark oil which was chromatographed on 700 g of Merck acid-washed alumina. Elution with 500 ml of hexane gave 0.22 g of a yellow oil. Elution with an additional 550 ml of hexane gave 0.77 g of a colorless oil which seemed most likely to contain the desired hydrocarbon. Other fractions collected have not been further investigated. The 0.77 g was rechromatographed on 370 g of Merck acid-washed alumina using a 6 foot by 3/4 inch column and collecting 17 ml fractions with hexane as the

solvent. The first 20 fractions gave 21 mg and the twenty-first gave 27 mg of material. The twenty-second fraction weighed 82 mg and in the infrared spectrum showed bands at 2996, 1667 (broad, weak), 1451, 1375, 756 and 712 cm^{-1}. The nmr ($CDCl_3$) showed signals at δ.83 (d, J=6.5 cps), δ1.20 (s) and δ5.2-5.8 (complex) in a ratio of 3:3:3 as expected for CVII. However, the remaining signals integrated for 18 protons and the purity of this fraction is questionable. The twenty-third fraction weighed 147 mg and was not further investigated. However, the twenty-fourth fraction (152 mg) showed infrared bands at 3069, 1640, 1429 and 885 cm^{-1} indicative of a gem-disubstituted olefin. The nmr ($CDCl_3$) showed signals at δ1.08 (d, J=6.5 cps), δ4.75 (d, J=1 cps) and δ5.42 (multiplet) but no integral numbers of acceptable magnitude could be assigned to the signals so it is concluded that the material is a mixture. The absence of a methyl singlet along with the signal at δ4.75 and the infrared data indicates that the major component contains an exo methylene group. Ten more fractions were collected but have not been investigated.

Preparation of Ketal CX

Ethylene glycol (2.5 g) was dissolved in benzene (200 ml) in a Dean-Stark phase-separating apparatus and the solution was refluxed one hour to remove water. The diketone LXXXVI (7.0 g) and p-toluenesulfonic acid (50 mg) were then added and the resulting solution was refluxed three hours with continuous removal of water. Analysis by glc on a 6 foot by 1/8 inch glass column of 3 percent SE-30 at 160°C and a helium flow rate of 88 ml/min showed starting material with R_T 3.8 min and a single product with R_T 6.6 min in the ratio 1:1.6. After an additional hour of

reflux the ratio had changed to 1:2. More ethylene glycol (1.0 g) was added in two equal portions after a total of four and eight hours of reflux. The mixture was cooled after 9.5 hours reflux and poured into 5 percent aqueous sodium bicarbonate solution. After shaking in a separatory funnel the organic layer was separated, washed with water, dried over magnesium sulfate and evaporated to give 8.3 g of a yellow oil which contained starting material and product in a 1:8 ratio. On standing overnight, the oil partially crystallized and was filtered and recrystallized from ether to give 4.5 g of ketal CX as a white solid, m.p. 89-90°C (lit.[54] 87-88°C); ν_{max}^{KBr} 1707, 1667 cm^{-1}. The ketal is very unstable and soon turns dark on standing.

Wolff-Kishner Reduction of CX. Preparation of Ketone CXII

Potassium hydroxide (20 g) and 95 percent hydrazine (20 ml) were added to diethylene glycol (100 ml) and the mixture warmed to effect solution. After cooling to room temperature, the solid ketal CX (4.3 g) was added and the mixture was heated with stirring at 150±5°C in an oil bath for 20 hours. The temperature was then raised to 190°C and excess water and hydrazine were slowly distilled from the reaction mixture over a four hour period. The solution was then cooled to room temperature and poured into water (500 ml). The water and hydrazine distillate were added to the aqueous solution and the mixture was extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated to give 3.6 g of a yellow oil (CXI) which showed an ether band at 1100 cm^{-1} and no carbonyl bands in the infrared spectrum. The remainder of the product (3.8 g) from the ketalization reaction above which did not crystallize was separately subjected to the Wolff-Kishner

reaction as described on the preceding page and the products from both reactions were combined to give 4.6 g of yellow oil. This material was dissolved in 150 ml of a mixture of equal portions of dioxane and 5 percent aqueous hydrochloric acid and stirred overnight at room temperature. The solution was then poured into water (300 ml) and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to give 3.7 g of a yellow oil. Distillation of this material at 76-78°C (0.5 mm Hg) gave 2.4 g of CXII as a pale yellow oil which on standing overnight crystallized to large colorless prisms, m.p. 34-35°C. (Found: C, 80.53; H, 10.64. Calc. for $C_{12}H_{18}O$: C, 80.90; H, 10.11 percent); ν_{max}^{KBr} 1672, 1615 cm^{-1}; λ_{max} 239 mμ(ε 15,060) and 312 mμ (ε 150) in 95 percent ethanol; Nmr ($CDCl_3$) δ1.01 (d, J=6.5 cps, 3H), δ1.28 (s, 3H), δ5.75 (d, J=1 cps, 1H).

Lithium-Ammonia Reduction of CXII. Preparation of trans-4,10-Dimethyl-trans-2-decalone (CXIII)

The unsaturated ketone CXII (2.00 g) was dissolved in tetrahydrofuran (50 ml) and approximately 200 ml of liquid ammonia was condensed into the solution by means of an acetone-Dry Ice condensor. Lithium (0.5 g) was added in small pieces and the resulting blue solution was stirred at reflux for 30 minutes. Ammonium chloride (7 g) was slowly added and the resulting mixture was allowed to evaporate overnight. Water (300 ml) was added to the residue which was then extracted with ether. The ether extract was washed with water, dried over magnesium sulfate then evaporated to give 1.6 g of a yellow oil. Distillation of 1.2 g at 60-63°C (0.1 mm Hg) gave 1.06 g of colorless oil which was analyzed on a 4 foot by 1/8 inch column of 10 percent SE-30 at 180°C

and a helium flow rate of 88 ml/min and showed the product with R_T 1.4 min (73 percent) and starting material with R_T 1.8 min (27 percent). Preparative glc using a 3 foot by 1/2 inch column of 10 percent SE-30 on 100/120 mesh Gas-Chrom Q at 140°C and a helium flow rate of 130 ml/min gave the analytical sample of CXIII. (Found: C, 79.35; H, 10.93. Calc. for $C_{12}H_{20}O$: C, 80.00; H, 11.11 percent); ν_{max}^{film} 1710 cm^{-1}; nmr (d_6-acetone) δ0.93 (d, J=7 cps, 3H), δ1.20 (s, 3H).

Preparation of l-Menthydrazide (l-Menthyl N-Aminocarbamate)

Following the published[63] procedure, l-menthol (156 g) and ethyl chloroformate (156 g) were mixed, 0.5 ml of pyridine was added, and the mixture refluxed for 17 hours. The mixture was then distilled at 20 mm Hg (water aspirator) and, after distilling about 50 ml of low boiling material, the product (212 g) was distilled at 125-126°C (lit.[63] 121°C, 9 mm Hg) as a colorless sweet smelling oil. This ethyl l-menthyl carbonate (200 g) was dissolved in 300 ml of freshly distilled n-butyl cellosolve and, after addition of hydrazine hydrate (70 g), the mixture was refluxed 44 hours. Approximately 150 ml of low-boiling material was distilled at atmospheric pressure and then 300 ml more was distilled under reduced pressure (water aspirator). The residue was poured into one liter of hot hexane whereupon a small amount of insoluble pink gum separated. Filtration gave a cloudy filtrate which on standing overnight gave 53 g of a white crystalline solid. After filtration and concentration to about one-half volume, more solid crystallized from the filtrate. Further concentration led to a total of 75 g of l menthydrazide (CXV), m.p. 95-97°C (lit.[63] 101.5-102°C); $\{\phi\}_{5461}^{25.0}$ - 164.4°C

(c = 0.3922, ethanol, d = 0.495) lit[63] $\{\Phi\}_D^{25}$ -171°C (c = 1.9612, ethanol, d = 2).

Preparation of the l-Menthydrazone CXVI of Ketone CXIII.

Partial Resolution of CXIII

The product from the lithium-ammonia reduction (0.95 g, 73 percent CXIII) and l-menthydrazide CXV (1.13 g) were dissolved in 10 ml of a solution prepared by dissolving 2 g of sodium acetate and one milliliter of glacial acetic acid in 100 ml of 95 percent ethanol. The resulting solution was refluxed on the steam bath for 70 hours and upon cooling to room temperature deposited 782 mg (40 percent) of a slightly yellow solid (S-1), {Φ}-97.4°C. The molecular rotations reported for this and the following solids were recorded in ethanol solution at the mercury green line (546.1 mμ) using a jacketed cell 0.525 decimeters in length at 25.0°C in a Bendix-Ericsson Automatic Polarimeter (No. M5911/1). Solid S-1 (732 mg) was dissolved in 20 ml of 95 percent ethanol and concentrated to 10 ml whereupon 33.0 mg of solid S-2 crystallized as very fine white needles, m.p. 197-98°C, {Φ}-42.5°C. The mother liquor (ML-2) on continued standing produced 43.8 mg of solid S-4, m.p. 197-98°C, {Φ}-66.8°C. The mother liquor was concentrated to one-half volume and on standing produced 181 mg of solid S-7, m.p. 197-99°C, {Φ}-45.5°C. The mother liquor (ML-7)has not been further investigated. The original mother liquor (ML-1), after filtration of S-1, was concentrated to one-half volume and on standing produced 130 mg of solid S-3, m.p. 175-76°C, {Φ}-163.9°. The mother liquor (ML-3) on further standing yielded an additonal 299 mg of solid S-5, m.p. 171-73°C, {Φ}-157.8°C. The mother liquor (ML-5) on cooling in an ice water bath produced 44.4 mg of solid

S-6, $\{\Phi\}$-21.2°C. The mother liquor (ML-6) has not been further investigated.

In order to regenerate the partially resolved ketone CXIII a portion of S-7 (53.8 mg) was added to 30 ml of a 10 percent solution of sulfuric acid in water--95 percent ethanol (1:1). The resulting solution was refluxed 4 hours. Approximately 5 ml of ethanol was then distilled and the remaining solution was steam-distilled with continuous ether extraction of the steam for 3 hours. The ether extract was dried over magnesium sulfate and evaporated to give 32.3 mg of a yellow oil. Analysis by glc on a 10 foot by 1/4 inch column of 10 percent SE-30 on 100/120 mesh Gas Chrom Q at 180°C and a helium flow rate of 80 ml/min showed peaks with retention times of 2.8 min (19 percent, menthol) and 8.2 min (64 percent, CXIII) along with six small peaks (total 17 percent). The component with R_T 8.2 min was collected by preparative glc after cooling the above column to 160°C. Under these conditions, the material had a retention time of 14.0 min as did racemic CXIII and the collected material was shown to be homogeneous on reinjection and to give a single peak on mixed injection with racemic CXIII.

The material gave the following ord curve (c = 0.36, d = 0.1 dm, methanol) $\{\Phi\}_{450}$-125°, $\{\Phi\}_{307}$-1800°, $\{\Phi\}_{268}$+2450°, $\{\Phi\}_{240}$+2275°. Addition of a trace of concentrated hydrochloric acid gave $\{\Phi\}_{450}$-100°, $\{\Phi\}_{307}$-963°, $\{\Phi\}_{268}$+875°, $\{\Phi\}_{240}$+625°. (Appendix II, Figure 1.)

Catalytic Reduction of CXVIII. Preparation of cis-4,10-Dimethyl-trans-2-decalone (CVIII)

The starting material CXVIII was previously synthesized by Zalkow[16] et al. and gave a peak of retention time 6.8 min on a 6 foot by 1/8 inch column of 5 percent Carbowax 20 M on 90/100 mesh AS at 120°C and a helium flow rate of 85 ml/min. An impurity (less than one percent) had a retention time of 5.8 min. The compound (390.5 mg) was dissolved in 50 ml of absolute ethanol with 41 mg of 5 percent platinum on carbon catalyst and stirred in the presence of excess hydrogen at atmospheric pressure for 5.3 hours. The system apparently leaked and an accurate measure of the volume absorbed could not be determined. The catalyst was removed by filtration and evaporation of the solvent gave 386 mg of a colorless oil which showed on glc peaks with R_T 6.0 min (95 percent) and 8.9 min (5 percent) under the conditions specified above. Distillation of the product afforded 200 mg of pure CVIII, b.p. 64-66°C (0.2 mm Hg) lit.[16] 70-73°C (0.5 mm Hg); Nmr ($CDCl_3$ δ0.91 (d, J=6 cps, 3H), δ0.89 (s, 3H); ord (c = 0.305, d = 0.1 dm, methanol $\{\Phi\}_{450}$-147.6°, $\{\Phi\}_{305.5}$-1800°, $\{\Phi\}_{266.5}$+1888.5°, $\{\Phi\}_{225}$+1015°. Addition of a trace of concentrated hydrochloric acid gave $\{\Phi\}_{450}$ ca. 0°, $\{\Phi\}_{305.5}$-176.8°, $\{\Phi\}_{266.5}$+118.0°, $\{\Phi\}_{225}$+29.5°. (Appendix II, Figure 2.)

Optical Rotatory Dispersion and Circular Dichroism of 5α-Cholestan-3-one (CXIX). Preparation of Dimethyl Ketal CXX

A solution was prepared by dissolving 151.2 mg of 5α-cholestan-3-one (CXIX) in methanol (Fisher Spectranalyzed) and diluting to 50 ml. approximately 3 ml of this solution was used in a 0.1 dm cell to obtain the ord curve $\{\Phi\}_{700}$+133.9°, $\{\Phi\}_{589}$+153.2°, $\{\Phi\}_{305.5}$+3121°, $\{\Phi\}_{287}$0°,

$\{\Phi\}_{268}$-2240°, $\{\Phi\}_{230}$-1614°, $\{\Phi\}_{215}$-1532°. (Appendix II, Figure 4.) A minute trace of concentrated hydrochloric acid was added by dipping a needle into the acid, wiping lightly with tissue and momentarily inserting the needle into the sample. Fifteen minutes were allowed for equilibration and then the ord spectrum was recorded again. The Cotton effect was almost imperceptible on the plain positive curve obtained (Appendix II, Figure 4) so another 3 ml sample of the original solution was used for circular dichroism measurements to determine quantitatively the extent of ketal formation. The original solution gave a molecular ellipticity of $\{\theta\}_{233}0$, $\{\theta\}_{289}$+4084, $\{\theta\}_{239}0$, Γ = 33 mμ. (Appendix II, Figure 4.)

Addition of a trace of acid as above reduced this to $\{\theta\}_{289}$+168, a 96 percent reduction. Addition of one microliter of water shifted the equilibrium to give $\{\theta\}_{289}$+211. Addition of more water gave the following results, total μl water added ($\{\theta\}_{289}$): 5 (337), 10 (674), 20 (926), 30 (1179), 40 (1410), 50 (1600), 60 (1810), 80 (2126), 100 (2379), 150 (2910), 200 (3221), and 250 (3452). (Appendix II, Figure 4.)

The remainder of the original solution (approximately 44 ml) was treated with a trace of concentrated hydrochloric acid and after 30 minutes solid sodium bicarbonate (ca. 0.5 g) which had been dried one hour at 110°C was added. After shaking, the material was filtered and the filtrate evaporated on the rotary evaporator to give 150 mg of a gum which slowly crystallized on cooling. Recrystallization from ether gave the dimethyl ketal CXX as a white crystalline solid, m.p. 83.5-84°C; ν_{max}^{KBr} 1110, 1060 cm^{-1}; Nmr ($CDCl_3$) methyl singlets at δ0.65 (3H), δ0.79 (6H), δ0.91 (6H), δ3.14 (3H) and δ3.19 (3H), (Appendix II, Figure 3); M^+ Calc. 432.397, Found 432.390.

Optical Rotatory Dispersion and Circular Dichroism of Hydroxydihydroeremophilone (XIX)

The crude natural product was recrystallized from methanol to give XIX as a white crystalline solid, m.p. 101-102°C (lit.[15] 99-102°C); ν_{max}^{KBr} 3438, 1692, 1634, 888 cm^{-1}; Nmr ($CDCl_3$) δ0.80 (d, J=5 cps, 3H), δ1.05 (s, 3H), δ1.83 (s, $W_{½h}$ 4 cps, 3H), δ3.78 (s, $W_{½h}$ 6.5 cps, 1H), δ4.01 (d, J= 11 cps, 1H), δ4.91 (s, $W_{½h}$ 3.5 cps, 2H); ord c = 0.583 from 700-308 mμ and c = 0.117 from 308-225 mμ, methanol d = 0.10 dm) $\{\Phi\}_{700}$+131.5°, $\{\Phi\}_{589}$ +182.7°, $\{\Phi\}_{546}$+215.7°, $\{\Phi\}_{317}$0°, $\{\Phi\}_{308}$-257.9°, $\{\Phi\}_{301}$0°, $\{\Phi\}_{272}$+3752°, $\{\Phi\}_{225}$+9561°; cd (c = 0.0247 from 354-317 mμ and c = 0.0049 from 317-240 mμ, methanol, d = 1.0 cm) $\{\Theta\}_{353}$0, $\{\Theta\}_{324}$+120.7, $\{\Theta\}_{317}$0, Γ=16 mμ and $\{\Theta\}_{317}$0, $\{\Theta\}_{290}$-2095, $\{\Theta\}_{238}$0, Γ+42 mμ.

Preparation of Hydroxydihydroeremophilone Acetate[15] (CXXI)

A solution of hydroxydihydroeremophilone (5.0 g) in anhydrous pyridine (40 ml) and acetic anhydride (20 ml) was stirred at room temperature for 12 hours, poured into 500 ml of water and extracted with five 75 ml portions of methylene chloride. The organic layer was washed three times each with 500 ml portions of 5 percent hydrochloric acid, 5 percent sodium bicarbonate and water. After drying over magnesium sulfate, the solvent was evaporated to give 5.3 g of crystalline acetate CXXI, m.p. 68-70°C (lit.[15] 68-70°C); ν_{max}^{KBr} 1733,1714, 1645, 885 cm^{-1}; Nmr ($CDCl_3$) δ0.81 (d, J=5.5 cps, 3H), δ1.05 (s, 3H), δ1.74 (m, 3H), δ2.13 (s, 3H), δ4.83 (m, 2H), δ5.17 (d, J=12 cps, 1H); ord (c = 0.416 from 700-313 mμ and c = 0.083 from 313-220 mμ, methanol, d=0.10 dm) $\{\Phi\}_{700}$+220.5°, $\{\Phi\}_{589}$+300.8°, $\{\Phi\}_{537}$+972.4°, $\{\Phi\}_{313}$+471.2°, $\{\Phi\}_{269}$+4371°,

$\{\Phi\}_{220}$+13565°; cd (c = 0.0030, methanol, d = 1.0 cm) $\{\theta\}_{322}$0, $\{\theta\}_{291}$-1989, $\{\theta\}_{256}$-276, Γ=32 mμ and $\{\theta\}_{256}$-276, $\{\theta\}_{220}$-1878.

Preparation of cis-8,9-Dihydroeremophilone (XCVI) from Hydroxydihydroeremophilone Acetate (CXXI)[15]

A solution of acetate CXXI (5.0 g) in toluene (20 ml) was added dropwise over 30 minutes to a vigorously stirred solution of calcium metal (3.3 g) in one liter of liquid ammonia at reflux. The solution remained dark blue while stirred for one hour and then 3 ml of freshly distilled bromobenzene was added dropwise to discharge the blue color. Water (100 ml) was then dropped in over one hour and the ammonia was allowed to evaporate overnight. After 100 ml of 5 percent hydrochloric acid had been slowly added, the solution was made strongly acid by cautious additon of concentrated hydrochloric acid (ca, 200 ml) and then extracted with five 100 ml portions of methylene chloride. The extract was washed with 5 percent sodium bicarbonate solution, then water, dried over magnesium sulfate and evaporated to give 6.6 g of a yellow oil. This material was then distilled at 80-58°C (0.05 mm Hg) to give 2.98 g of cis-8,9-dihydroeremophilone (XCVI) as a colorless oil, ν_{max}^{film} 1705, 1640, 890 cm^{-1}; Nmr (neat) δ0.78 (d, J=5 cps, 3H), δ1.03 (s, 3H), δ1.74 (s, $W_{\frac{1}{2}h}$ 3 cps, 3H), δ4.75 (s, $W_{\frac{1}{2}h}$ 3 cps, 2H); ord (c= 0.498, methanol, d = 0.10 dm)$\{\Phi\}_{450}$+128.0°, $\{\Phi\}_{342}$+0°, $\{\Phi\}_{312}$-972.0, $\{\Phi\}_{302}$0°, $\{\Phi\}_{270}$+4060°; cd (c = 0.0226, methanol, d = 1.0 cm)$\{\theta\}_{334}$0, $\{\theta\}_{295}$-3176, $\{\theta\}_{235}$0, Γ=34 mμ.

Preparation of Enol Acetate CXXII

cis-Dihydroeremophilone XCVI (1 g) and p-toluenesulfonic acid (50 mg) were dissolved in isopropenyl acetate (Eastman) and heated on the steam bath for 48 hours. The mixture was then evaporated in vacuo (water aspirator) to a volume of approximately 10 ml. Analysis by glc using a 6 foot by 1/8 inch glass column of 3 percent SE-30 on 100/120 mesh Gas-Chrom Q at 140°C and a helium flow rate of 100 ml/min showed starting material at R_T 5.3 minutes and two minor products with R_T 8.0 and 8.7 minutes in a ratio of about 10:1:3, respectively.

An additonal 50 ml of isopropenyl acetate was added and the solution heated 24 hours with continuous removal of acetone by application of a slight vacuum. Analysis then gave a ratio of approximately 1:1:3 for the three components. This procedure was repeated for three days adding additional isopropenyl acetate as necessary to finally attain a ratio of about 1:4:12. The excess isopropenyl acetate was then evaporated and the residue was dissolved in 50 ml of ether. The ether solution was washed by pouring into 100 ml of 5 percent sodium bicarbonate, shaking and quickly separating the layers. The ether extract was washed with water, dried over magnesium sulfate and evaporated to give 2.2 g of a dark oil. Analysis by glc gave the same results as were obtained prior to workup. An attempt was made to purify the material by chromatography on neutral alumina but the enol acetate apparently hydrolyzed on the column. The first fraction (69 mg) eluted with 200 ml of benzene had approximately the same composition as the material placed on the column and the remaining fractions collected were mainly (50-95 percent) cis-dihydroeremophilone. The compound showing 8.7 minutes was

collected by preparative glc on the column described on the preceding page to give the enol acetate CXXII, ν_{max}^{film} 1755, 1689, 1640, 1219, 890 cm^{-1}; Nmr ($CDCl_3$) δ0.83 (d, J=5.5 cps, 3H), δ0.98 (s, 3H), δ1.74 (m, 3H) δ2.12 (s, 3H), δ4.76 (m, 2H).

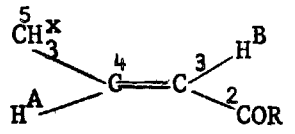
CHAPTER IV

DISCUSSION OF RESULTS

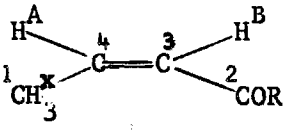
As stated in Chapter I, the primary objective of this research was to investigate the Robinson annelation reaction of 2-methyl-1,3-cyclohexanedione (LXXXIV) with trans-3-penten-2-one (LXXXIII) as a means of synthesizing the bicyclic diketone LXXXV could serve as a key intermediate in the synthesis of a number of eremophilane sesquiterpenes as summarized in Chart 2.

The first step was the synthesis of the starting material trans-3 penten-2-one (LXXXIII). This material was prepared according to the procedure of Wilds and Djerassi[57] by the base-catalyzed condensation of acetone and acetaldehyde followed by dehydration of the 4-hydroxy-2-pentanone thus produced. The product is assigned the trans stereochemistry on the bases of its mode of formation (acid-catalyzed dehydration) and its nmr spectrum. The latter showed a simple ABX_3 system with the C-1 protons appearing as a singlet at δ2.17. The C-3 proton (H_B) appeared as a doublet of quartets at δ6.05 with J_{AB}=16 cps and J_{BX}=-1.5 cps; the relative signs of the coupling constants were assumed by analogy with those of methyl trans-crotonate[64] (XCVII). The C-4 proton (H_A) at δ6.82 had the same multiplicity with J_{AB}=16 cps and J_{AX}=6.5 cps. The C-5 protons (H_X) at δ1.85 appeared as a doublet of doublets with J_{AX}=6.5 cps and J_{BX}=-1.5 cps. Baldwin[65] has reported the nmr of both cis (XCVIII)- and trans (LXXXIII)-3-penten-2-one giving only the chemical shifts without discussing the multiplicity, coupling constants, or solvents used. The significant difference reported between cis and trans isomers was the chemical shift of the C-5 protons. In the cis isomer these protons appeared at δ2.12

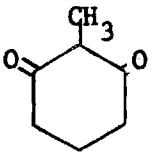
while in the trans isomer they were at δ1.90 in close agreement with the δ1.85 observed here. In addition, Baldwin[65] reported the C-4 proton (H_A) in the cis isomer at δ6.09 and in the trans isomer at δ6.71 while in the present case this proton appeared at δ6.82. The coupling constants also were in better agreement with those of methyl trans-crotonate[64] XCVII (J_{AB}15.5, J_{AX}=6.85, J_{BX}=-1.67 cps) than those of methyl cis-crotonate XCIX (J_{AB}=11.4, J_{AX}=7.27, J_{BX}=1.82 cps).



LXXXIII. R=CH_3
XCVII. R=OCH_3



XCVIII. R=CH_3
XCIX. R=OCH_3

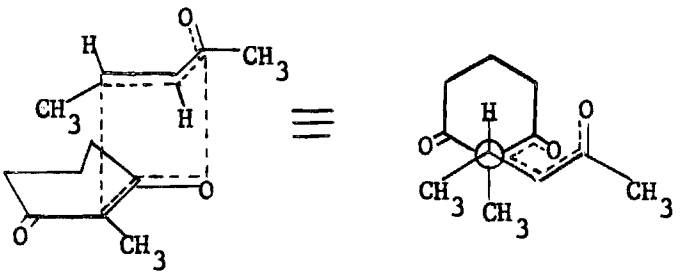


LXXXIV

The other starting material for the Robinson annelation reaction, 2-methyl-1,3-cyclohexanedione (LXXXIV) was prepared by catalytic hydrogenation at high pressure of 2-methylresorcinol following the procedure[58] for reduction of resorcinol.

Attempts to cyclize LXXXIV with LXXXIII in pyridine, sodium methoxide-methanol, and pyrrolidine gave on workup only very small amounts of the product. The conditions eventually found successful in bringing about the Robinson annelation reaction (LXXXIII-LXXXVI) were similar to those employed[60] in the reaction of methyl vinyl ketone with LXXXIV. In this procedure, the first step involves a Michael addition of the anion from LXXXIV to the ketone LXXXIII in methanol solution. This is then followed by replacement of the methanol with benzene and pyrrolidine. The mixture is then refluxed to remove water and bring about the final cyclization. In the present case, although it appeared no reaction had occurred in the Michael addition step, the benzene and pyrrolidine were nevertheless added and the

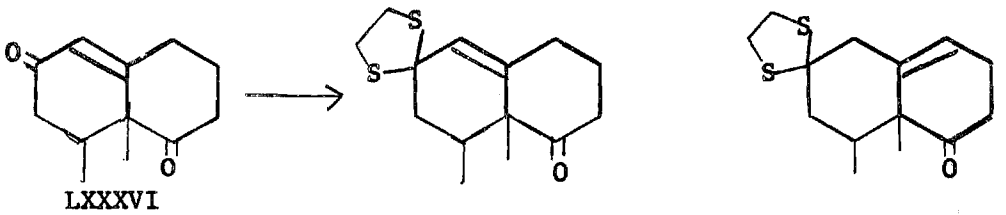
sequence completed. Reaction apparently occurred only after addition of the pyrrolidine. It is likely that the Michael addition is reversible with an unfavorable equilibrium constant so that the pyrrolidine is necessary to bring about cyclization of the initial adduct C to give hydroxy ketone CI which can undergo irreversible dehydration. In this manner, the equilibrium may be shifted toward product LXXXVI. It was subsequently found more convenient to replace the methanol with ethanol and combine all of the reactants initially. In this manner, a product was obtained which was shown by glc to contain two major components in a ratio of approximately 6:1 which were expected to be LXXXV and LXXXVI, respectively. The major component was expected to have the cis relationship between the methyl groups on the basis of steric and electronic factors in the Michael addition which were expected to favor the transition state shown in CII. The major component was subsequently isolated as a crystalline solid, m.p. 81.5-83°C, which had infrared and nmr spectra which were consistent with either LXXXVI or LXXXV.



CII

In determining the relative stereochemistry of the methyl groups of the product it was felt that, rather than investigate a sequence of reactions with that sole purpose, it would be more profitable to proceed with the synthesis as outlined in Chart 2 and establish the stereochemistry of the methyl groups by comparison of a synthetic product with the natural material known to have cis methyl groups.

The first step, preparation of thioketal CIII, was readily accomplished by treatment of a solution of LXXXVI (LXXXV) in glacial acetic acid with ethanedithiol and p-toluenesulfonic acid catalyst. Reaction occurred exclusively at the α,β-unsaturated carbonyl due to the sterically hindered environment in which the nonconjugated carbonyl occurs. An interesting observation was made during this reaction by means of glc. Prior to workup two peaks were observed at retention times of 15.2 and 17.1 minutes in a ratio of 1.5:1, respectively. After workup, in which water was added to the reaction solution followed by extraction with chloroform, glc analysis of the product showed the same two peaks in a ratio of 29:1. The major component was obtained in pure form by column chromatography on neutral alumina as a slightly yellow, rather unstable oil which was shown to be CIII by means of its infrared and nmr spectra. The former showed the 6-membered cyclic ketone at 1705 cm^{-1} while the latter showed the vinyl proton as a singlet at δ5.67. The second component (R_T 17.1 minutes) was felt to be the isomeric thioketal CIV rather than the product of addition of two moles of ethanedithiol to LXXXVI (LXXXV) because of the relatively small difference in retention times of the two components. While 2-octalones such as LXXXVI (LXXXV) as well as Δ^4-3-keto steroids commonly react with ethylene glycol to give ketals in which the double bond has migrated the same compounds usually give thioketals in which double bond migration has not occurred. The present case would appear to be an example of an equilibrium between forms in which migration has (CIV) and has not (CIII) occurred with the position of the equilibrium being strongly dependent upon the nature of the solution. This aspect of this reaction deserves further attention.



LXXXVI
(LXXXV)

CIII

CIV

Desulfurization of CIII was accomplished by refluxing the compound in ethanol with Raney nickel catalyst (activity grade W-2). Filtration of the catalyst and evaporation of the ethanol gave a yellow oily product which showed four components by glc analysis in a ratio of 1:86:7:6 on an SE-30 column. Column chromatography resulted in partial purification to give a sample which was used in the unsuccessful dimethyl carbonate reaction described below. This material was subsequently found to be an approximately 2.3:1 mixture. Distillation of a portion of the material at 51-55°C (0.025 mm Hg) led to extensive decomposition but gave a small amount of a colorless oil which was shown by glc analysis on an SE-30 column to be 95 percent of one component and 5 percent of another. The peak corresponding to the major component was resolved however, using a Carbowax 20M column. On this column the mixture showed three components in a 76:19:5 ratio, the two major components possibly being the two double bond isomers CV resulting from isomerization of the double bond by the catalyst. A sample of the most abundant component containing only about 3 percent impurity was obtained when the reaction was repeated on a large scale and the crude product was carefully chromatographed on alumina. The purer fractions thus obtained were crystallized at Dry Ice-acetone temperature. This material showed infrared absorption at 1705

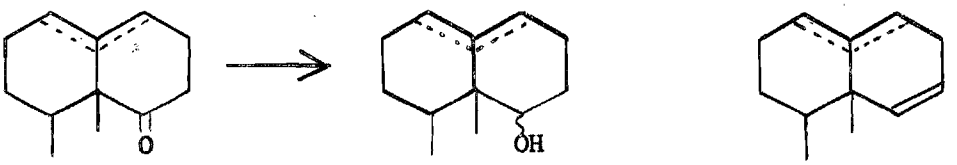
and 1653 cm^{-1} and its nmr spectrum showed a multiplet for the vinyl proton at δ5.41 in addition to a methyl singlet at δ1.26 and a methyl doublet (J=6.5 cps) at δ0.83. These data are consistent with the assignment of structure CV but do not distinguish between the two double bond isomers.

The next step proposed in the sequence involved attachment of a carboalkoxy group α to the carbonyl group in CV. The procedure first attempted was that of Corey et al.[62] wherein the enolate anion of the ketone is prepared by reaction with sodium hydride and added to dimethyl carbonate. In the present case, the product of the reaction showed very strong absorption in the infrared at 3400 cm^{-1} and a weak carbonyl absorption at 1705 cm^{-1}. Analysis by glc showed the product to be a complex mixture of starting material (18 percent) and three products in a ratio of 15:9:50. An attempt to purify the material by column chromatography was unsuccessful but a fraction was obtained in which only a small amount of starting material remained. This material gave an nmr spectrum which had several signals in the region δ3.35-3.85 and several from δ5.25-6.1 indicative of a mixture of olefinic alcohols. The ketone carbonyl had apparently been reduced to an alcohol in the reaction!

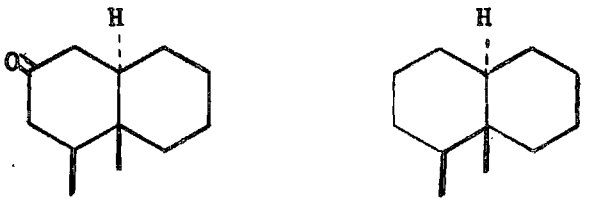
In another attempt to introduce the α-carboalkoxy group into CV by reaction of the enolate anion with diethyl oxalate[16] the reaction product again showed hydroxyl absorption in the infrared at 3400 cm^{-1}. Moreover, a direct comparison by glc of this product and that from the dimethyl carbonate reaction showed that the two major components in each were identical. The source of difficulty was most likely the "sodium hydride" which apparently reduced the carbonyl group.

That the product in the two reactions above was a mixture of alcohols was shown by sodium borohydride reduction of ketone CV (97 percent

one isomer). The product of this reaction consisted of two major components in a ratio of 68:29 and two minor components in ratio of 2:1. The two major components had the same retention times as the major products of the dimethyl carbonate and diethyl oxalate reactions above. The product had infrared absorption bands at 3400 and 1655 cm^{-1} and was felt to be a mixture of α- and β-alcohols CVI. An attempt to separate the mixture by column chromatography was unsuccessful so that the crude mixture was used as such in the dehydration reactions described below.



CV CVI CVII



CVIII CIX

Since the alcohol mixture CVI was available, it was felt that simple dehydration would give diene CVII which could be hydrogenated to a mixture of 1,9-dimethyl-cis-and trans-decalins having either cis or trans methyl groups. Comparison with the dimethyl decalin CIX, which could be obtained by Wolff-Kishner reduction of the readily available decalone CVIII known[16] to possess the cis methyl groups, would then establish the relative stereochemistry of the two methyl groups.

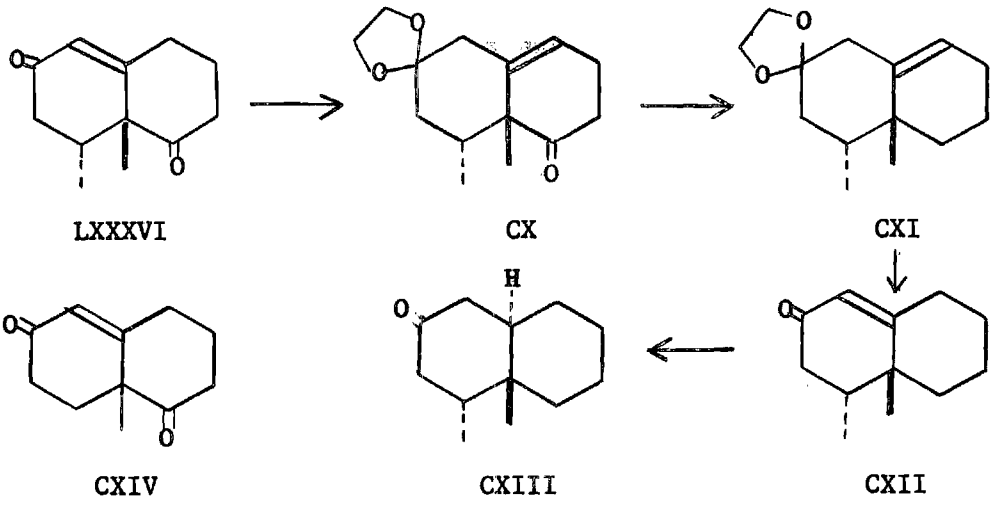
The first attempt to prepare CVII involved the use of phosphorous oxychloride as the dehydrating agent. Although it was not profitable to attempt purification of the complex mixture obtained in this reaction, an interesting observation was made which is relevant to the question of the relative stereochemistry of the two methyl groups. As stated previously, sodium borohydride reduction gave two alcohols in a ratio of approximately 2.3:1. During the phosphorous oxychloride dehydration, after about half of the dehydrating agent had been added, the reaction mixture was analyzed by glc and it was found that this ratio had decreased to 1.3:1, that is, the major component was reacting faster. Since the first step in dehydrations with this reagent is ester formation and since it is well established[66a] that equatorial alcohols esterify faster than their axial epimers, the β-configuration (equatorial) is assigned to the hydroxyl group in the major component. Since the major component also has a much greater retention time on the glc this assignment is also consistent with the generalization[66b] that a compound with an equatorial polar group is less mobile than its axial epimer. Sodium borohydride reduction of sterically hindered ketones such as CV is generally subject to "steric approach control"[66c] meaning that the major product is that which arises from attack of the reagent from the less hindered side of the carbonyl group. Examination of molecular models of CV indicates that approach from the top or β face of the molecule would be preferred if the methyl groups are either cis or trans. Such "steric approach control" would lead to a preponderance of the axial α-alcohol. However, if the methyl groups are trans "steric approach control" would lead to a severe methyl-hydroxyl 1,3-diaxial interaction and in such a case "product development control"[66c] might become the dominant factor and thus

lead to a preponderance of the more stable equatorial β-alcohol. These tentative arguments suggest that the ketone CV and thus the diketone obtained in the Robinson annelation reaction may possess the trans methyl groups (LXXXVI) rather than the cis relationship (LXXXV) required for synthesis of eremophilane sesquiterpenes.

Other attempts to prepare CVII included pyrolysis of the acetate and xanthate esters. When CVI was treated with acetic anhydride in pyridine solution a mixture of two acetates was formed. This material was resistant to pyrolysis at 537°C on a column of glass helices. Since xanthates pyrolyze under milder conditions this ester was prepared from CVI by reaction with potassium, carbon disulfide, and methyl iodide in benzene. Heating at 215±5°C led to elimination of carbonyl sulfide and methyl mercaptan with formation of an oily product which was chromatographed on alumina. The hexane eluent was very carefully rechromatographed but no homogeneous material could be obtained. One fraction obtained as a colorless oil had infrared bands at 3069, 1640, 1429 and 855 cm^{-1} indicative of a gem-disubstituted olefin. The nmr showed signals at δ1.08 (d, J=6.5 cps), δ4.75 (d, J=1 cps) and δ5.42 (multiplet) but no integral numbers of acceptable magnitude could be assigned to these signals so it was concluded that this material was a mixture. The absence of a methyl singlet along with the signal at δ4.75 and the infrared data indicate that the major component of the mixture possesses an exo-methylene group. The nature of this interesting rearrangement has not been deduced and is worthy of further consideration.

It was at this point that the report by Coates and Shaw[54] appeared. These workers investigated the reaction of the pyrrolidine enamine of 2-

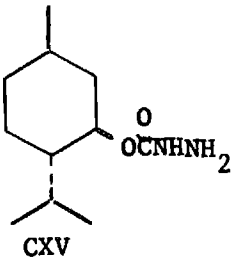
methyl-1,3-cyclohexanedione with 3-penten-2-one in benzene, acetic acid, and sodium acetate and reported a major product (m.p. 82.5-83.5°C) for which the trans stereochemistry of the methyl groups was indicated by chemical and physical evidence. From the similarity of melting points and spectral data it was evident that this product was identical to LXXXVI (m.p. 81.5-83°C). It was felt that conclusive evidence with regard to the relationship of the methyl groups in LXXXVI could be obtained by conversion of LXXXVI to decalone CXIII as shown below. Resolution of CXIII into its optically active enantiomers and investigation by means of optical rotatory dispersion (ord) would then give information about the relative and absolute configuration of the methyl groups.



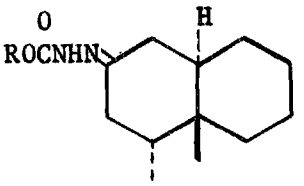
Treatment of LXXXVI with ethylene glycol and p-toluenesulfonic acid in refluxing benzene led to selective ketalization of the α,β-unsaturated carbonyl to give ketal CX, m.p. 89-90°C(lit.[54] 87-88°C) which had carbonyl absorption in the infrared at 1707 cm^{-1}. It is interesting to note that Corey et al.[67] found that ketalization of the closely related Wieland-Miescher ketone CXIV under similar conditons led to the exclusive ketalization of the saturated carbonyl group. Wolff-Kishner reduction of CX gave CXI as a

yellow oil which had no carbonyl absorption in the infrared. This material was hydrolyzed at room temperature with 5 percent hydrochloric acid in aqueous dioxane to the α,β-unsaturated ketone CXII, m.p. 34-35°C, with carbonyl absorption at 1672 cm^{-1}. Lithium-ammonia reduction of CXII in tetrahydrofuran gave the desired decalone CXIII; ν_{max}^{film} 1710 cm^{-1}, nmr (d_6-acetone) δ0.93 (d, J=7 cps, 3H), δ1.20 (s, 3H). The trans ring fusion was assigned on the basis of the established[68] steric course of the reaction which involves axial protonation at the β-position of that conformation of the intermediate radical anion which allows maximum orbital overlap.

Partial resolution of CXIII was accomplished by reaction of the racemic material with l-menthyl N-aminocarbamate ("l-menthydrazide", CXV)[63] followed by fractional crystallization of the diastereoisomeric "l-menthydrazones" (XCVI and CXVII) thus formed. Optically active CXIII was obtained by hydrolysis of one of the fractions, m.p. 197-99°C, $\{\Phi\}_{546.1}^{25.0}$ -45.5°. Since this material was not recrystallized to constant molecular rotation (because of the small amount available) the resolution cannot be said to be complete but on the basis of the relatively large amplitude of the Cotton effect of the regenerated CXIII resolution appears to be essentially complete. The regenerated, optically active CXIII was isolated from the hydrolysis mixture by steam-distillation and ether extraction. The material for ord studies was collected by preparative glc and in methanol solution (c = 0.36 g/100 ml) showed a negative Cotton effect (Appendix II, Figure I) with the trough at 307 mμ, $\{\Phi\}$-1800° and the peak at 268 mμ, $\{\Phi\}$ +2450°. A minute trace of concentrated hydrochloric acid was added to the solution by dipping a needle into the acid, wiping lightly with tissue, and momentarily inserting the needle into the solution. After a few minutes were allowed for equilibration the ord curve (Appendix II, Figure 1) was again recorded and showed a 57 percent reduction (a = -42.5 to =18.4) in the amplitude of the Cotton effect.

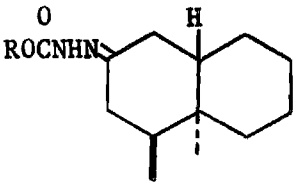


CXV



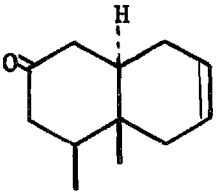
CXVI.

R=l-menthyl

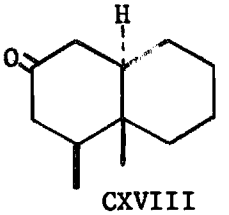


CXVII.

R=l-menthyl



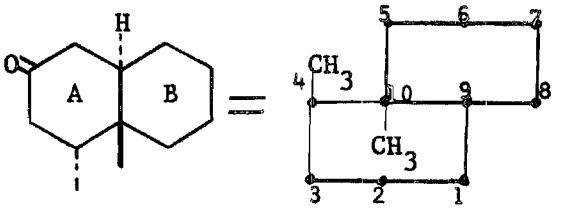
CXVIII



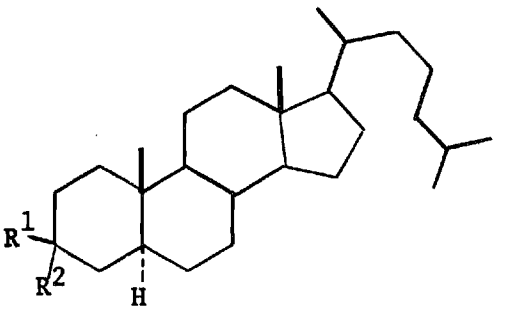
CXVIII

For comparison, the ketone CVIII was prepared by catalytic hydrogenation of the octalone CXVIII of known absolute configuration.[16] The ord curve of CVIII (Appendix II, Figure 2) in methanol (c = 0.305 g/100 ml) showed a negative Cotton effect (a = -36.8) with the trough at 305.5 mμ, $\{\Phi\}$ -1800° and the peak at 266.5 mμ, $\{\Phi\}$ $+1889^{\circ}$. Addition of a trace of acid to this solution produced a 92 percent reduction in the amplitude of the Cotton effect. These data establish the absolute configuration of the levorotatory isomer of CXIII isolated in the resolution as well as the relative stereochemistry of the methyl groups. The absolute configuration shown below for CXIII is assigned to this levorotatory isomer on the basis of the negative Cotton effect. As shown in the accompanying octant projection ring B lies in the back upper right (negative) octant and this ring would make a rather large negative contribution (a = -50 to -60) to the amplitude of the Cotton effect of both CXIII and CVIII. Klyne[69] has reported approximate values which may be allotted for amplitude-contributions of substituents of various types attached at different positions

on a cyclohexanone ring. For methyl groups in the back upper left (positive) octant two carbons removed from the carbonyl group (that is, C-4 in CXIII and CVIII) an amplitude contribution of +25 is allotted for an equatorial methyl group and +20 for an axial methyl group. Thus the methyl groups at C-4 in both CXIII (axial methyl) and CVIII (equatorial methyl) would make small positive amplitude-contributions while the C-10 methyl lying in a symmetry plane would make no contribution. Thus, we would predict negative Cotton effects for both CXIII and CVIII in the absolute configurations shown, with the former having the larger absolute (more negative) value for the amplitude with a difference of about five. The observed results are in excellent agreement with these predictions.



CXIII



CXIX. $R^1 \equiv R^2 = O$

CXX. $R^1 = R^2 = OCH_3$

The relatively small reduction (57 percent) in amplitude of the Cotton effect of CXIII as compared to that observed for CVIII (92 percent) upon the addition of a trace of acid firmly establishes the trans-diaxial relationship of the C-4 and C-10 methyl groups in CXIII. Ketal (or hemiketal) formation would introduce new 1,3-diaxial interactions in CXIII but not in CVIII and therefore, this reaction, with its attendant decrease in the amplitude of the Cotton effect, is inhibited in the former case. Although the 57 percent reduction observed for CXIII is larger

than the approximately 10 percent reduction reported[70] for 2-keto steroids, the 92 percent reduction of CVIII is likewise larger, under the particular conditions employed here, than the previously reported[16] 72 percent. In order to further investigate this observation, the ord curve of 5α-cholestan-3-one (CXIX) in methanol (Appendix II, Figure 4) was recorded and found to give a positive Cotton effect (a = +53.6) with the peak at 305.5 mμ, $\{\Phi\}$ + 3121° and the trough at 268 mμ, $\{\Phi\}$ -2240°. (The methods involved in interpreting ord and cd data are illustrated by sample calculations on 5α-cholestan-3-one in Appendix III.) Addition of a minute trace of acid, as described previously, led to such an extensive decrease in amplitude that the Cotton effect was almost imperceptible on the plain positive background curve (Appendix II, Figure 4). In order to obtain quantitative information on this decrease in amplitude, recourse was made to circular dichroism (cd). The cd curve of 5α-cholestan-3-one in methanol (Appendix II, Figure 4 insert) exhibited a positive Cotton effect at 289 mμ with a molecular ellipticity $\{\theta\}$ + 4084 and addition of a minute trace of acid gave $\{\theta\}$ + 168 corresponding to a 96 percent reduction in amplitude. This is to be contrasted with the previously reported[71] 64 percent reduction upon addition of 0.01 ml of acid to approximately the same volume of solution as used in the present study. Anticipating that the amount of water introduced along with the acid was the cause of this variation, carefully measured microliter quantities of water were added in increments to the solution. As would be expected, this shifted the ketone-ketal equilibrium back toward the ketone with an accompanying incremental increase in the molecular ellipticity approaching the original value (before acid was added). Addition of water was halted after a total of 250 microliters, because the solution became cloudy. At this point the molecu-

lar ellipticity had increased from the +168 (96 percent reduction) after addition of a trace of acid to +3452, a mere 15 percent reduction from the value of +4084 before addition of acid. The values of {θ} for addition of various amounts of water are given in the experimental section (Chapter III) and are shown in the cd insert in Figure 4, Appendix II as a number of curves of increasing molecular ellipticity. Clearly the reduction in amplitude of a Cotton effect upon addition of acid is strongly dependent upon the amount of water introduced with the acid and the relative percent reduction in amplitude is significant only when two compounds are compared under identical conditions.

There appears to be considerable question in the literature as to whether it is ketal or hemiketal formation which is responsible for the decrease in amplitude of the Cotton effecton addition of acid to solutions of ketones in methanol. In a detailed study of the acid-catalyzed reaction of methanol with a number of monocyclic ketones, Wheeler[72] determined the extent of reaction by measuring the decrease in intensity of ultraviolet absorption and interpreted his results in terms of hemiketal formation. Two years later Djerassi[71] first applied the reaction to ord and, referring to Wheeler's work, interpreted the decrease in amplitude of Cotton effects as being due to hemiketal formation. A short time later in his classical book [73] on ord Djerassi wrote an entire chapter on the reaction in which he used the term (hemi)ketal indicating that in certain cases ketals could be isolated. Crabbe' in his authoritative work[70] several years later refers alternately to both ketal and hemiketal formation while in the latest review of the of the subject Klyne[69] refers exclusively to hemiketal formation. Since an equilibrium between ketone, hemiketal and

ketal is undoubtedly involved, there is most likely no simple answer to the question with ketal or hemiketal formation depending on the particular ketone involved. The almost quantitative disappearance of the ketone under the conditions used here, however, offered an opportunity to answer the question for 5α-cholestan-3-one (CXIX). A methanolic solution of CXIX was treated with a minute trace of concentrated hydrochloric acid and allowed to stand for 30 minutes to reach equilibrium. Dry, solid sodium bicarbonate was then added to remove the acid and prevent the equilibrium from shifting as the methanol was evaporated to give the dimethyl ketal CXX as a crystalline solid, m.p. 83.5-84°C. The infrared spectrum of this material showed a lack of carbonyl absorption with ether bands at 1110 and 1060 cm^{-1} and the nmr spectrum (Appendix III, Figure 3) showed the two methoxyl groups at δ3.14 and δ3.19. Thus, in this case at least, the decrease in amplitude of the Cotton effect is due to ketal formation.

As stated previously, the results of optical rotatory dispersion established the trans-diaxial relationship of the C-4 and C-10 methyl groups in CXIII and thus the Robinson annelation product LXXXVI lacked the stereochemistry required for conversion to the eremophilane sesquiterpenes. As stated previously, Coates and Shaw[54] using slightly different reaction conditions succeeded in obtaining the desired intermediate LXXXV and at this point their synthesis of calarene[39] (XXXVIII) appeared in the literature. For these reasons, this method of approach was abandoned and, in anticipation of a proposed synthesis of cis-8,9-dihydroeremophilone (XCVI) in this laboratory, a method was sought by which XCVI might be converted into eremophilone. The scheme shown in Chart 3 appeared most promising. Hydroxydihydroeremophilone (XIX) had previously[15] been converted into XCVI and the same procedure was used here.

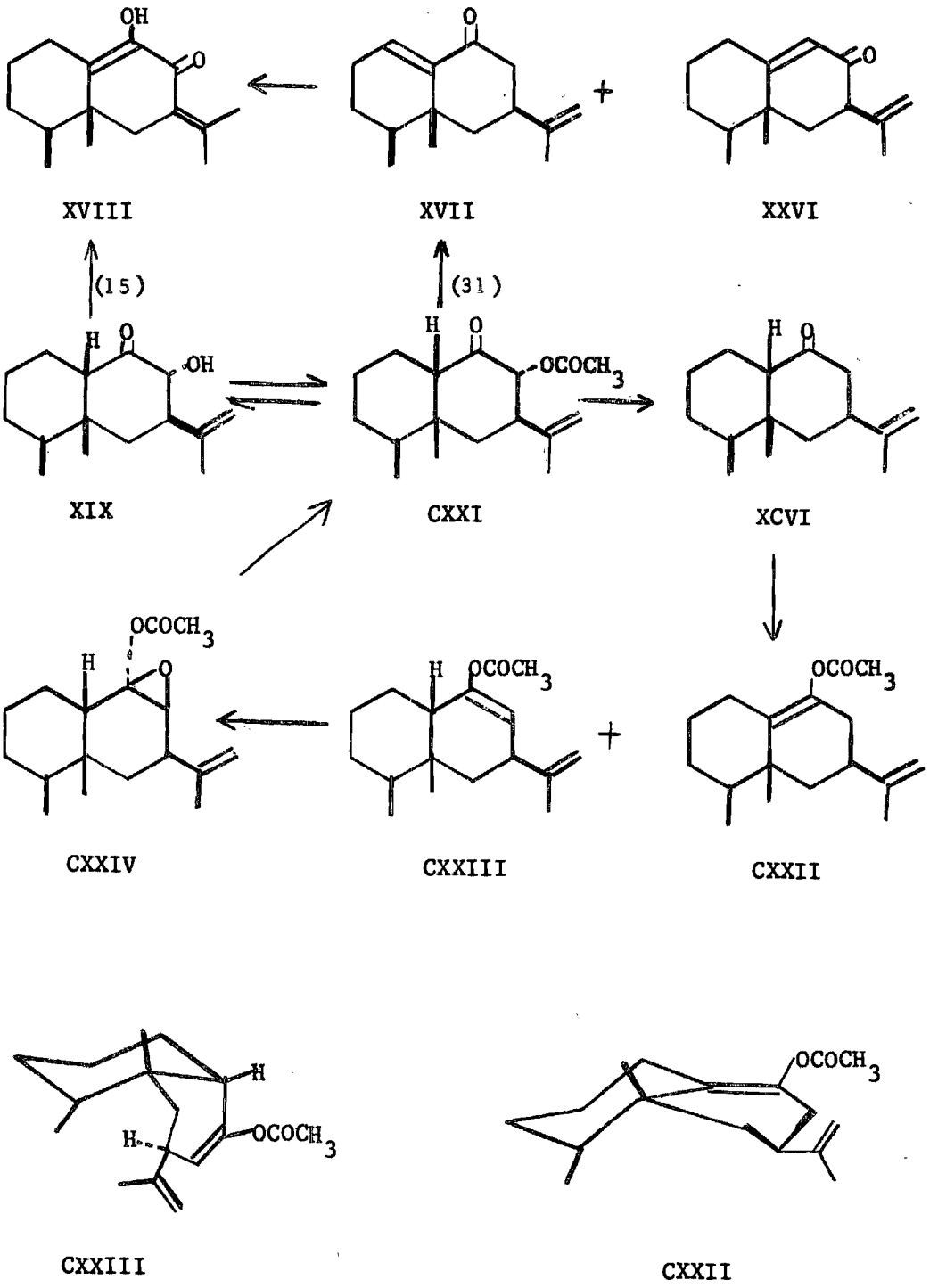


Chart 3. The Interconversions of Eremophilone, Hydroxyeremophilone, and Hydroxydihydroeremophilone.

Recrystallization of the crude natural product gave XIX, m.p. 101-02°C (lit.[15] 99-102°C), which showed a negative Cotton effect in its ord and cd curves. Treatment with acetic anhydride in pyridine converted XIX to its acetate CXXI, m.p. 68-70°C (lit.[15] 68-70°C). Calcium-ammonia reduction of CXXI gave cis-8,9-dihydroeremophilone (XCVI) as a colorless oil, b.p. 80-85°C (0.05 mm Hg).

With XCVI now in hand it was desired to convert the compound back into hydroxydihydroeremophilone (XIX) as shown in Chart 3. A total synthesis of cis-8,9-dihydroeremophilone (XCVI) would then constitute a total synthesis of hydroxydihydroeremophilone (XIX). Since hydroxydihydroeremophilone (XIX) has previously been converted into eremophilone (XVII) and into alloeremophilone (XXVI)[31] as well as into hydroxyeremophilone (XVIII)[15] and since eremophilone has likewise been converted to hydroxyeremophilone[6], this sequence would also constitute a total synthesis of these three natural products. The method envisioned for conversion of XCVI into XIX, as shown in Chart 3, involved preparation of the enol acetate CXXIII followed by epoxidation to give CXXIV. Rearrangement and hydrolysis would then give hydroxydihydroeremophilone (XIX). As expected, reaction of XCVI with isopropenyl acetate and p-toluenesulfonic acid gave a mixture of two enol acetates in a ratio of 3:1. Unfortunately, an attempt to separate the two products by column chromatography on neutral alumina led to extensive hydrolysis to give back starting material XCVI. From the small amount of material which did not hydrolyze it was possible to isolate a small amount of the major product by preparative glc. Structure CXXII is assigned to this compound on the basis of its nmr spectrum which shows only two vinyl protons, a multiplet at δ4.76 which is due to the isopropenyl group. It was expected that CXXII would be the major product of the acetylation since,

as may be seen in the conformational drawings of CXXII and CXXIII (Chart 3), the latter isomer would be less stable because of greater steric interaction of rings A and B. It is also obvious that epoxidation of CXXIII should occur from the β side of the molecule as predicted in CXXIV. Since a substantial amount of the minor product (presumably CXXIII) is produced in the acetylation and since the major product CXXII itself offers the possibility of direct conversion to eremophilone (by dehydration of a tertiary α-hydroxy ketone which might be formed via expoxidation) great promise is offered for further work in this approach to the synthesis of the eremophilane sesquiterpenes.

CHAPTER V

CONCLUSIONS

The Robinson annelation reaction of 2-methyl-1,3-cyclohexanedione with trans-3-penten-2-one has been found to give two products. The major product has been identified as the diketone LXXXVI. The nonconjugated carbonyl of LXXXVI is in a sterically hindered environment, thus selective operations may be carried out at the α,β-unsaturated carbonyl.

Diketone LXXXVI has been converted into trans-dimethyl-trans-2-decalone (CXIII) and the latter has been partially resolved by fractional crystallization of its diastereomeric l-methydrazones CXVI and CXVII. Optical rotatory dispersion of optically active CXIII regenerated from CXVI has established the trans-diaxial relationship of the C-4 and C-10 methyl groups as well as the absolute configuration of the levorotatory isomer.

The reduction in amplitude of a Cotton effect upon addition of acid to a methanol solution of a ketone is strongly dependent upon the amount of water introduced with the acid and the relative percent reduction in amplitude is significant only when two compounds are compared under identical conditions.

The question of ketal vs. hemiketal formation on treatment of a methanol solution of 5α-cholestan-3-one with acid has been answered by the isolation of the dimethyl ketal CXX.

A preliminary investigation has been made on a proposed method of correlating cis-8,9-dihydroeremophilone (XCVI) with hydroxydihydroeremophilone (XIX).

CHAPTER VI

RECOMMENDATIONS

The minor product of the Robinson annelation reaction should be isolated since it is most likely LXXV. This compound would have structural features making it suitable for the synthesis of a number of the eremophilane sesquiterpenes.

The reaction of LXXXVI with ethanedithiol is worthy of further investigation. The product which disappears on workup should be isolated by preparative glc and identified. If it is CIV, as suspected, a study of its equilibration with CIII would be of considerable theoretical interest.

The structure of the product formed on pyrolysis of the xanthate ester of CVI should be established since the absence of a methyl singlet in its nmr spectrum indicates an unusual rearrangement has occurred.

Standard conditions should be developed for treatment of methanol solutions of optically active ketones with acid under anhydrous conditions so that meaningful figures may be obtained for the relative percent reduction in amplitude of Cotton effects for ketones in various steric environments. The effect of addition of small amounts of water on the amplitude should be studied under conditions allowing calculation of equilibrium constants. Such equilibrium constants may be used in determining the energies of various 1,3 diaxial interactions.

The correlation of cis-8,9-dihydroeremophilone (XCVI) and hydroxydihydroeremophilone (XIX) should be completed as outlined in Chart 3 since the synthesis of XCVI would then provide a total synthesis of four of the naturally occurring eremophilane sesquiterpenes.

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APPENDIX I

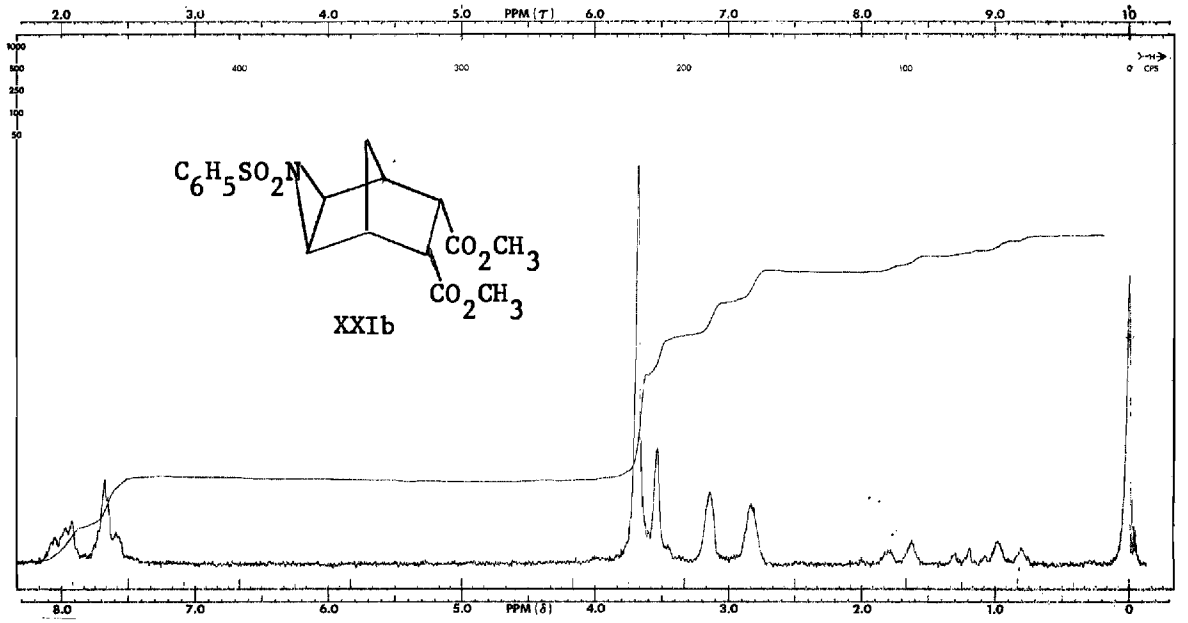

Figure 1. Nmr Spectrum of Aziridine XXIb.

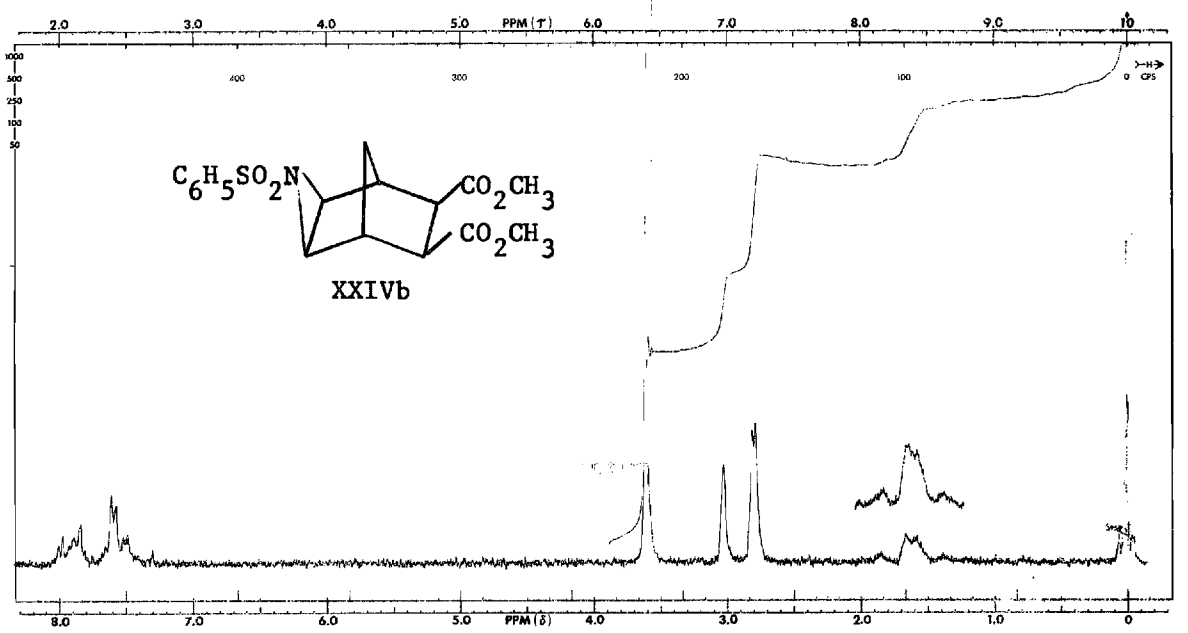

Figure 2. Nmr Spectrum of Azridine XXIVb.

APPENDIX I (Continued

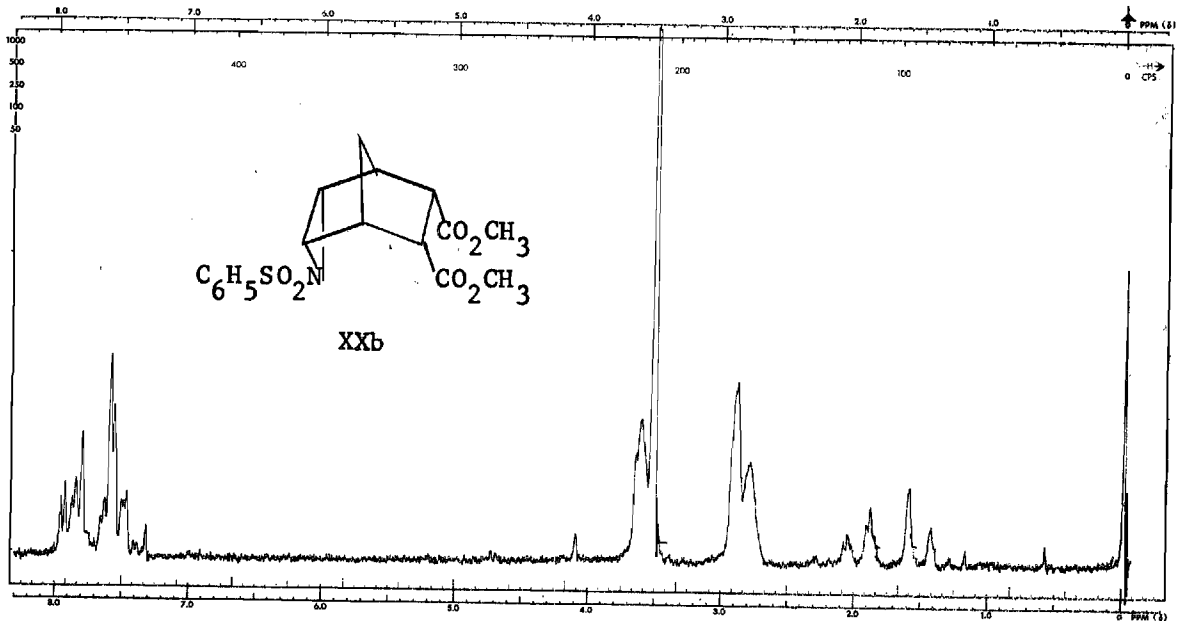

Figure 3. Nmr Spectrum of Aziridine XXb.

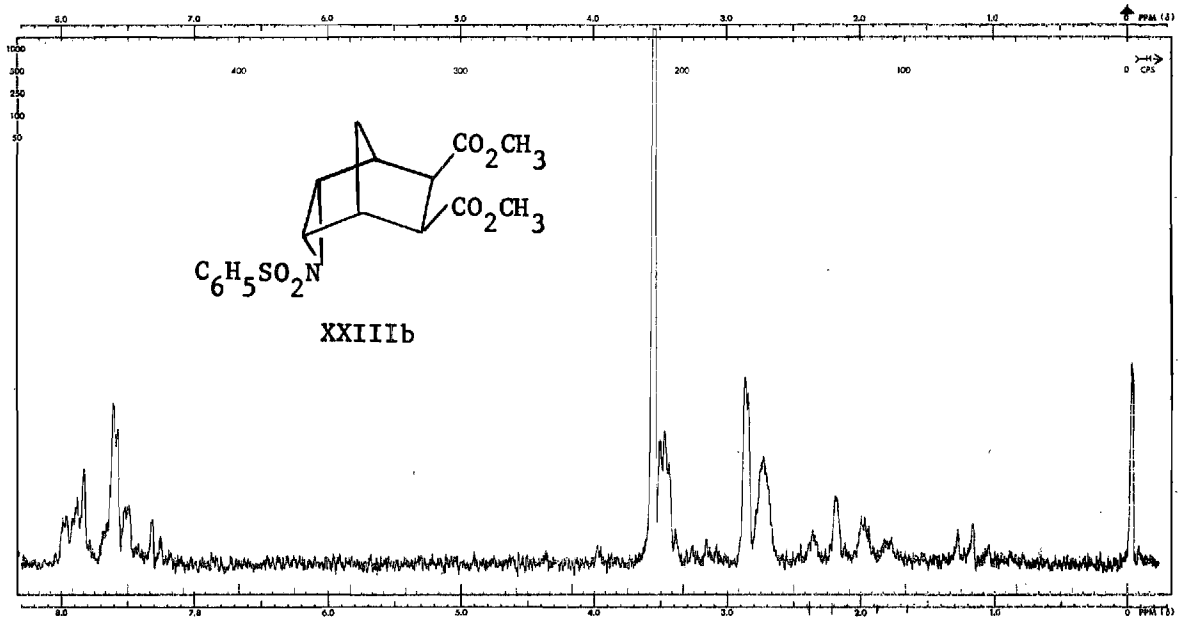

Figure 4. Nmr Spectrum of Aziridine XXIIIb.

APPENDIX II

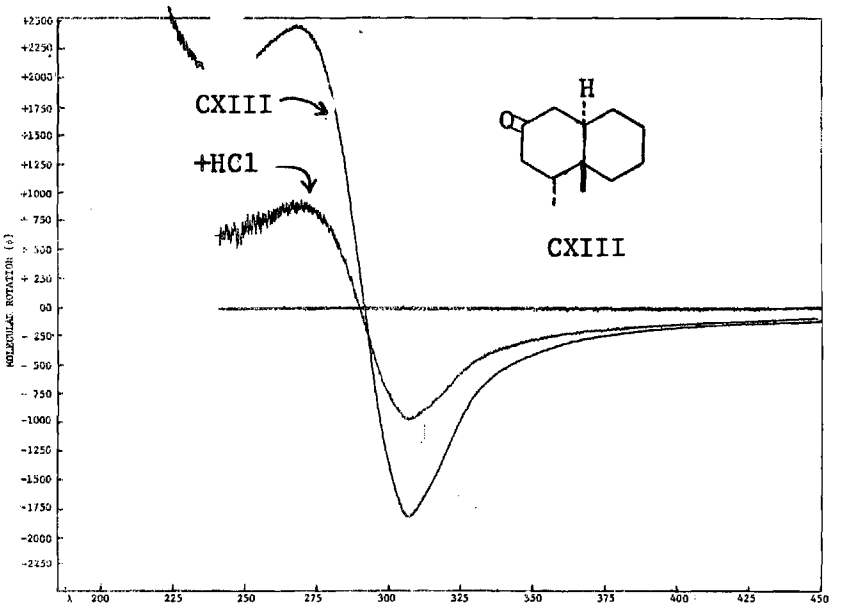

Figure 1. Optical Rotatory Dispersion of Ketone CXIII.

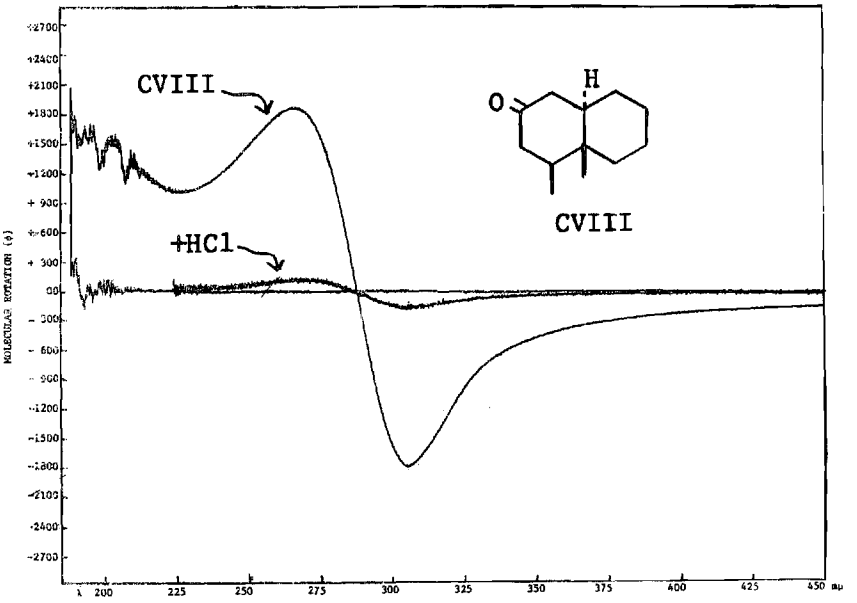

Figure 2. Optical Rotatory Dispersion of Ketone CVIII

APPENDIX II (Continued)

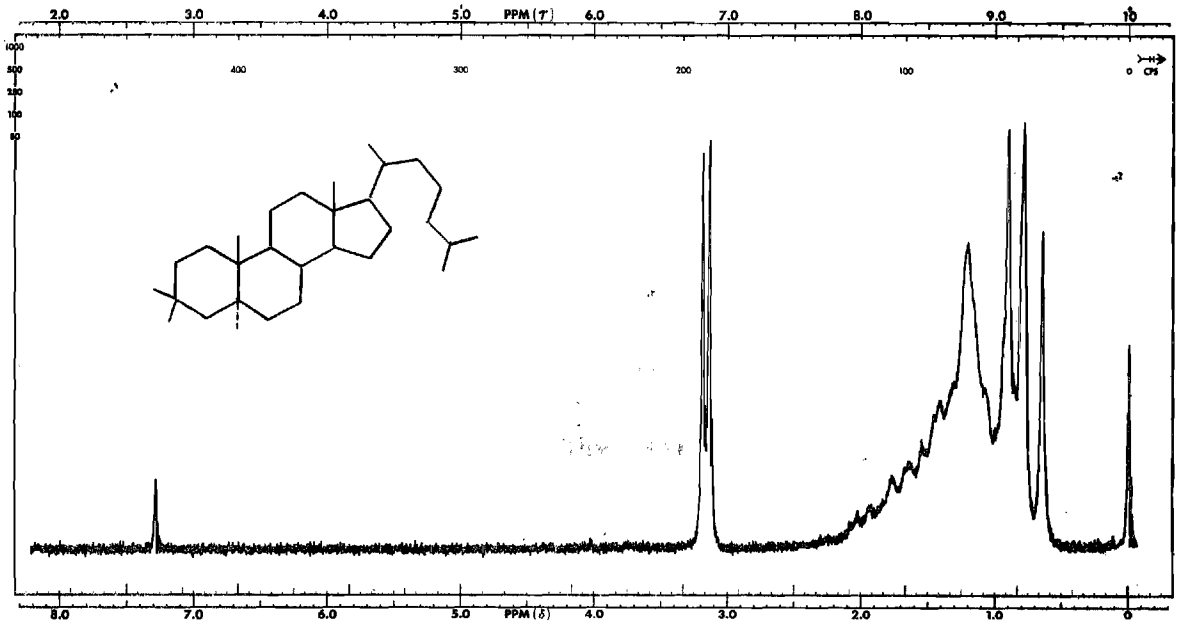

Figure 3. Nmr Spectrum of Dimethyl Ketal CXX.

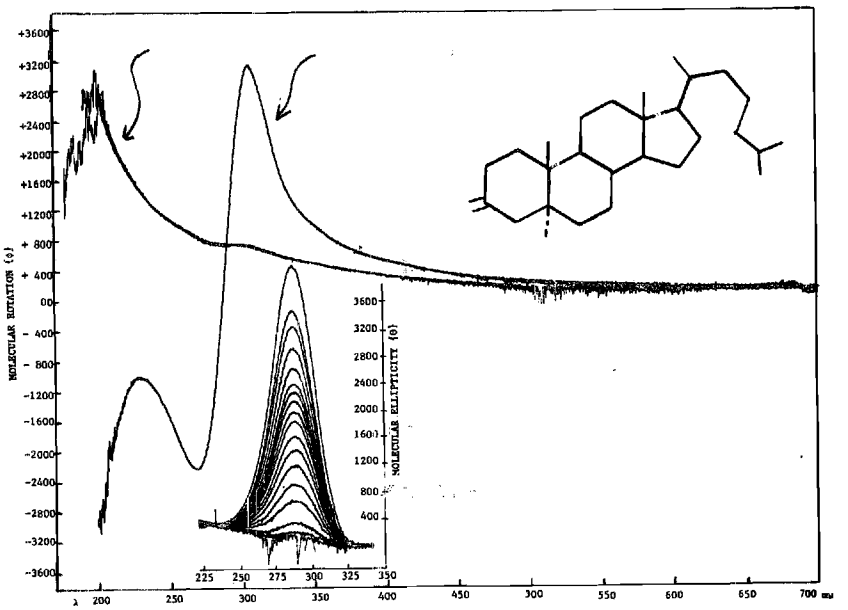

Figure 4. Optical Rotatory Dispersion and Circular Dichroism of 5α-Cholestan-3-one(CXIX).

APPENDIX III

Sample Calculations

Optical Rotatory Dispersion of 5α-Cholestan-3-one

c = Concentration (g/100 ml) = 0.3024

d = length of cell (decimeters) = 0.10

λ = wavelength (millimicrons)

α_λ = observed rotation (degrees) at wavelength λ

$\{\alpha\}_\lambda$ = specific rotation at wavelength $\lambda = \frac{100}{dc}$

$\{\Phi\}_\lambda$ = molecular rotation at wavelength $\lambda = \frac{\{\alpha\}(\text{mol. wt.})}{100}$

a = amplitude of Cotton effect $= \frac{\{\Phi\}_{\lambda_1} - \{\Phi\}_{\lambda_2}}{100}$

where λ_1 is the longer wavelength extremum and λ_2 is the shorter wavelength extremum.

$$\alpha_{305.5} + 0.2445^\circ \{\alpha\}_{305.5} = \frac{(100)(0.2445)}{(0.1)(0.3024)} = +805.5^\circ \quad \{\Phi\}_{305.5} \frac{(805.5)(386}{100} = 3121^\circ$$

$$\alpha_{268} - 0.1755^\circ \{\alpha\}_{268} = \frac{(100)(0.1755)}{(0.1)(0.3024)} = -580.4^\circ \quad \{\Phi\}_{268} = \frac{(-580.4)(386)}{100} = -2240^\circ$$

$$a = \frac{(3121) - (-2240)}{100} = +53.61.$$

Circular Dichroism of 5α-Cholestan-3-one

$$\{\theta\}_\lambda = \frac{4500}{\Pi \ell c} \log_e 10 \text{ (CD range) (recorder response)}$$

where $\{\theta\}_\lambda$ = molecular ellipticity at wavelength λ

ℓ = lenght of cell (centimeters) = 1.0 cm

Π = 3.1416

c = molar concentration = $7.834 \cdot 10^{-3}$

$\log_e 10 - 2.3026$

CD range = ± 0.01

recorder response = 0.97 full scale

$$\{\Phi\}_{289} = \frac{(4500)(2.3026)(0.01)(0.97)}{(3.1416)(10)(7.834 \cdot 10^{-3})} = 4083$$

Γ = bandwidth at half-height = 33 mμ.

VITA

Ronnie Lee Hale, son of Mr. and Mrs. Clayton Hale, was born on December 6, 1942, in Maud, Oklahoma. He attended the Maud public schools and graduated in 1960. He entered Murray State College, Tishomingo, Oklahoma in September 1960 and received the Associates of Science degree in June 1962. He entered Oklahoma State University in 1962 and obtained the Bachelor of Science degree from the University with a major in chemistry in June 1964.

In June 1964, he was awarded a National Science Foundation Co-Operative Graduate Fellowship and began graduate work at Oklahoma State University, receiving the Master of Science degree in January 1966. He began graduate work at the Georgia Institute of Technology in September 1965 and was awarded the Rayonier Fellowship in September 1966 and the American Cyanamid Fellowship in September 1967. He was awarded a National Institutes of Health, Public Health Service, Postdoctoral Fellowship in June 1968 for postdoctoral studies at Stanford University under the direction of Dr. Carl Djerassi.