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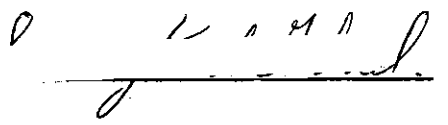

7/25/68

PART I

THE STEREOCHEMISTRY OF BICYCLIC EPOXIDATIONS

PART II

STUDIES IN THE SYNTHESIS OF SOME NATURAL PRODUCTS

A THESIS

Presented to

The Faculty of the Graduate Division

by

Sammy Karl Gabriel

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

May, 1969

PART I

THE STEREOCHEMISTRY OF BICYCLIC EPOXIDATIONS

PART II

STUDIES IN THE SYNTHESIS OF SOME NATURAL PRODUCTS

Approved:

Chairman

Date approved by Chairman: 5/29/69

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I thank the National Institutes of Health for financial support during the course of my graduate studies.

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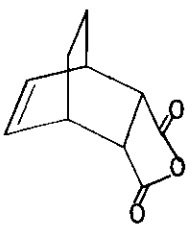
GLOSSARY OF ABBREVIATIONS

glc	gas-liquid chromatography
cps	cycles per second
M^+	molecular ion in mass spectrum
R_T	retention time (glc)
R_f	distance relative to solvent front (tlc)
tms	tetramethylsilane
s	singlet
d	doublet
q	quartet
m	multiplet
tlc	thin-layer chromatography
m.p.	melting point
cm^{-1}	wave numbers (infrared)
in.	inch
min	minute

SUMMARY

PART I

In order to determine the extent of anhydride participation in the epoxidation of bicyclic systems, a study was undertaken, using bicyclo-(2.2.2)-5-octene-2,3-endo,cis-dicarboxylic anhydride (XIX) as a model system. Following treatment of (XIX) with trifluoroperacetic acid, two epoxides could be obtained; namely, 3-Oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic anhydride (XX) and 3-Oxatricyclo(3.2.2.$0^{2,4}$ endo)-nonane-5,6-endo,cis-dicarboxylic anhydride (XXI). Quantitative determination of the products using gas-liquid chromatography revealed that the ratio of endo to exo epoxidation was 1/3 at room temperature. Although cooling increased the amount of exo-epoxide, dilution caused no significant change in the ratio. Lactone XXVII was subjected to epoxidation conditions which gave only the exo-epoxide. From this study it was concluded that anhydride participation need not be involved to explain the stereochemistry; the stereochemistry is governed by steric factors.



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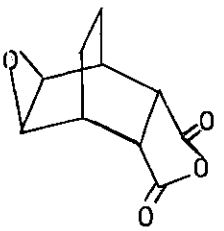

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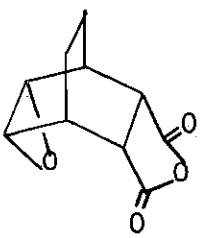

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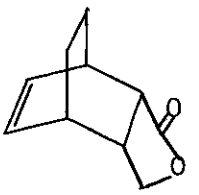
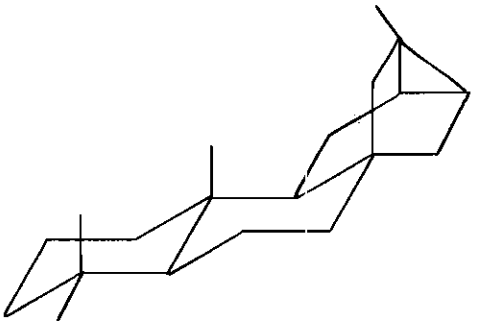


XXVII

PART II

A suitable synthesis leading to the formation of isotrachylobane (VIII) was sought, using maleopimaric acid as a starting material. Alcohol XXII, obtained by a reaction sequence, was treated with mixed-hydride reagents (lithium aluminum hydride and aluminum chloride) in an attempt to form the cyclopropane ring. The products isolated from the reaction mixtures were isomeric, unsaturated compounds which were characterized and shown to be unsaturated isomers of isotrachylobane.



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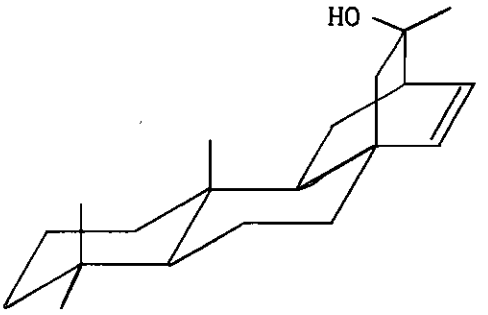
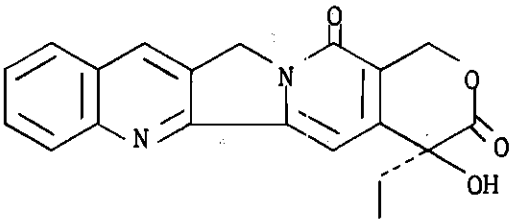


XXII

Camptothecin (XXXIII), a rare natural product, is a very powerful tumor inhibitor. Primary oxidation reactions were attempted in an effort to generate a suitable intermediate, capable of being converted, eventually, into camptothecin. After many unsuccessful attempts, LIV was formed which could conceivably be a useful precursor of camptothecin.



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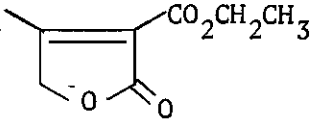


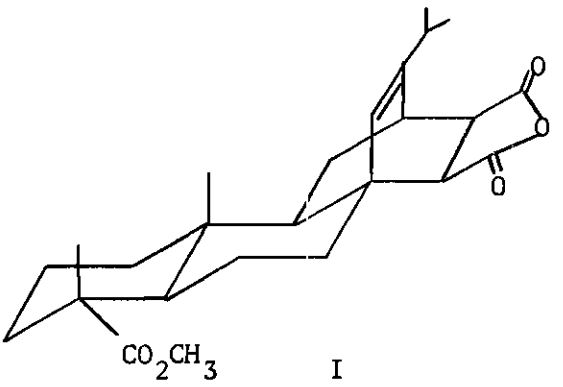
LIV

PART I

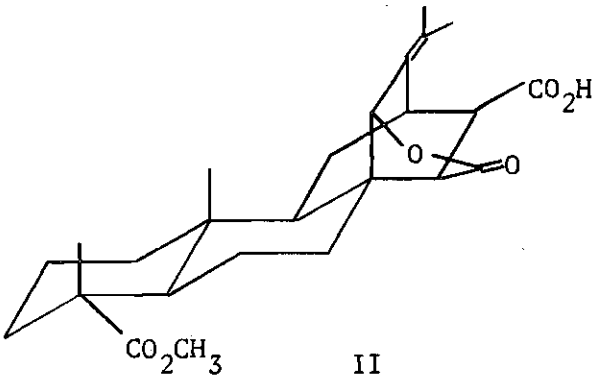
CHAPTER I

INTRODUCTION

The ozonolysis of methyl maleopimarate (I) was first investigated by Wienhaus and Sanderman in 1934[1]. Subsequently, the reaction was reinvestigated in 1940 by Ruzicka and LaLande[2] and in 1965 by Zalkow, Kilkarni, and Girotra[3a]. From these investigations, three ozonolysis products have been isolated and the structures elucidated:



I



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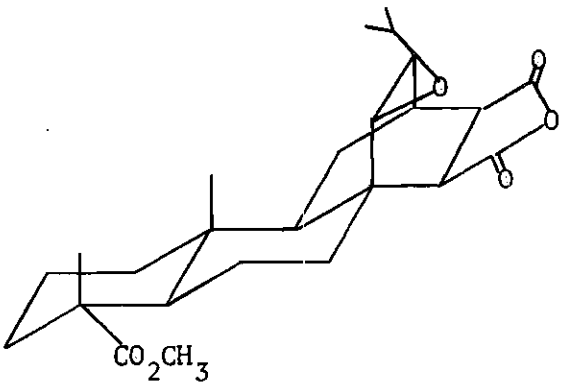
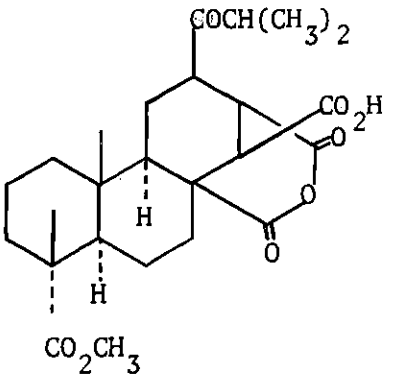


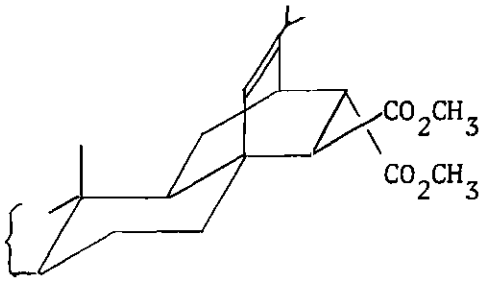
III



IV

II, m.p. 226-227°C[4], III, m.p. 289-290°C[3a], and IV, m.p. 250°C[3a,5].

An investigation of III proved to be of interest. It was found that III could also be generated from I by the action of trifluoroperacetic acid[3a] but was produced only very slowly in the presence of m-chloroperbenzoic acid[3b]. Treatment of III with diazomethane-methanol was ineffective in contrast to the facile esterification of I under the same conditions. It has been found recently that treatment of V with trifluoroperacetic acid resulted in the formation of VI via the intermediate epoxide which was isolated when m-chloroperbenzoic acid was used[3b].



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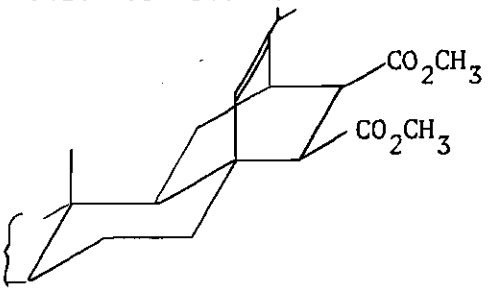
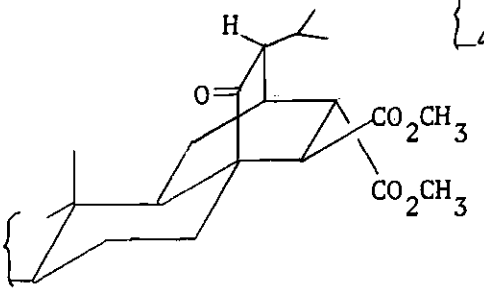
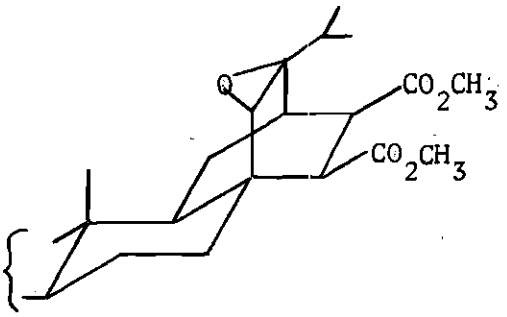


VII

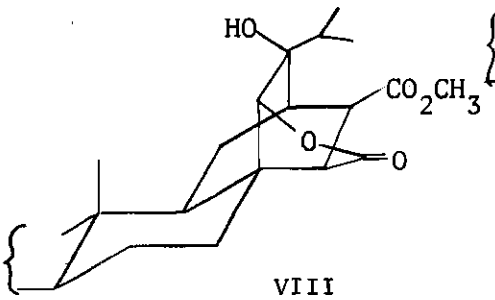


VI

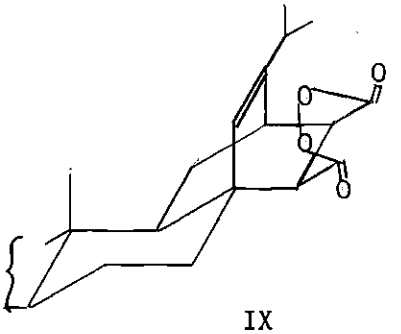
In contrast, the treatment of VII with trifluoroperacetic acid resulted in the isolation of a hydroxy γ-lactone rather than an epoxide. Structure VIII was assigned to the resulting hydroxy lactone, postulated as arising via intermediate epoxide VIIa, followed by a trans opening due to participation of the ester group.



VIIa



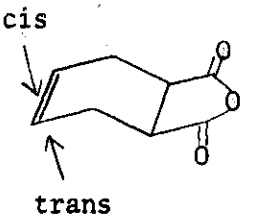
VIII



IX

The stereospecificity of the epoxidation was explained as follows. In the case of V, the face of the double bond anti to the angular C-10 methyl group is the least hindered side due to the fact that the C-15 carbomethoxy group is down. In VII the anti face is the more hindered side due to the cis carbomethoxy groups. In the case of I, it was postulated that the anhydride moiety might be converted, by ozone in acetic acid or trifluoroperacetic acid, into an intermediate peroxide, such as IX, which could then undergo an intramolecular reaction to form III.

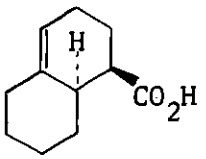
The idea of intermediate peroxide formation from an anhydride group was first postulated by Henbest[6] to explain the cis epoxidation of cis-Δ^4-tetrahydrophthalic anhydride, X. Gray and Heitmeier[7] maintained that the observed stereospecificity arose because the cyclohexene



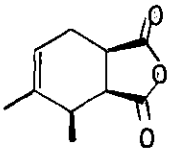
X

ring in cis-Δ^4-tetrahydrophthalic anhydride exists as an "equatorial half-boat" (as shown in X) and exo attack occurs in the same manner as in norbornyl anhydrides. Norbornyl anhydrides and imides are reported to yield exclusively exo epoxides[7].

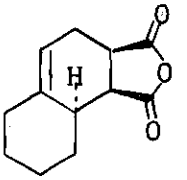
However, in a series of studies it has been reported that the epoxidation of XI gave a quantitative yield of trans epoxide[8a] while XII[8b] and XIII[8c], substituted cis-Δ^4-tetrahydrophthalic anhydrides, gave a cis:trans ratio of 1:2 and 1.2:1 respectively. It is difficult to rationalize these results on the basis of steric ground or on the assumption of the formation of intermediate cyclic peroxides.



XI



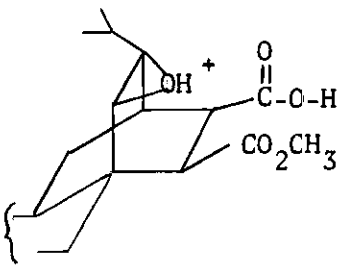
XII



XIII

In 1953 Barton[9] stated that the opening of an epoxide ring always occurs by a backside attack, resulting in a trans-diaxial product. This fact was further substantiated in 1959[10]. Langlois and Gastambide postulated the first exception to the rule in 1965[11a]. These workers maintained that, since the infrared spectrum indicates intramolecular hydrogen bonding (3460 cm ^{1}) and the hydroxyl function could be oxidized

in good yield only under strenuous conditions, the hydroxyl grouping was both endo and secondary. Thus the compound represented by VIII should properly be represented as XV. It was rationalized that XV, obtained both by the action of methanol-sulfuric acid upon III and by the action of p-nitroperbenzoic acid upon VII, arose via the intermediate XIV which undergoes cis opening of the epoxide ring. Recently[11b] an epoxide has been isolated by treatment of VII with m-chloroperbenzoic acid which, upon exposure to trifluoroacetic acid was converted into the same hydroxylactone as was obtained directly from VII as described above. Hence, if Langlois and Gastambide[11a] are correct, this must be the syn epoxide rather than the anti epoxide VIIa. (Only one other report of cis opening of an epoxide has been observed in the literature)[12]. In a study of the model system XVI, it was found that treatment with p-nitroperbenzoic acid gave a crude product which was devoid of any γ-lactone functions[11a].



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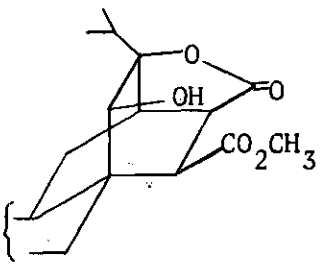

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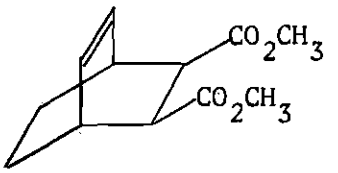
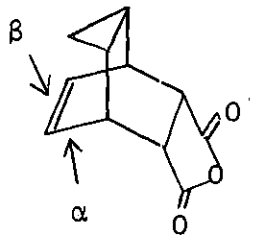
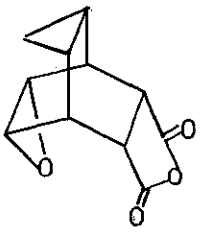


XVI

The epoxidation of the tricyclic compound XVII was found to yield a single epoxide which was endo to the anhydride system (XVIII)[13]. The stereospecificity of the reaction was attributed to hindrance of the β* face due to the cyclopropane ring. It is of interest that the epoxide ring of XVIII was unaffected by acidic or basic solutions.



XVII



XVIII

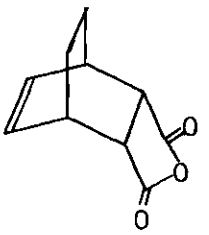
Purpose of the Investigation

In view of the arguments presented pertaining to the epoxidation of methyl maleopimarate (I), trimethyl maleopimarate (VII), and trimethyl fumaropimarate (VI), it seemed of interest to obtain more information regarding intramolecular epoxidations. As a model system, bicyclo(2.2.2)-5-octene-2,3-endo,cis-dicarboxylic anhydride (XIX) was chosen, due to the resemblance of this system with the bicyclic portion of methyl maleopimarate.

The purpose of this investigation was to determine whether the anhydride moiety participates in an intramolecular epoxidation of the

*The αβ-nomenclature follows established usage[14].

bicyclic double bond by observation of the stereochemistry of the products.



XIX

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded with Perkin-Elmer 237B and Beckman IR-5 spectrophotometers 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 the solvent specified. Chemical shifts are reported in ppm downfield from the internal standard, tetramethylsilane. The abbreviations s,d,t,q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; coupling constants are reported in cycles per second. Gas-liquid chromatography (glc) was performed using an F & M Biomedical Gas Chromatograph, Model 400, with a glass column and a hydrogen flame detector. All glc analyses were accomplished using a 6 ft by 1/8 in. glass column packed with 10 percent SE-30 on 100-120 mesh Gas-Chrom Q at 190°C with a helium flow rate of 88 ml/min unless stated otherwise. Mass spectra were recorded using a Varian M-66 mass spectrometer. Thin-layer chromatography (tlc) was performed using silica gel coated microscope slides. Visualization was accomplished using iodine vapors. Carbon and hydrogen microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mülheim, West Germany.

CHAPTER III

EXPERIMENTAL

Preparation of Bicyclo(2.2.2)-5-octene-2,3-endo,cis-dicarboxylic Anhydride (XIX)

Bromination of Cyclohexene

Following a previously described procedure[15], a three-necked, three liter, round-bottomed flask, equipped with a magnetic stirrer, dropping funnel, and thermometer, was placed in a dry ice-acetone bath. Cyclohexene (723 g) was added to the flask followed by addition of liquid bromine until a slight color persisted. Caution was taken that the temperature of the reaction material remained below 0°C. When a definite bromine color persisted, the addition was stopped and the resulting solution was stored in the refrigerator. After 12 hours the entire solution solidified in quantitative yield (2100 g). This solid was allowed to melt at room temperature and the resulting liquid was used in the next reaction without purification.

Dehydrohalogenation of Dibromocyclohexane. Formation of 1,3-Cyclohexadiene.

Using the method of Hine, et al.[15], a three-necked, three liter, round-bottomed flask, equipped with a dropping funnel, a ground glass stirrer, a thermometer in the liquid, a fractionating column, and a fractionating head equipped with a cold-finger condensor and thermometer, was charged with one liter of ethylene glycol and 500 g of sodium

hydroxide. This mixture was heated to and maintained at 220°C. Cyclohexene dibromide (615 g) was slowly dropped into the hot solution at a rate such that the distillate vapors maintained a temperature of less than 100°C. The distillate consisted of a water layer, which was discarded, and an organic layer, which was dried over magnesium sulfate. After removal of the drying agent, the organic layer yielded 150 g of 75 percent 1,3-cyclohexadiene as determined by glc.

Formation of XIX

Employing the procedure of Diels and Alder [16], maleic anhydride (24 g) was added to a solution of 1,3-cyclohexadiene (25 g; 75% purity), prepared as previously described, in 60 ml of dry benzene. The reaction vessel was allowed to stand at room temperature for 20 minutes at which time a very vigorous, spontaneous reaction took place. After the reflux had ceased, the reaction material was allowed to cool to room temperature whereupon crystals of the addition product precipitated from the mother liquor in quantitative yield. Recrystallization from benzene gave XIX, m.p. 145-147°C (lit.[16] 147°C).

Preparation of Authentic Samples of 3-Oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic Anhydride (XX) and 3-Oxatricyclo(3.2.2.2.$0^{2,4}$ endo)-nonane-5,6-endo,cis-dicarboxylic Anhydride (XXI) and the Corresponding Dimethyl Esters

A mixture of XIX (8.90 g; 0.05 moles) and anhydrous disodium hydrogen phosphate (28.0 g; 0.20 moles) in 50 ml of methylene chloride was cooled to ice-bath temperature. To this was added at 0° a solution of trifluoroperacetic acid, prepared by the dropwise addition at 0°C

of 90 percent hydrogen peroxide (2.1 ml; 0.07 moles) to a suspension of trifluoroacetic anhydride (19 ml; 0.09 moles) in 25 ml of methylene chloride. After the addition was complete, the reaction mixture was allowed to warm to room temperature with stirring for 24 hours.

The mixture was filtered and the solid thus obtained was washed with several portions of methylene chloride. The combined filtrate was washed with water, dried over anhydrous magnesium sulfate, and concentrated to give the crude product. Additional material was obtained by dissolving the original solid in a five percent sodium carbonate solution and extracting with methylene chloride. A total of 7 g of product was collected. Recrystallization from acetone gave, first, square crystals of 3-oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic anhydride (XX) which sintered at 208°C and 217°C and melted at 221-223°C (lit.[13] 207-208°C); ν_{max}^{KBr} 1830, 1775, 1250, 1215, 1080, 950, 915 cm^{-1}; nmr (CF_3CO_2H) δ: 1.43 (d, $H_{7a,8a}$, J=11 cps), 1.92 (d, $H_{7s,8s}$, J=11 cps), 2.96 (2H, $W_{1/2h}$ = 9 cps), 3.44 (2H, $W_{1/2h}$ = 4 cps), 3.64 (2H, $W_{1/2h}$ = 6 cps).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.91; H, 5.20

Found: C, 61.87; H, 5.20

Treatment of XX with diazomethane in methanol-ether gave the dimethyl ester, XXII, m.p. 93-94°C from ether; ν_{max}^{KBr} 1733, 1235, 1205, 1167 cm^{-1}; nmr ($CDCl_3$), δ: 1.18 (2H, d, J=11 cps), 1.88 (2H, d, J=11 cps), 2.50 (2H, $W_{1/2h}$ = 8 cps), 3.05 (2H, $W_{1/2h}$ = 3 cps), 3.44 (2H, $W_{1/2h}$ = 8 cps), 3.60 (6 H).

Continued concentration of the acetone gave diminishing amounts of the square crystals until the mother liquor gave needle-like crystals

of 3-oxatricyclo-(3.2.2.$0^{2,4}$ endo)nonane-5,6-endo,cis-dicarboxylic anhydride (XXI). Recrystallization from acetone gave the analytical sample of XXI, m.p. 183-185°C; ν_{max}^{KBr} 1860, 1835, 1785, 1250, 1100, 970, 915 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.91; H, 5.20

Found: C, 61.99; H, 5.17

Treatment of XXI with diazomethane in methanol-ether gave the dimethyl ester, XXIII, m.p. 89-90°C from ether; ν_{max}^{KBr} 1724, 1224, 1188 cm^{-1}; nmr ($CDCl_3$) δ: 1.61 (4H, $W_{1/2h}$ = 4 cps), 2.50-2.80 (broad signal upon which a sharp signal is superimposed, total area corresponds to 4), 3.22 (2H, $W_{1/2h}$ = 7 cps), 3.64 (6H).

Thin-layer chromatography of the crude recovered product using a 1:1 ethyl acetate:benzene eluent solution indicated three spots (when visualized with iodine vapors) with R_f values of 0.65 (XIX), 0.58 (XX) and 0.42 (XXI). Tlc of the dimethyl esters, formed by treatment of a sample of crude product in methanol-ether with diazomethane gave R_f 0.68, 0.61 and 0.40, respectively, under the same conditions as above.

Preparation of Hydroxylactonic Ester XXV

A solution containing 3.0 g of m-chloroperbenzoic acid (85% pure, FMC Corporation) in 25 ml of methylene chloride was added to a solution of XXIV (2.6 g) dissolved in 25 ml of methylene chloride. After stirring at room temperature for 48 hours, the solution was washed with 10 percent sodium nitrite solution followed by 10 percent sodium carbonate solution and finally dried over anhydrous magnesium sulfate. Removal of

the solvent gave 1.62 g of neutral material, m.p. 64-66°C. Tlc of the recovered material using a 1:1 ethyl acetate:benzene solvent system indicated two spots (when visualized with iodine vapors) with R_f 0.36 (XXV) and 0.64 (XXIV). The nmr of the recovered product in chloroform-d indicated a 90 percent abundance of XXV by virtue of the methyl ester signal in the δ 3.50-3.64 region. Following recrystallization from ether and drying at 60°C and 29 mm pressure for five hours, pure XXV was obtained giving a melting point of 89-91° (lit[13] m.p. 93-94°C); ν_{max}^{KBr} 3472, 3370, 1775, 1730 cm^{-1}; nmr (benzene) δ:3.50 (3H), 3.95 (H_5,$J_{5,6}$ = 4.5 cps), 4.38 (H_6).

Epoxidation of XIX Under Standard Conditions. Quantitative Determination of Products

Epoxidation at Reflux Temperature

To a mixture of XIX (1.78 g) and anhydrous sodium sulfate (5.7 g) in 50 ml of methylene chloride was added a solution of trifluoroperacetic acid prepared as previously described with trifluoroacetic anhydride (2.5 ml) and 90 percent hydrogen peroxide (0.5 ml). After addition was complete, the mixture was heated at reflux for 30 minutes followed by stirring at room temperature for 12 hours. The solution was filtered using the water aspirator and the remaining solid was washed with two 15 ml portions of methylene chloride. The filtrates were combined and concentrated to near dryness using a rotary evaporator. Benzene (50 ml) was added to the semi-solid product followed by reconcentration to dryness. The last traces of solvent were removed by a vacuum pump to give 1.98 g of solid crude product.

If this crude product was esterified using a methanol-ether solution of diazomethane within one hour of workup, there resulted the following product retention times and percentages, using a 6 ft x 1/8 inch glass column packed with 10 per cent SE-30 on 100-120 mesh Gas-Chrom Q at 190°C with a helium flow rate of 88 ml/min: 1.3 min (0%; XXIV), 1.8 min (45%; XXII), 2.6 min (24%; XXIII) and 3.6 min (29%; XXV).

However, when the crude recovered product was allowed to stand open to the atmosphere at room temperature for four weeks and then esterified, the following results were obtained by glc under the same conditions as above: 1.3 min (0%), 1.8 min (2%), 2.6 min (26%) and 3.6 min (70%).

Epoxidation at Ice-bath Temperature

To a mixture of XIX (1.78 g) and anhydrous sodium sulfate (5.7 g) in 50 ml of methylene chloride, cooled to ice-bath temperature, was added over a period of 20 minutes, a solution of trifluoroperacetic acid, prepared as previously described with trifluoroacetic anhydride (2.5 ml) and 90 per cent hydrogen peroxide (0.5 ml) in 15 ml of methylene chloride. The resulting mixture was allowed to stir at ice-bath temperature for four hours and then allowed to warm slowly to room temperature. The solution was then filtered using the water aspirator. The remaining solid was washed with methylene chloride. The filtrates were combined and concentrated to near dryness using a rotary evaporator. Benzene (50 ml) was added to the semi-solid followed by reconcentration to dryness. The last traces of solvent were removed by vacuum pump to give 2.05 g of crude, solid material.

Esterification within one hour of workup of a sample of the crude recovered product using a methanol-ether solution of diazomethane resulted in the following product percentages as determined by glc, using the exact conditions given above: 1.3 min (48%; XXIV), 1.8 min (41%; XXII), 2.6 min (5%; XXIII) and 3.6 min (6%; XXV).

When the crude recovered product was allowed to stand open to the atmosphere at room temperature for four weeks and then esterified, the following results were obtained by glc: 1.3 min (47%), 1.8 min (3%), 2.6 min (6%), 3.6 min (34%) and 3.7 min (10%; unidentified).

Preparation of Diol XXVI and Lactone XXVII

Following a previously reported procedure[17], solid XIX (17.8 g) was added to a solution of lithium aluminum hydride (4.6 g) in 200 ml of diethyl ether. After three minutes the mixture began to effervesce spontaneously. When effervescence had ceased, the reaction vessel was heated at reflux for 3.5 hours. Wet ether and water were cautiously added to the cooled solution. The mixture was then acidified with an aqueous 10 percent hydrochloric acid solution and extracted with three 50 ml portions of ether. The combined ethereal extracts were washed with a cold 10 percent aqueous sodium hydroxide solution until the base solution was no longer colored. The ether solution was then washed with water, dried over anhydrous magnesium sulfate, and concentrated by use of a rotary evaporator to give 11 g of crude neutral material. Recrystallization from ether gave XXVI, m.p. 103-105°C (lit[17] 104-106°C); ν_{max}^{KBr} 3250, 1655, 1605, 1350, 1050 cm^{-1}.

The sodium hydroxide wash solutions were acidified to pH 2 with a 10 percent hydrochloric acid solution and then extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated to dryness by rotatory evaporator giving 2.8 g of solid material. Recrystallization from ether-petroleum ether (30-60°C) gave crystals (2.5 g) of XXVII, m.p. 90-91°C (lit[17] 91-92.5°C); ν_{max}^{KBr} 1750, 1630, 1605 cm^{-1}.

Epoxidation of Lactone XXVII

To a mixture of XXVII (0.82 g) and anhydrous sodium sulfate (2.8 g) in 50 ml of methylene chloride was added a solution of trifluoroperacetic acid, prepared from trifluoroacetic anhydride (1.25 ml) and 90 percent hydrogen peroxide (0.25 ml) in 10 ml of methylene chloride. After addition was complete, the solution was refluxed for 30 minutes. Filtration, followed by removal of solvent, gave 0.9 g of the product, the glc (See Chapter II) of which showed 25 percent unreacted XXVII and 75 percent exo epoxide XXVIII. Slow recrystallization from ether gave pure XXVIII, m.p. 175-176°C; ν_{max}^{KBr} 1755, 1185 cm^{-1}; nmr (d_6-acetone) δ:1.08 (d, J=10 cps, H_{7a}, H_{8a}), 1.50 (d, J=10 cps, H_{7s}, H_{8s}).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.72; H, 6.72

Found: C, 66.59; H, 6.54

Epoxidation Using Trifluoroacetic Acid and Hydrogen Peroxide

Epoxidation of XIX with Trifluoroacetic Acid as Solvent

To a solution of XIX (1.8 g) in trifluoroacetic acid (6 ml) at room temperature was added 90 percent hydrogen peroxide (0.5 ml). After two hours of stirring, a sample of the reaction mixture was quenched with

a methanolic-ethereal solution of diazomethane. Analysis of the mixture using a 6 ft by 1/8 in. glass column packed with 10 percent SE-30 on 100/120 mesh Gas Chrom Q at 200°C with a helium flow rate of 88 ml/min gave four peaks with retention times and percentages of 1.8 min (4%), 2.6 min (22%), 3.7 min (22%), and 4.7 min (52%). Retention times correspond to authentic samples of XXIV, exo epxoide XXII, endo epoxide XXIII and hydroxy-lactone XXV, respectively, alone and admixture of authentic samples.

Epoxidation of XIX without Drying Agent

Hydrogen peroxide (90%; 0.5 ml) was added to a solution of XIX (1.8 g) in 50 ml of methylene chloride containing 3.0 ml of trifluoroacetic acid at room temperature. A sample was taken after two hours of stirring and quenched with a methanolic-ethereal diazomethane solution. Analysis of the reaction material by glc using a 6 ft by 1/8 in glass column packed with 10 percent SE-30 column at 200°C and a helium flow rate of 88 ml/min led to retention times and percentages of 1.5 (59%), 2.6 min (15%), 3.7 min (11%) and 4.5 min (11%) corresponding to XXIV, XXII, XXIII and XXV, respectively.

Epoxidation of a 2×10^{-1} M Solution of XIX

To a mixture of XIX (1.8 g) and anhydrous sodium sulfate (5.7 g) in 50 ml of methylene chloride and 3.0 ml of trifluoroacetic acid at room temperature was added 90 percent hydrogen peroxide (0.5 ml). After stirring at room temperature for 48 hours, a sample was withdrawn from the reaction vessel and treated with an excess of methanolic-ethereal diazomethane. Analysis of the esterified mixture by glc (See Chapter II) using a 10 percent SE-30 column at 205° gave retention times and percent-

ages of 1.4 min (67%), 2.4 min (14%), 3.6 min (8%) and 4.4 min (11%) corresponding to XXIV, XXII, XXIII and XXV, respectively.

Epoxidation of a 1 x 10^{-1}M Solution of XIX

Hydrogen peroxide (90%; 0.5 ml) was added to a mixture of XIX (1.8 g) and anhydrous sodium sulfate (5.7 g) in 100 ml of methylene chloride containing 3.0 ml of trifluoroacetic acid. The mixture was allowed to stir at room temperature for one week. A sample was then removed from the reaction vessel and treated with a methanolic-ethereal solution of diazomethane. Analysis of the sample by glc (See Chapter II) using a 10 percent SE-30 column at 200°C gave retention times and percentages of 1.4 min (68%), 2.6 min (17%), 3.6 min (8%) and 4.4 (7%) corresponding to XXIV, XXII, XXIII and XXV, respectively.

After standing for 19 months, the esterified sample was again analyzed by glc. Peaks corresponding to XXIII and XXV were observed with retention times of 3.6 min and 4.4 min, respectively, in a ratio of 1:3.5. No exo epoxide was observed.

Epoxidation of a 5 x 10^{-2}M Solution of XIX

In the same manner as above, a mixture of XIX (1.8 g) and anhydrous sodium sulfate (5.7 g) in 200 ml of methylene chloride and 3 ml of trifluoroacetic acid was treated with 90 percent hydrogen peroxide (0.5 ml). After stirring at room temperature for one week, a sample was taken, treated with a solution of methanolic ethereal diazomethane and analyzed by glc (see Chapter II) using an SE-30 column at 180° to give peaks with retention times and percentages of 3.4 min (23%), 4.3 min (21%) and 6.1 min (56%) corresponding to XXII, XXIII and XXV, respectively.

Epoxidation of a 2.5×10^{-2} M Solution of XIX

In the same manner as above, XIX (1.8 g) and anhydrous sodium sulfate (5.7 g) in a solution of 400 ml of methylene chloride and 3 ml of trifluoroacetic acid was treated with 90 percent hydrogen peroxide. After one week of stirring, a sample was taken, treated with methanolic ethereal diazomethane and analyzed by glc (See Chapter II) using a 10 percent SE-30 column at 190°C. Peaks were observed with retention times and percentages of 3.2 min (21%) and 4.6 min (79%) corresponding to XXIII and XXV, respectively. No exo epoxide was observed.

Attempted Epoxidation of XIX with 30 percent Hydrogen Peroxide

To a mixture of XIX (1.78 g) and anhydrous disodium hydrogen phosphate (6.5 g) in 50 ml of methylene chloride was added 30 percent hydrogen peroxide (1.8 ml) over a 30 minute period. The mixture separated into a clear solution and a white precipitate. After stirring for eight hours, the liquid was decanted from the precipitate. The gummy solid was washed with several portions of methylene chloride which were combined with the original solution. After concentration to near dryness on the rotary evaporator, benzene was added and removed to leave a solid residue (1.7 g). A sample of the residue was treated with a methanolic ethereal solution of diazomethane and analyzed by glc (See Chapter II). Only one peak with a retention time of 1.4 minutes, corresponding to the dimethyl ester of XIX, was observed.

Attempted Epoxidation of XIX with 90 percent Hydrogen Peroxide

Hydrogen peroxide (90%; 0.6 ml) was added to a mixture of XIX (1.7 g) and anhydrous disodium hydrogen phosphate (6.5 g) in 50 ml of methylene chloride. The combined mixture was allowed to stir at room

temperature for 30 minutes. After heating at reflux for 30 minutes, the mixture was allowed to cool to room temperature with stirring for 12 hours. The solution was then filtered and the residue was washed with methylene chloride. After concentration of the combined filtrates by rotary evaporator, 1.56 g of material remained. An additional 0.05 g of material was recovered by dissolving the solid residue in water and extracting with methylene chloride and ether. An infrared spectrum of the combined solid material exactly matched a spectrum of authentic starting material.

Attempted Epoxidation of XIX with 90 percent Hydrogen Peroxide Using p-Toluenesulfonic Acid as Catalyst

To a solution of XIX (1.8 g) in 50 ml of methylene chloride containing anhydrous sodium sulfate (5.7 g) and a catalytic amount of p-toluenesulfonic acid (0.1 g) was added 90 percent hydrogen peroxide (0.5 ml). The mixture was stirred at room temperature for 30 minutes and then refluxed for 30 minutes. A sample taken from the cooled reaction solution was analyzed by glc, using a 6 ft by 1/8 in glass column of 10 percent SE-30 at 200°C with a helium flow rate of 88 ml/min showed only one peak with retention time of 1.4 minutes corresponding to the dimethyl ester of the starting compound XXIV.

Hydrobromination of Bicyclo(2.2.1)-5-Heptene-2,3-endo,cis-dicarboxylic Anhydride XXIX. Formation of XXXI.

Following a published procedure[18], XXIX (5 g) was heated in 250 ml of water until the mixture became homogeneous. Bromine was then added to the cooled solution until a slight coloration remained. A quantitative recovery (7.95 g) of crystalline bromo-alcohol XXX was obtained

from the cold aqueous solution. After drying the crystals in the air, XXX gave m.p. 116-117 (lit[18] 116°C). A portion of the bromo-alcohol was esterified with ethereal diazomethane to give the bromolactonic ester XXXI. Recrystallization from petroleum ether (60-90°C) gave crystals of m.p. 76-77°C (lit[18] 77°C); ν_{max}^{KBr} 1730, 1780 cm^{-1}.

Treatment of XXXI with Sodium Methoxide

Methanol, which was dried by refluxing over magnesium methoxide, was distilled directly into a dry three-necked round-bottomed flask, equipped with a pressure equalizing addition funnel under a nitrogen atmosphere. Distillation was ceased when ca. 15 ml of liquid collected in the addition funnel and ca. 100 ml had collected in the flask. Metallic sodium (0.69 g) was introduced into the addition funnel and allowed to react with the methanol while XXXI (8.25 g) was added to the methanol in the flask. After cooling to room temperature, the sodium methoxide-methanol solution was slowly added to the liquid in the flask. Upon completion of the addition, the solution was heated to reflux for one hour and then allowed to stir at room temperature for 16 hours. Following the addition of 100 ml of benzene, the solution was concentrated by means of a rotary evaporator until a fine white precipitate formed. Removal of the solid by vacuum filtration gave a quantitative yield (3.25 g) of sodium bromide as determined by the water solubility and the formation of a precipitate with a silver nitrate solution.

The remaining filtrate was concentrated to near dryness to give 7.02 g of a gummy material which still contained some solvent. Crystallization of the gum from a small amount of ether gave 2.5 g of XXXII as white crystals, m.p. 130-131.5°C; ν_{max}^{KBr} 3375, 3080, 2920, 2620, 1720,

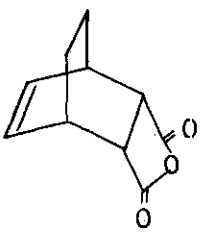
1700 cm^{-1}; nmr (CD_3CN) δ:1.53 (2H,t,J=1.5 cps) 1.8-2.1 (complex quartet, total area corresponds to 2H), 2.37 (1H,m), 2.86 (1H,d,J=1.5 cps), 3.63 (3H,s), 3.97 (1,t,J=1.5 cps). The mass spectrum failed to give a molecular ion. The first observable peak appeared at M^+-18 = 194.0443 (Calc. for $C_{10}H_{10}O_9$, M^+ = 194.0579). A tentative structure was assigned. Upon melting, an effervescence was noted and a new liquid, XXXIII was formed, b.p. < 145°C; ν_{max}^{KBr} 1795, 1730, 1440, 1270, 1210, 1130, 980 cm^{-1}. The mass spectrum gave the parent peak at M^+ = 194. The infrared spectrum was identical in all respects with an authentic sample of XXXIII obtained by other workers.[19]

CHAPTER IV

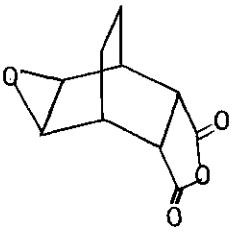
DISCUSSION OF RESULTS

As stated in Chapter I, the purpose of this problem was to study the possible intramolecular participation of a nearby anhydride moiety in the epoxidation of a double bond. It was anticipated that, by observation of the stereochemistry of the products arising from the epoxidation of bicyclo(2.2.2)-5-octene-2,3-endo,cis-dicarboxylic anhydride (XIX), the extent of the participation could be determined.

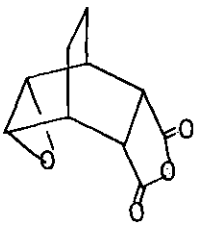
The preparation of XIX was accomplished by formation of 1,3-cyclohexadiene via the route described by Hine, et al.[15], followed by treatment of the diene with maleic anhydride, in the manner of Diels and Alder[16]. The resulting product was purified by recrystallization from benzene until the literature[16] melting point was obtained.



XIX



XX

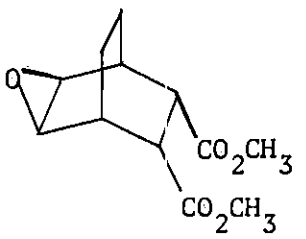


XXI

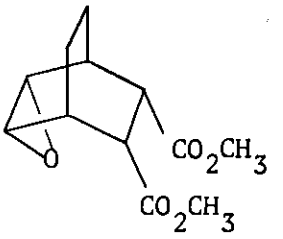
In order to study the stereochemistry of the epoxidation products of XIX, it was necessary to obtain authentic samples of XX and XXI. Both epoxides were isolated from the reaction mixture resulting from the treat-

ment of XIX with trifluoroperacetic acid[20] in the presence of disodium hydrogen phosphate. The crude product was slowly recrystallized from acetone to yield square crystals of 3-oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic anhydride (XX) which gave infrared absorptions for the anhydride function at 1830 and 1775 cm^{-1}. An absorption at 1250 cm^{-1} was assigned to the epoxide function[21]. Treatment of the anhydride with diazomethane resulted in the formation of ester XXII which exhibited absorption in the infrared spectrum at 1733 cm^{-1}.

Continued concentration of the mother liquor, after removal of XX, resulted in fine needle-like crystals of 3-oxatricyclo(3.2.2.$0^{2,4}$ endo)-nonane-5,6-endo,cis-dicarboxylic anhydride (XXI) which showed absorptions in the infrared spectrum for the anhydride function at 1835 and 1785 cm^{-1} and for the epoxide function at 1250 cm^{-1}. The infrared spectrum of the dimethyl ester showed absorption for the ester functions at 1724 cm^{-1}.



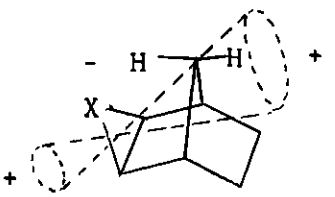
XXII



XXIII

The stereochemistry of the endo and exo epoxides was determined from the nmr spectra which exhibited the chemical shifts indicated in

Table 1. An investigation of the chemical shifts of the bridge protons at C-7 and C-8 was of particular interest. Compound XX, possessing an exo epoxide ring, exhibited the resonance signals for the C-7 and C-8 anti protons at ca. 30 cps higher field than the C-7 and C-8 syn protons. The dimethyl ester XXII gave the resonance signals for the anti protons at ca. 42 cps higher field than the syn protons. On the other hand, the syn and anti bridge protons were magnetically equivalent for both the endo epoxy compounds, XXI and XXIII. These differences in chemical shifts are in line with the observations of Tori, et al.[22], in which it was found that XXXV and XXXVI (Table 1) gave similar results, due to the long-range anisotropic shielding effect of an epoxide ring. This effect has been noted in other tricyclic systems and has been attributed to ring current effect as shown below[23].

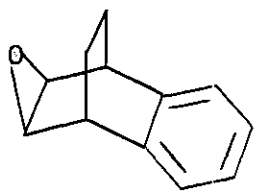


X = N, O

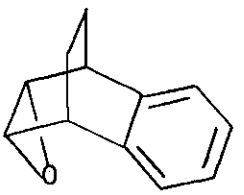
The epoxidation of the unsaturated dimethyl ester XXIV with m-chloroperbenzoic acid resulted in the formation of hydroxy lactonic ester XXV. The infrared spectrum showed absorptions at 3472 and 3370 cm^{-1} for the hydroxyl group, at 1775 cm^{-1} for the γ-lactone, and at 1730 cm^{-1} for

Table 1. The Chemical Shifts of the Protons of Some Bicyclic Compounds Containing an Epoxide Ring.

Compound	Solvent	δ in ppm					
		H_1, H_4	H_2,H_3	H_{7a},H_{8a}	H_{7s},H_{8s}	H_5,H_6	$-OCH_3$
XIX	$CDCl_3$	3.15	3.16	1.62	1.37	6.25	----
XX	CF_3CO_2H	2.96	3.44	1.43	1.92	3.64	----
XXI	DMSO-d_6	2.73	3.05	1.6	1.6	3.37	----
XXXIV	$CDCl_3$[24]	2.92	3.00	1.55	1.27	6.33	3.58
XXII	$CDCl_3$	2.50	3.05	1.18	1.88	3.44	3.60
XXIII	$CDCl_3$	2.65	2.70	1.61	1.61	3.22	3.64
XXXV	$CDCl_3$[25]	3.33	----	2.03	1.04	3.33*	----
XXXVI	$CDCl_3$[25]	3.41	----	1.75	1.39	3.41*	----



XXXV

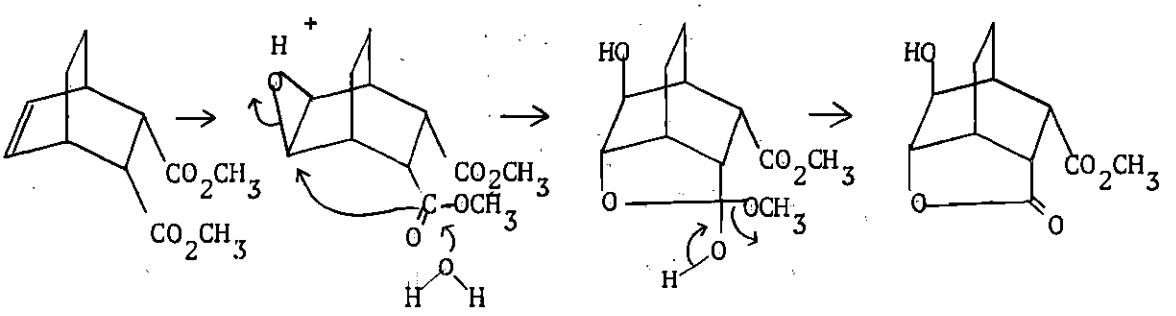


XXXVI

*The numbering system has been altered from that given by Tori, et al.[25], to allow the protons on the oxirane ring to correspond with the previous compounds.

the ester. A possible explanation for the formation of XXV is shown below (Scheme 1).

Scheme I



XXIV XXV

It was found that epoxidation XIX with trifluoroperacetic acid in the presence of anhydrous disodium hydrogen phosphate resulted in less than a quantitative recovery of reaction product despite repeated washings of the solid precipitate with methylene chloride. For this reason the epoxidations were done in the presence of anhydrous sodium sulfate. Analysis of the crude reaction products was first accomplished by observation of the ester resonance signals in the nmr spectra but a more satisfactory method of analysis was attained by use of gas chromatography (glc). Thus, a typical procedure of epoxidation was dissolution of the reactant (0.01 mole) in methylene chloride containing a suspension of anhydrous sodium sulfate (0.04 mole) to which a solution of trifluoroperacetic acid was added (ca. 0.01 mole). Following removal of the precipitate and concentration of the solvent, the crude reaction

product was treated with diazomethane and subjected to analysis by glc. The results of the epoxidation studies by this method are summarized in Table 2.

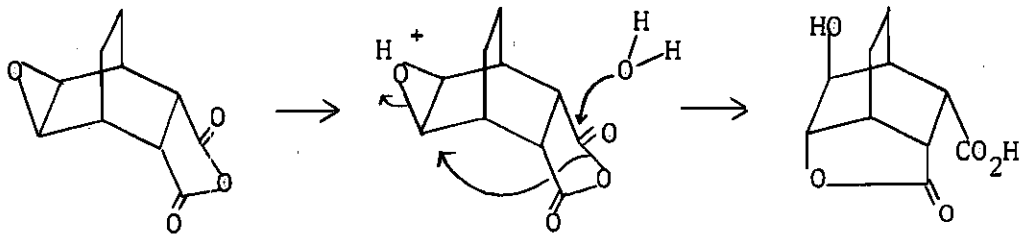
Table 2. Epoxidation with Trifluoroperacetic Acid[26]

		Percent Products			
Run	Alkene	Starting Material	Endo Epoxide	Exo Epoxide	Hydroxy-lactone
1	XIX	0	24	45	29
2	XIX	0	26	2	70
3	XIX	48	5	41	6
4	XIX	47	6	3	34
5	XXIV	0	21	2	66
6	XXVII	25	0	75	

Using the standard conditions (See Chapter III), XIX was treated with trifluoroperacetic acid followed by 30 minutes of heating at reflux. Analysis of the esterified product mixture showed the product composition to be 45 percent exo epoxide XXII, 24 percent endo epoxide XXIII, and 29 percent hydroxy lactone XXV (Run 1, Table 2). The crude reaction product which remained following removal of the solvent was allowed to stand open to the atmosphere for four weeks. Esterification of a sample of the material after this time, followed by glc analysis, revealed that the relative amounts of products had changed; e.g., 2 percent exo epoxide XXII, 26 percent endo epoxide XXIII, and 70 percent hydroxy lactone XXV (Run 2,

Table 2). It is obvious by a comparison of the relative percentages that the exo epoxide, XX, was converted, upon standing, to the hydroxy lactone XXXVII. A plausible explanation, due to the fact that traces of trifluoroacetic acid and water were present, is shown below.

Scheme 2



XX XXXVII

The epoxidation of XIX was repeated at ice-bath temperature. Analysis by glc of the esterified product revealed that the relative values were 48 percent unsaturated XXIV, 41 percent exo epoxide XXII, 5 percent endo epoxide XXIII, and 6 percent hydroxy lactone XXV (Run 3, Table 2). As in the previous case, the product ratios were altered when the crude material was allowed to stand in the solid state for four weeks. Analysis by glc after this time gave 47 percent unsaturated XXIV, 3 percent exo epoxide XXII, 6 percent endo epoxide XXIII, and 34 percent hydroxy lactone XXV. In addition, an unidentified compound was observed with a peak area of 10 percent (Run 4, Table 2).

The dimethyl ester, XXXIV, was epoxidized using the standard conditions given above. Analysis of the reaction product by glc gave 2 percent exo epoxide XXII, 21 percent endo epoxide XXIII, and 66 percent

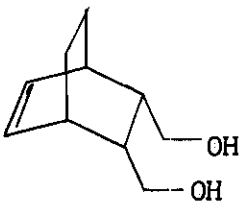
hydroxy lactone XXV. Thus, the transformation of the exo epoxide into the hydroxy lactone, which occurs over a period of days in the case of the anhydride XIX, requires only a very short period of time in the case of the dimethyl ester (Run 2, Table 2).

As stated previously, the exo epoxide XX is converted into hydroxy lactone XXXVII upon standing in the solid state, as shown by the data in Table 2. Therefore, a more meaningful comparison is provided by the ratio

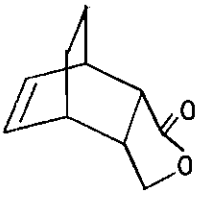
$$\frac{\text{percent endo epoxide}}{\text{percent exo epoxide + hydroxy lactone}} = \frac{\alpha \text{ attack}}{\beta \text{ attack}}$$

Thus from Table 2 it can be seen that the dimethyl ester (Run 5) gives the same ratio (1/3) as does the anhydride XIX (Runs 1 and 2) on epoxidation in refluxing methylene chloride, but at 0°C the ratio for XIX (Runs 3 and 4) drops to 1/7.

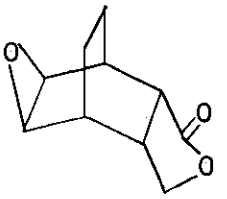
In order to gain further insight into the function of the anhydride moiety, it was determined that the epoxidation of lactone XXVII would provide useful information. The reduction of XIX, reported previously by Birch, et al.,[17] was accomplished using lithium aluminum hydride. From the neutral reaction product was obtained diol XXVI which exhibited no carbonyl in the infrared but showed absorptions at 3250, 1350 and 1050 cm^{-1} for the primary alcohols. From the acidified base-soluble portion of the reaction product was obtained lactone XXVII which exhibited an infrared band at 1750 cm^{-1} for the γ-lactone.



XXVI



XXVII



XXVIII

Lactone XXVII was then treated with trifluoroperacetic acid in the usual manner to yield a single epoxide, XXVIII (Run 6, Table 2). The epoxide ring was exo as shown by the nmr spectrum in which the C-7 and C-8 anti protons appeared at δ 1.08 (d,J=10 cps) while the C-7 and C-8 syn protons appeared at δ 1.50 (d,J=10 cps), in line with the data shown for the exo epoxides shown in Table 1.

An attempt to epoxidize diol XXVI under the standard conditions given above resulted in a very complex mixture of products (as determined by both glc and tlc), presumably due to oxidation of the alcohol functions.

It was reasoned that, if the anhydride moiety forms an intermediate peroxide which accounts for the endo epoxidation, then in the presence of only hydrogen peroxide, the endo epoxide should be the major product[26]. The addition of 30 percent hydrogen peroxide to a methylene chloride solution of XIX resulted in recovery of the starting material. The attempt was repeated using 90 percent hydrogen peroxide, again with no apparent reaction. A third attempt was made in which a catalytic

amount of p-toluenesulfonic acid was added to the solution of 90 percent hydrogen peroxide and XIX. Analysis of the reaction mixture revealed only starting material.

Since the solubility of p-toluenesulfonic acid is not very great in methylene chloride, it was thought that a more soluble acid might accomplish the desired epoxidation. For that reason trifluoroacetic acid was used. Addition of 90 percent hydrogen peroxide to a solution of XIX in trifluoroacetic acid, followed by analysis of an esterified sample showed 22 percent exo epoxide XXII, 22 percent endo epoxide XXIII and 52 percent hydroxy lactone XXV, which was not significantly different from epoxidation using the standard conditions.

The result of the above epoxidation may be interpreted in one of two ways. Either the anhydride moiety formed an intermediate peroxide which then reacted intramolecularly to form the endo epoxide and, because of the low dilution, also reacted intermolecularly to form the exo epoxide, or the trifluoroacetic acid reacts with hydrogen peroxide to form trifluoroperacetic acid which then reacted with the double bond in the regular manner. Emmons and Pagano[20] have found that an equilibrium exists between trifluoroacetic acid and hydrogen peroxide.

$$CF_3CO_2H + H_2O_2 \rightleftharpoons CF_3CO_3H + H_2O$$

In order to evaluate the possibilities, dilution studies were carried out in which the concentration of the intermediate peroxy-anhydride, if formed, would be sufficiently low enough to minimize the intermolecular reaction and maximize the intramolecular reaction. Conversely, if the epoxidation arises solely via trifluoroperacetic acid, the ratio of the

epoxides should remain essentially constant.

The dilution studies are summarized in Table 3. From the results

Table 3. Epoxidation of XIX with Hydrogen Peroxide and Trifluoroacetic Acid.

Run	Conc. of XIX[a]	Percent Products			
		Starting Material	Endo Epoxide	Exo Epoxide	Hydroxy Lactone
1	1.66 M[b]	4	22	22	52
2	2×10^{-1} M[c]	59	11	19	11
3	2×10^{-1} M	67	8	14	11
4	1×10^{-1} M	68	8	17	7
5	5×10^{-2} M	--	21	23	56
6	2.5×10^{-2} M	--	--	21	79

[a]In methylene chloride containing anhydrous sodium sulfate unless otherwise specified.

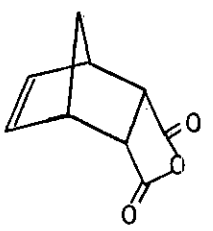
[b]Trifluoroacetic acid as sole solvent; no anhydrous sodium sulfate.

[c]No anhydrous sulfate.

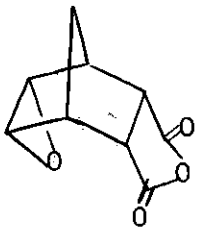
it can be seen that epoxidation of XIX occurs in the presence of trifluoroacetic acid and hydrogen peroxide in essentially the same α/β ratio as observed using trifluoroperacetic acid generated from trifluoroperacetic acid anhydride and hydrogen peroxide (See Table 2). Moreover, the dilution of XIX resulted in a slight decrease of the α/β ratio rather than an increase expected for an intramolecular participation of the anhydride moiety. Thus at concentrations of 1×10^{-1} to 5×10^{-2} to $2.5 \times$

10^{-2} M, the α to β ratio varied from 1:3 to 1:3.5 to 1:3.7, respectively.

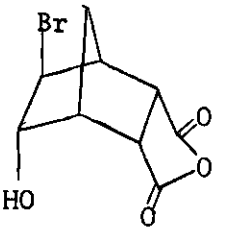
In an attempt to form 3-oxatricyclo(3.2.1.$0^{2,4}$ endo)octane-5,6-endo,cis-dicarboxylic anhydride (XXXVIII), XIX was treated with bromine and water to give a quantitative yield of bromo-alcohol XXX. A portion of the bromo-alcohol was esterified with diazomethane to give XXXI, a known compound[18], which gave infrared bands at 1780 cm^{-1} for the lactone and 1720 cm^{-1} for the ester.



XXIX



XXXVIII



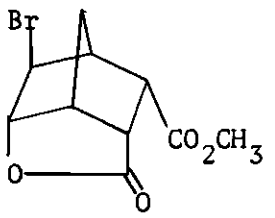
XXX

Treatment of XXXI with an equivalent amount of sodium methoxide in methanol resulted in a quantitative recovery of sodium bromide following the addition of benzene to the reaction mixture. Removal of the solvent gave an oil which was crystallized from ether to give crystalline XXXII. The structure was assigned from the following. The infrared spectrum gave absorptions at 3375 cm^{-1} (hydroxyl), 1720 cm^{-1} (ester), and 1700 cm^{-1} (acid). The mass spectrum did not give a parent ion but a peak appeared at M^{+}-18 = 194.0443 which was shown by exact mass determination to be

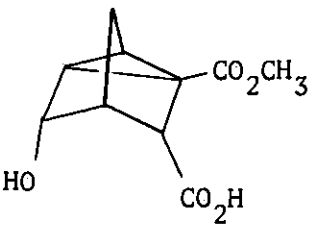
$C_{10}H_{10}O_4$. Upon melting, during which effervescence was noted, an oil was formed.

An infrared spectrum of the oil was identical in all respects with the infrared spectrum of an authentic sample of XXXIII obtained by other workers[19]. A mass spectrum of XXXIII gave a molecular ion at $M^+ = 194$.

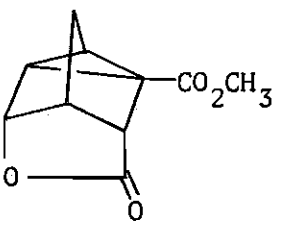
Scheme 3



XXXI



XXXII



XXXIII

Thus from the above evidence, XXXII was assigned the structure shown above.

Since the conclusion of this study Zalkow and Baxter* have observed that epoxidation of XIX with m-chloroperbenzoic acid can be accomplished in 85% yield at room temperature after twelve days in methylene chloride to give essentially the same ratio of α to β attack (73% exo, 22%, endo and 5% lactone).

*Private communication.

CHAPTER V

CONCLUSIONS

The epoxidation of bicyclic anhydride XIX resulted in the formation of both endo- and exo-epoxides.

Dilution caused no significant change in the ratio of α to β epoxidation of XIX.

Under the conditions utilized, lactone XXIII gave solely β epoxidation due to steric interaction.

The stereochemistry of the bicyclic systems studied was due to steric factors rather than anhydride participation.

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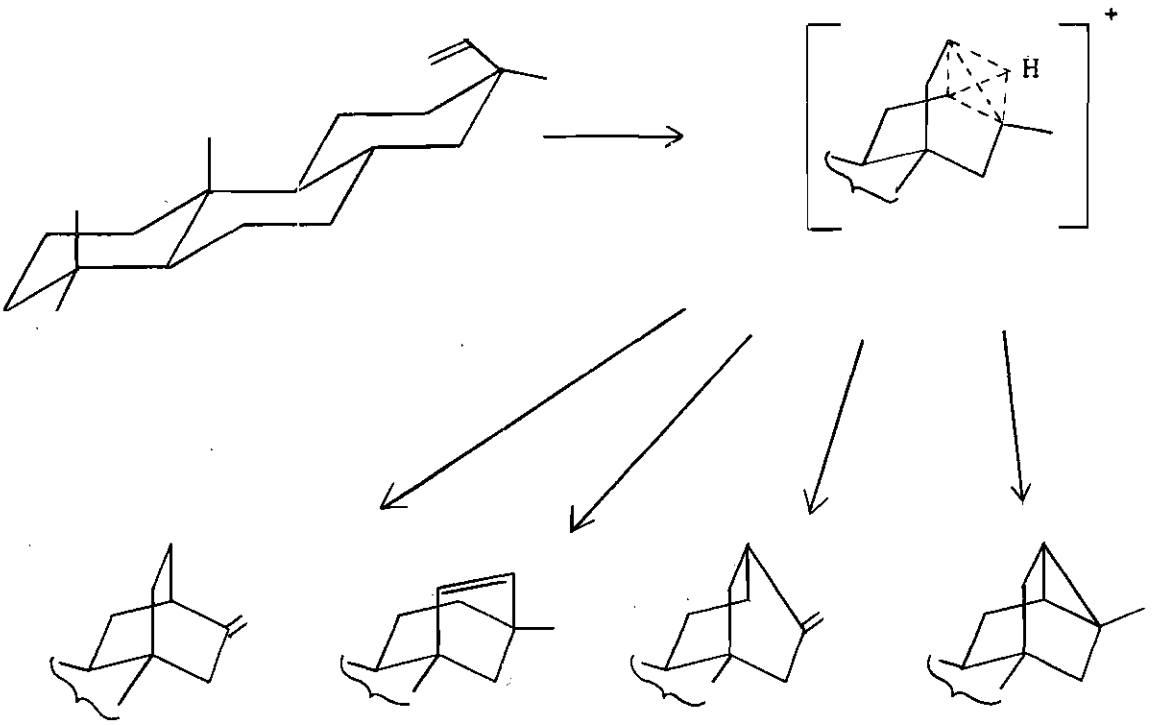
PART II

CHAPTER I

INTRODUCTION

In 1955 Wenkert postulated the biogenetic pathway for the formation of tetracarbocyclic diterpenes and diterpenoid alkaloids in which he suggested that cyclization of a pimaradiene-type cation proceeds via a bridged carbonium ion as illustrated in Scheme 1[1].

Scheme 1



I II III IV

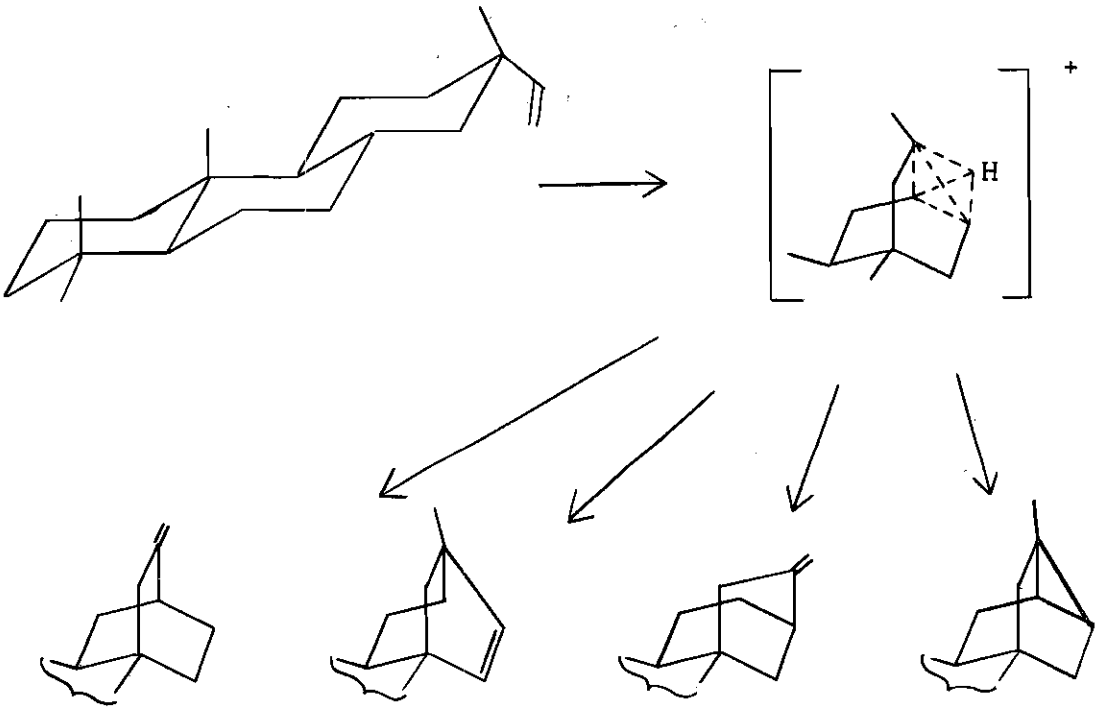
Since the postulation, atisirene[2] (I), hibaene[3] (II), kaurene[4] (III), and trachylobane[5] (IV) have been isolated from natural sources, lending support to the idea. Furthermore, the in vitro synthesis of hibaene from a pimaradiene precursor has been reported[6].

Investigations into the acid-catalyzed skeletal rearrangement of the diterpene hydrocarbons have been conducted under various conditions in an effort to interrelate the compounds via the postulated intermediate. Although hibaene (II) would not rearrange in hydrogen chloride solutions of light petroleum, diethyl ether, or ethyl acetate, it was found that hibaene would rearrange in acidic solutions of benzene, chloroform, or acetonitrile to form the kaurene skeleton (III)[7]. In hydrogen chloride-chloroform solutions, trachylobane (IV) formed the atisirene (I) and kaurene (III) skeletons[8] in a 24:1 ratio while in acetic acid-acetic anhydride-perchloric acid solution, hibaene (II) was obtained in addition to atisirene and kaurene[9]. It was found that kaurene rearranges in acidic chloroform to the extent of ca. four percent[8]. It was concluded that a common intermediate was not attained; however, the role of the solvent system seems to be a very important consideration in the rearrangement.

An extension of Wenkert's postulation to include precursors of the isopimarene type would lead to the formation of neoatisirene (V), isohibaene (VI), phyllocladene (VII), and isotrachylobane (VIII)[8,10]. Of this group, only the phyllocladene skeleton has been found in nature. However, the in vitro syntheses of isohibaene and isohibane from isopimaradiene precursors has been reported[11, 12] and the synthesis of

neoatisirene has been accomplished[10].

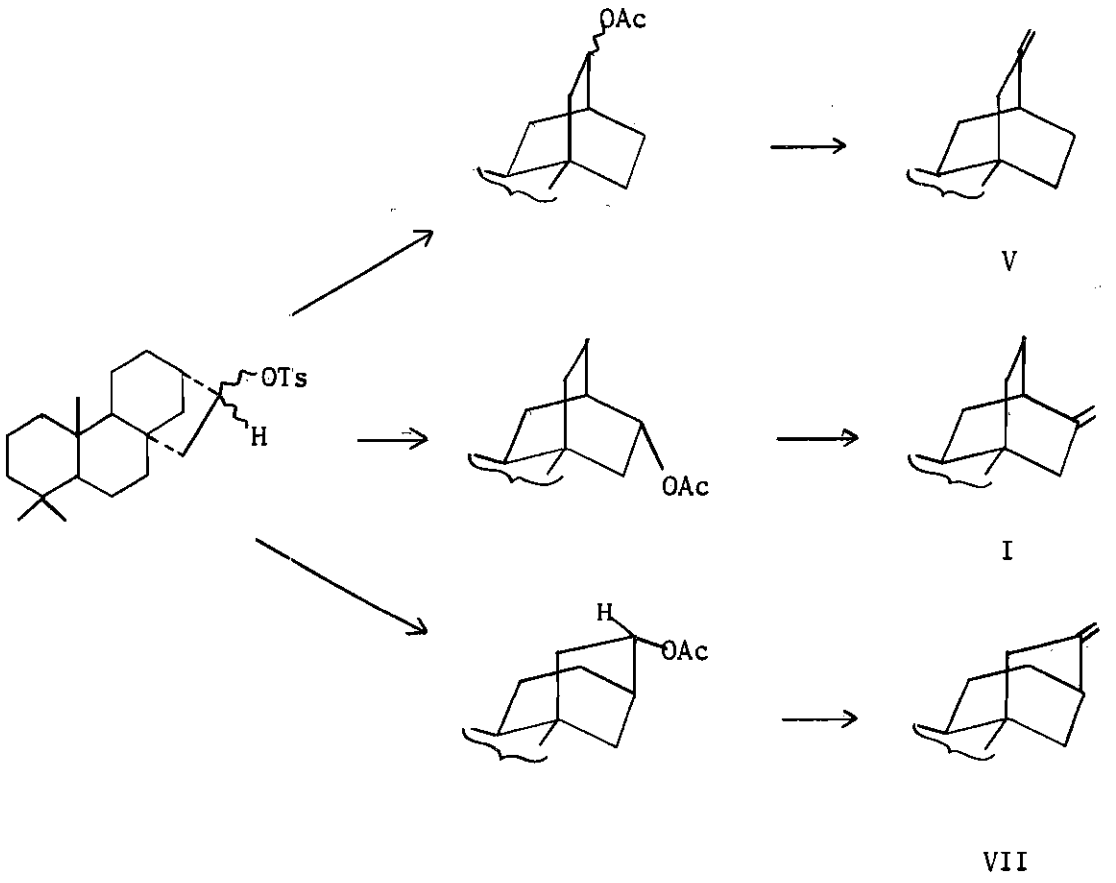
Scheme 2



V VI VII VIII

It is of interest to note that the acetolysis of the epimeric p-toluenesulfonates of 17-norkauran-16-ol has been reported to form six acetates, three of which have been converted, respectively, into phyllocladene (VII), atisirene (I), and neoatisirene (V)[13]. Thus, in the absence of the C-17 methyl grouping, rearrangement has interrelated skeletons arising from both postulated biogenetic pathways as shown in Scheme 3.

Scheme 3



Rationale to the Proposed Synthesis of Isotrachylobane

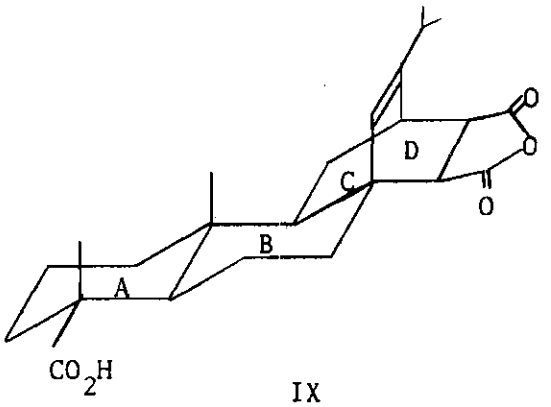
The original goal of this portion of the thesis was the synthesis of the enantiomer of trachylobane (IV), the parent hydrocarbon of a group of compounds isolated from the seed pods of Trachylobium verrucosum Oliv[5,9]. The importance of the hydrocarbon stems from the fact that its discovery in nature completes the set of naturally occurring compounds which may be derived by Wenkert's postulated biogenetic pathway.

Maleopimaric acid (IX), which is commercially available, was selected as the starting material. The stereochemistry of maleopimaric acid has been firmly established, as shown[14]. Thus, the A, B, and C rings are stereochemically correct for the synthesis. Transformation

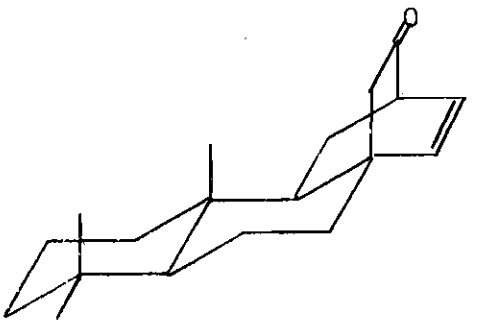
of IX into IV was seen to involve removal of the isopropyl group of ring C, removal of the anhydride moiety of ring D, and reduction of the acid function of ring A, which had been accomplished previously[14], followed by the placement of a methyl group at C-16 and finally, formation of the cyclopropane ring.

Before the synthesis was completed, Herz and co-workers[15] reported the synthesis of trachylobane via a different but similar route. Thus, the attention was diverted from the original goal.

It was anticipated that an intermediate in the originally proposed synthesis, X, could lead to isotrachylobane VIII, postulated as a



IX



X

possible product arising from an isopimaradiene precursor as mentioned previously. Placement of a methyl group at C-14 and generation of the cyclopropane ring would result in the formation of isotrachylobane. Thus, the purpose of this work was to study reactions which could lead to the synthesis of isotrachylobane.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points were determined on a Thomas-Hoover apparatus, and are uncorrected. Infrared spectra were recorded with Perkin-Elmer 237B and Beckman IR-5 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 the solvent specified. Chemical shifts are reported in ppm downfield from the internal standard, tetramethylsilane. The abbreviations s,d,t,q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; coupling constants are reported in cycles per second. Gas-liquid chromatography (glc) was performed using an F & M Biomedical Gas Chromatograph, Model 400, with glass column and a hydrogen flame detector. Mass spectra were recorded using a Varian M-66 mass spectrometer. Thin-layer chromatography (tlc) was performed using silica gel-coated microscope slides. Visualization was accomplished using iodine vapors. Ozone was produced using a Welsback Model T-408. Laboratory Ozonator which produced ca. 8 g of ozone per hour. Carbon and hydrogen microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Mülheim, West Germany.

CHAPTER III

EXPERIMENTAL

Formation of the Trimethyl Ester (XI) of Maleopimaric Acid

Phosphorous trichloride (225 ml) was added to maleopimaric acid (48 g, Eastman, practical grade). Following three hours at reflux temperature, the excess phosphorous trichloride was removed on a steam bath using a water aspirator. The residue was washed with anhydrous ether (150 ml) and concentrated to dryness under vacuum. Methanol (300 ml) was cautiously added to form a yellow solution which was stirred at reflux for 48 hours. The warm solution was vacuum filtered and allowed to cool to room temperature. Upon standing, crystals formed in the filtrate. Recrystallization from methanol gave the crystalline product XI (35.4 g) which was dried for 24 hours at 50°C under reduced pressure to give m.p. 100-103°C (lit.[16] m.p. 100-103°C) ν_{max}^{KBr} 1725 cm^{-1}.

Ozonolysis of Trimethyl Ester XI

Ozonolysis of XI for 48 hours

A stream of ozone (ca. five percent in oxygen) was passed through a solution of trimethyl ester XI (35.4 g) in glacial acetic acid (287 ml) at room temperature for 48 hours. After the addition of water (30 ml), the solution was stirred for three hours and then concentrated to a viscous gum by means of a rotary evaporator. The residue was dissolved in ether (350 ml) and extracted with portions of an ice-cold five percent sodium hydroxide solution until all the aqueous layer

remained colorless. After washing with distilled water (100 ml), the organic layer was dried over anhydrous magnesium sulfate. Concentration to dryness by rotary evaporator gave 13.5 g of non-acidic material.

Separation of Ketones XII and XIV

The non-acidic fraction of the ozonolysis mixture (13.5 g) was refluxed for one hour in a solution of methanol (140 ml), glacial acetic (4.1 g), and Girard's T reagent (5.4 g). The cooled solution was then poured into a solution of sodium bicarbonate (5.6 g) in water (560 ml). The slightly basic solution was extracted with ether until the aqueous layer was colorless. The ether extract was dried over anhydrous magnesium sulfate and concentrated to give non-crystalline non-ketonic material (4.6 g).

The aqueous solution was then acidified with 6 N hydrochloric acid (28 ml). After standing for 2 hours, a precipitate formed (5.33 g) which was removed by filtration. Recrystallization of the precipitate from methanol gave XII with m.p. 165-167°C (lit[17] 168-169°C); ν_{max}^{KBr} 1725, 1665 cm^{-1}.

The aqueous filtrate which remained turned red upon standing open to the atmosphere at pH 1. Chloroform extraction gave a red organic layer which was washed with water and dried over anhydrous magnesium sulfate. The chloroform was removed to give 2.9 g of non-crystalline ketone. Crystallization from methanol gave XIV with m.p. 193-194°C (lit[17] 193-194°C); ν_{max}^{KBr} 1745, 1740, 1725 cm^{-1}.

Ozonolysis of XI for 12 hours

A stream of ozone (ca. five percent in oxygen) was passed through a solution of trimethyl ester XI (30.0 g) in glacial acetic acid (230

ml) at room temperature for 12 hours. After the addition of water (15 ml), the solution was stirred for three hours and then concentrated to a viscous gum by rotary evaporator. The residue was dissolved in ether and extracted with an ice-cold five percent solution of sodium hydroxide until the aqueous solution remained colorless. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporator to give 28.1 g of neutral material. Separation of the ketonic products from the non-ketonic products with Girard's T reagent as described above gave 12.7 g of ketonic product.

Ozonolysis of XI for 24 hours

A stream of ozone was passed through a solution of trimethyl ester XI (30.0 g) in glacial acetic acid (230 ml) at room temperature for 24 hours. Following the procedure as described above, 22.3 g of neutral material was recovered. Separation of the ketonic portion from the non-ketonic portion as described previously gave 14.2 g of ketonic material.

Re-ozonolysis of Non-ketonic Neutral Ozonolysis Fraction.

The non-ketone fraction (30.0 g), obtained from the Girard's T reagent separation of the 12 hours ozonolysis described above, was dissolved in glacial acetic acid (230 ml). Using the procedure given above, neutral material (27.9 g) was obtained which was separated as above to give 9.2 g of the ketone mixture.

Baeyer-Villiger Reaction on XII

A solution of trifluoroperacetic acid* was added dropwise over a 15 minute period to a stirred suspension of dry, finely ground disodium hydrogen phosphate (31.0 g) and XII (14.8 g) in methylene chloride (45 ml). When addition was complete, the mixture was heated at reflux for one hour. After cooling the solution it was filtered by vacuum and the residual insoluble inorganic salts were washed with methylene chloride. The organic layer was washed with 10 percent sodium carbonate, dried over anhydrous sodium sulfate, and concentrated using a rotary evaporator to give the crude enol acetate XIII (9.2 g). ν_{max}^{KBr} 1725, 1670 cm^{-1}.

The crude material was stirred with methanol (200 ml), dioxane (200 ml), and 6 N hydrochloric acid (100 ml) for 10 hours at room temperature. Water (1200 ml) was then added and the resulting solid was collected by filtration. After one crystallization from methanol, ketone XIV (7.97 g) was recovered to give m.p. 193-194°C, (lit.[17] 191-193°C), identical in all respects with XIV as described above.

Alkaline Epimerization of XIV

To a solution of XIV (9.0 g) in methanol (40 ml) was added a 6.5 percent solution of sodium hydroxide (150 ml). After three hours at reflux, the solution was cooled, diluted with water (350 ml), then acidified with ice-cold 50 percent hydrochloric acid and extracted with

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*Prepared in situ by dropwise addition of 9.0 ml of trifluoroacetic anhydride to a suspension of 1.4 ml of 90 percent hydrogen peroxide in 15 ml of methylene chloride.

ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated *via* rotary evaporator to give a viscous gum. This material was treated with an excess of an ethereal solution of diazomethane to give 7.74 g of crude product; ν_{max}^{KBr} 1725 cm^{-1}.

The crude product (7.74 g) was heated at reflux in a solution of water (38 ml), sodium hydroxide (1.45 g), and methanol (20 ml). After 30 minutes at reflux, the solution was cooled and diluted with water (500 ml). The basic solution was extracted with ether. The aqueous solution was then acidified with 6 *N* hydrochloric acid and extracted with 500 ml of ether. The latter ether extract was washed with water, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporator. The crude residue was recrystallized from acetone-ethyl acetate to give XVI (7.34 g) of m.p. 260-268°C (lit.[14] 260-268°); ν_{max}^{KBr} 1725-1700 (broad).

Lead Tetraacetate Oxidative Bis-decarboxylation of XVI

The diacid ester ketone XVI (8.1 g) was dissolved in anhydrous pyridine (150 ml) at 70°C under a nitrogen atmosphere. Lead tetraacetate (8.1 g) was added to the stirred solution. After 10 minutes, when the initial reaction had subsided, an additional 4.1 g of lead tetraacetate was added and the solution was refluxed for 1.5 hours. The pyridine was removed *via* rotary evaporator leaving a viscous brown gum. The residue was acidified with a cold 6 *N* hydrochloric acid and extracted with portions of ether until the organic layer remained colorless. The organic layers were then combined and washed with water until the aqueous layer was neutral to pH paper. The organic layer was

then dried over magnesium sulfate and concentrated by rotary evaporator to give 7.8 g of brown residue which was crystallized from benzene-ether to give 1.7 g of XVII with m.p. 158-160°C (lit.[14] 166-168°C).

Preparation of Ketal XVIII

To a round-bottomed flask equipped with a Dean-Stark water separator, was added a mixture of XVII (9 g), benzene (75 ml), freshly distilled ethylene glycol (8 ml), and p-toluenesulfonic acid monohydrate (0.05 g). After 30 hours of reflux, the mixture was allowed to cool and then poured into an excess of five percent sodium carbonate. The organic layer was washed several times with water, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporator. Following trituration with petroleum ether (30-60°C), the gum (10 g) crystallized to give XVIII which had m.p. 94-95°C (lit.[18] 98-99°C); ν_{max}^{KBr} 1725 cm^{-1}.

Reduction of Ester XVIII

A solution of XVIII (3.5 g) in dry diethyl ether (40 ml) was added dropwise to a well stirred suspension of 0.5 g of lithium aluminum hydride in 50 ml of anhydrous diethyl ether. After addition was complete, the reaction mixture was heated at reflux for five hours. Ethyl acetate was added to the cooled solution, followed by slow addition of water. After washing with a saturated ammonium chloride solution, the organic layer was removed and the aqueous layer washed with five portions of ether. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, and concentrated to dryness by rotary evaporator to give known, non-crystalline XIX (3.2 gm); ν_{max}^{film} 3350, 1605 cm^{-1}.

Oxidation of XIX. Preparation of Aldehyde XX

A complex of chromic anhydride (10.7 g) in anhydrous pyridine (60 ml) was added to a solution of XIX (7.8 g) in anhydrous benzene (30 ml). The mixture was allowed to stand at room temperature for 12 hours and then poured into ice-water. The organic layer was separated and the aqueous layer was extracted several times with ether. The combined organic layer and ether extracts were washed several times with water, dried over anhydrous magnesium sulfate, and concentrated to give aldehyde XX (5.4 g). Recrystallization from ether-petroleum ether (30-60°C) gave m.p. 127-128°C; ν_{max}^{KBr} 2780, 2680, 1723, 1621 cm^{-1}; nmr ($CDCl_3$) δ: 1.07 (S, 3H), 1.12 (S, 3H), 3.88 (S, 4H), 6.04-6.10 (2H), 9.26 (5, 1H).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09

Found: C, 76.16; H, 9.08

The mass spectrum of this compound showed the parent peak at m/e 330 (<5%) and the base peak at m/e 244 (M -86).

Reduction of XX

A mixture of XX (5.4) gm., diethylene glycol (80 ml), 95 percent hydrazine (12 ml), and potassium hydroxide (10 g) was heated gently to dissolve the potassium hydroxide and then refluxed for four hours. Excess water and hydrazine were removed by vacuum distillation after which more 95 percent hydrazine (12 ml) was added. The solution was then heated at reflux for six hours. Upon cooling to room temperature, the reaction mixture was diluted with 200 ml water and extracted three times with 100 ml portions of ether. The combined organic layer was washed with water until the was was neutral to pH paper. After washing

with a saturated brine solution, the organic layer was dried over anhydrous sodium sulfate and concentrated by rotary evaporator to give 5.3 g of crude XXI. Recrystallization from methanol gave crystals of m.p. 99-100°C (lit.[18] 90-90.5°C); ν_{max}^{KBr} 1620, 1095 cm^{-1}.

Hydrolysis of Ketal XXI

Concentrated hydrochloric acid (1 ml) was added to a solution of XXI (5.2 gm) in 50 ml of methanol, 100 ml dioxane, and 15 ml of water. After standing at room temperature for one hour, the solution was diluted with ca. 200 ml of water followed by extraction with three 100 ml portions of ether. The combined ether extracts were washed successively with six 75 ml portions of water, one portion of saturated brine solution, and finally dried over anhydrous sodium sulfate. Following removal of the solvent by rotary evaporator, there remained a solid material which was recrystallized from methanol to give 2.90 gm of crystalline X, m.p. 118-119°C (lit.[19] 123-124°C); ν_{max}^{KBr} 1712, 1610, 705 cm^{-1}.

Reaction of Ketone X with Methyl Magnesium Bromide. Formation of Tertiary Alcohol XXII

To a stirred solution of X (3.6 gm) in 150 ml of anhydrous ether,* under a dry nitrogen atmosphere and cooled to solid dry ice, was slowly added 11 ml of 1.3 M methyl magnesium bromide in anhydrous ether.**

*Freshly distilled from lithium aluminum hydride under a nitrogen atmosphere.

**Gratefully obtained from Dr. F. Walker.

Following completion of the addition, the reaction vessel was repacked in dry ice and allowed to warm slowly to room temperature over a 12 hour period. A saturated aqueous ammonium chloride solution (ca. 50 ml) was added until hydrolysis was complete. The mixture was then washed with two portions of water, dried over anhydrous sodium sulfate, and concentrated by rotary evaporator. Following removal of the last traces of solvent in vacuo, there remained 4.0 g of crude solid material. Glc analysis of the crude material using a 6 ft by 1/8 in glass column containing 5 percent Carbowax 20 M on 90-100 mesh AS at a temperature of 220°C and a helium flow rate of 88 ml/min indicated three compounds with retention times and percentages of 2.0 min (1%), 9.3 min (89%), and 11.4 min (1%). The compound with a retention time of 11.4 min was identified as X by comparison of the retention time with a known sample, both separately and upon admixture. Thin-layer chromatography (tlc) of the crude solid using chloroform indicated three compounds, when visualized with iodine vapors, with R_f values of 0.12, 0.58, and 0.87, respectively. Known samples of XXII and X had R_f values of 0.58 and 0.87, respectively, under the same conditions.

The crude material was recrystallized from petroleum ether (30-60°C) to give 3.4 g of crystalline XXII, m.p. 121-122°C; ν_{max}^{KBr} 3330, 3040, 1615, 1370, 1125, 690 cm^{-1}; nmr ($CDCl_3$) δ 0.83 (s, 3H), 0.87 (s,3H), 1.13 (s,3H), 1.18 (s,3H), 1.78 (s,1H, disappears upon addition of D_2O), 5.77-6.24 (complex signal, total area corresponds to 2H).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.28; H, 11.18

Found: C, 83.39; H, 11.39

Attempted Formation of the p-Nitrobenzoate of XXII

In a dry box which had a dry nitrogen atmosphere, a solution of 1.6 M n-butyl lithium (Foote) in hexane (1.25 ml) was added to a solution of XXII (0.580 g) in 200 ml of hexane. After the mixture was allowed to stir at room temperature for 30 minutes, a hexane solution of 0.370 g of p-nitrobenzoyl chloride was added. The reaction mixture was allowed to stand with periodic stirring as a yellow precipitate slowly formed. After five hours the reaction vessel was removed from the dry box, and the reaction material was vacuum filtered to give a clear solution and a yellow residue. The solvent was removed from the filtrate to give 0.5 g of solid crude material. Glc analysis, using 5 percent Carbowax 20 M under the same conditions given previously, gave retention times and percentages of 3.9 min (26%) and 9.7 min (73%). The compound with a retention time of 9.7 minutes was shown to be unreacted XXII.

The crude recovered material was resubjected to the reaction conditions. Following workup in exactly the same manner as above, the crude mixture gave the same glc analysis as above when the same glc conditions were used. The crude recovered material was resubjected to the reaction conditions a third time using 4 ml of 1.6 M n-butyl lithium and 0.370 g p-nitrobenzoyl chloride. Analysis of the crude recovered material using a 6 ft by 1/8 in glass column packed with 3 percent Ucon LB-550-X on 100/120 mesh Gas Chrom Q at 188°C and a helium flow rate of 88 ml/min gave retention times and percentages of 5.3 min (25%) and 23.3 min (75%). Under the same conditions a known sample of XXII has a retention time of 23.3 minutes. Investigation into the formation of the ester was discontinued.

Treatment of Tertiary Alcohol XXII with Lithium Aluminum Hydride and Aluminum Chloride (1:3)

Aluminum chloride (0.145 g; 1.12×10^{-3} mole)* was added to a 15 ml portion of di-n-butyl ether** under a nitrogen atmosphere. To the resulting mixture was added 0.014 g (0.36×10^{-3} mole) of lithium aluminum hydride*** followed by dropwise addition of a solution of XXII (0.100 g) in 5 ml of di-n-butyl ether. When addition was complete, the reaction mixture was heated at reflux for three hours. The reaction vessel was then cooled to ice-bath temperature and wet diethyl ether was added until the mixture separated into a clear solution and a flocculent precipitate. The clear solution was separated from the precipitate via vacuum filtration and the residue washed with three portions of diethyl ether. The combined filtrated was washed once with water and then dried over anhydrous magnesium sulfate. The solvent was removed via high vacuum distillation at room temperature with the collector trap in a dry ice-acetone mixture, leaving 0.09 g of a residual liquid.

Glc analysis of the liquid, using a 6 ft by 1/8 in glass column packed with 5 percent Carbowax 20 M on 100/120 mesh Gas Chrom Q at 200°C and a helium flow rate of 88 ml/min indicated a single produce with a retention time of 2.3 minutes. Upon standing, XXII solidified, m.p. 78-82°C; ν_{max}^{KBr} 2920, 2860, 1650, 1450, 690 cm^{-1}; nmr (CCl_4) δ:**** 0.87 (s,6H), 0.97 (s,3H), 1.11 (s,3H) 5.1-5.6 (complex signal, total area

*Fisher anhydrous, sublimed, technical grade.

**Freshly eluted through acid-wash alumina.

***Ventron, Metal Hydrides Division.

****$CHCl_3$ used as internal standard (δ 7.26) relative to TMS.

corresponds to 3H). The mass spectrum gave the parent ion at M^+ = 270 (Calc. for $C_{20}H_{30}$, M^+ = 270.)

Treatment of Tertiary Alcohol XXII with Lithium Aluminum Hydride and Aluminum Chloride (1:1)

Aluminum chloride (0.139 g; 1.08×10^{-3} mole) was added to a 15 ml portion of di-n-butyl ether under a nitrogen atmosphere. To the resulting mixture was added 0.041 g (1.08×10^{-3} mole) of lithium aluminum hydride followed by the addition of a solutionof XXII (0.100 g; 0.36×10^{-3} mole) in 10 ml of di-n-butyl ether. Following three hours at reflux temperature, cooling, and addition of wet ether, the clear solution was concentrated to give 0.091 g of nonvolatile liquid. Analysis of glc, using a 5 percent Carbowax column at 200°C under the conditions given above, showed peaks with retention times of 2.0, 2.2, 2.8, and 3.0 minutes, respectively. Using the same column at 140°C and a helium flow rate of 160 ml/min gave retention times and percentages of 5.7 min (16%), 6.7 min (20%), 8.3 min (22%) and 11.9 min (42%). Separation of the mixture (0.15 g) by preparative thin-layer chromatography on silica gel (1 mm) using hexane as a liquid phase indicated four bands, when visualized using a berberine hydrochloride-methanol spray (1.5% solution) and ultraviolet light, with R_f 0.68, 0.60, 0.48, and 0.28, respectively. Following removal and elution with diethyl ether, the band at R_f 0.60 gave 0.019 of crystalline XXIV, m.p. 65-69°C; ν_{max}^{KBr} 2930, 1640, 875 cm^{-1}; nmr (CCl_4) δ:* 0.85 (s,3H), 0.90 (s,3H), 0.93 (s,3H), 4.50 (broad, 1H), 4.72 (broad, 1H), 6.04 (broad, 2H). The mass spectrum gave the parent ion at M^+ = 270 (Calc. for $C_{20}H_{30}$, M^+ = 270). The pure sample of XXIV was found

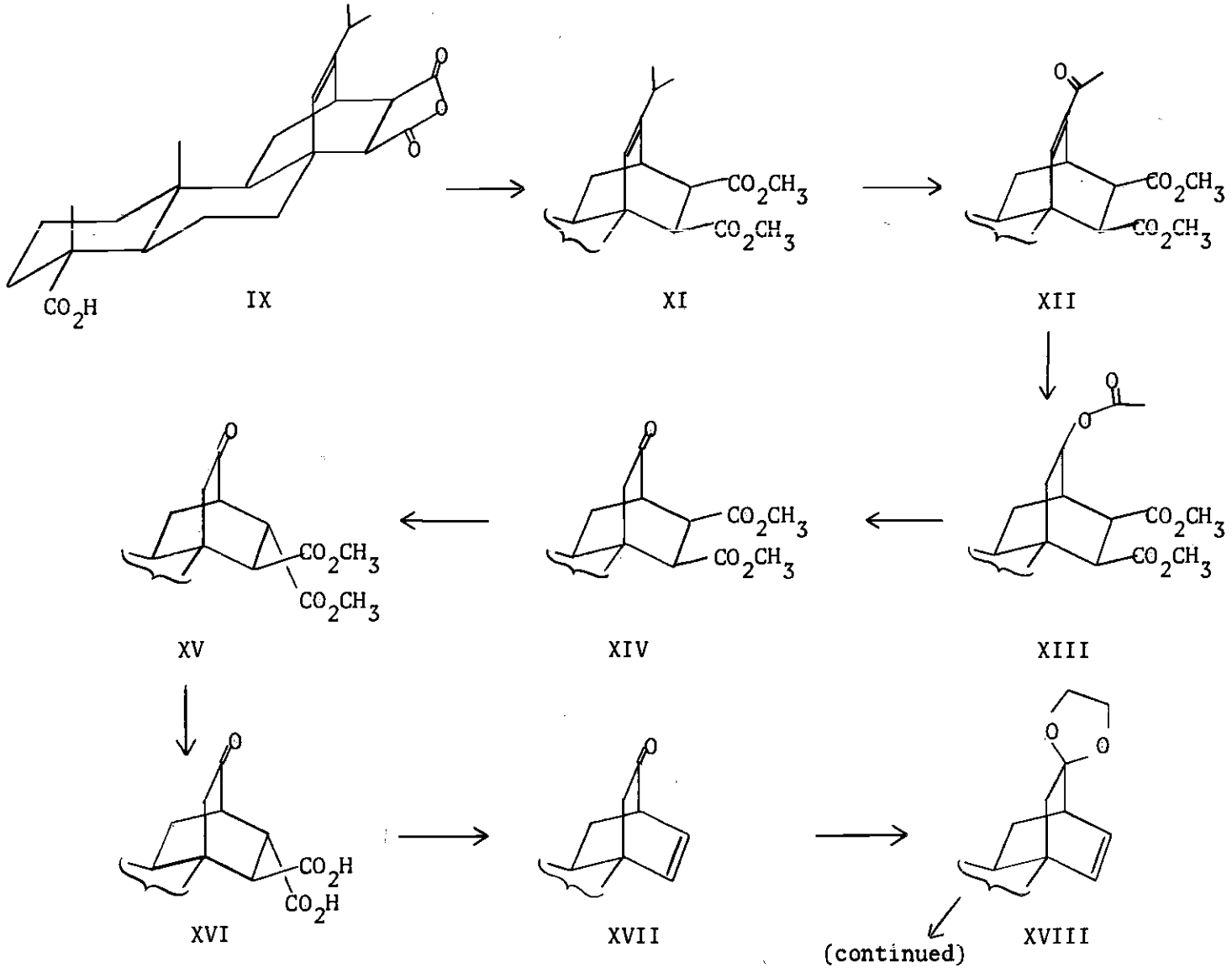
*Chloroform used as internal standard; (δ 7.26) relative to TMS.

to have a retention time of 11.9 minutes when subjected to the 5 percent Carbowax column at 140°C and a helium flow rate of 160 ml/min.

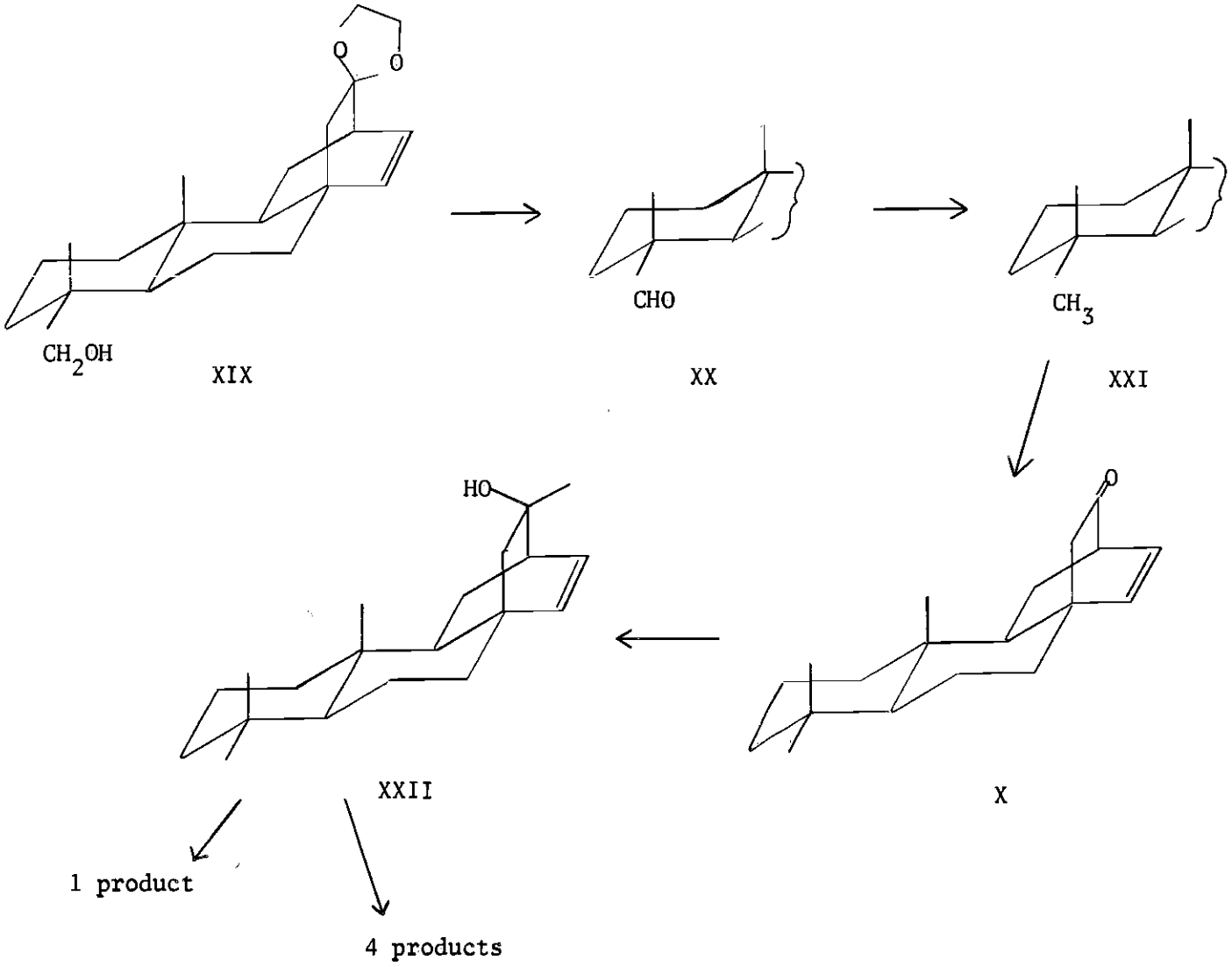
The above reaction was rerun using larger quantities. To aluminum chloride (0.695 g; 5.4×10^{-3} mole) in 75 ml of di-n-butyl ether was added solid lithium aluminum hydride (0.205 g; 5.4×10^{-3} mole) followed by addition of XXII (0.500 g; 1.8×10^{-3} mole) in 5 ml of di-n-butyl ether. Following the given procedure, removal of the solvent from the filtrate gave 0.5 g of a liquid. Glc analysis of the liquid, using a 5 percent Carbowax 20 M column, as above at 155°C and a helium flow rate of 110 ml/min gave retention times and percentages of 4-5 min (1%), 6 min (58%), and 7.3 min (41%). The compound with a retention time of 7.3 min was identified as XXIV. Separation of 0.1 g of the mixture by preparative thin-layer chromatography on silica gel (1 mm), using hexane as the liquid phase and visualized with berberine hydrochloride-methanol and ultraviolet light as before, gave two distinct bands at R_f 0.60 and 0.54, respectively. Removal of the band with R_f 0.60, followed by elution with diethyl ether, gave 0.045 g of XXV which crystallized upon removal of the solvent by rotary evaporator, m.p. 59-60°C; ν_{max}^{KBr} 3030, 2930, 1650, 1600, 790 cm^{-1}; nmr (CCL_4) δ:* 0.61 (s,3H), 0.85 (s,3H), 0.93 (s,3H), 1.13 (d,J=1.5 cps,3H), 5.50 (s,1H), and 5.90-6.30 (m,2H). The mass spectrum gave the parent ion at $M^+ = 270$ (Calc. for $C_{20}H_{30}$, $M^+ = 270$). Glc analysis of pure XXV gave a retention time of 6 minutes using a 5 percent Carbowax 20 M column and conditions given above.

*$CHCl_3$ used as internal standard; (δ 7.26) relative to TMS.

Scheme 4



Scheme 4 (Continued)



CHAPTER IV

DISCUSSION OF RESULTS

As mentioned previously, the goal of this portion of the thesis was to study a sequence of reactions which could lead to the synthesis of isotrachylobane using maleopimaric acid as a starting material as shown in Scheme 4. The generation of intermediate X from maleopimaric acid was accomplished using procedures given in a series of publications[14,16,17,18].

The trimethyl ester of maleopimaric acid (XI) was formed using phosphorous trichloride and methanol[16]. Ozonolysis of XI in acetic acid resulted in an acidic portion and a neutral portion of reaction products[17]. From the neutral portion two ketones, XII and XIV were obtained using Girard's T reagent to achieve separation. It was found in the current investigation that when IX in glacial acetic acid was exposed to ozone for various periods of time, the amount of the neutral fraction obtained varied as did the amount of ketones formed as shown in Table 1. From Table 1, it may be seen that either 12 hours (with re-ozonolysis of the neutral non-ketonic material) or 24 hours exposure to ozone results in ca. 50 percent recovery of ketonic material. However, 48 hours exposure results in only ca. 15 percent ketonic material. Thus a period of longer than 24 hours appears to destroy the desired ketones.

Treatment of XII, using Bayer-Villiger conditions, enol acetate XIII which was hydrolyzed under acidic conditions to give ketone XIV[17].

Table 1. Ozonolysis[a] of XI for Various Periods of Time.

Time, hours	weight in grams		
	XI	Neutral fraction	ketones
12	30	28.1	12.7
12[b]	--	27.9	9.2
24	30	22.3	14.2
48	30	13.5	4.6

[a]In each case the stream of oxygen contained ca. 5 percent ozone and the solvent was 230 ml of glacial acetic acid at room temperature.

[b]Re-exposure to ozone of the neutral non-ketonic portion recovered from previous 12 hour ozonolyses.

Alkaline epimerization of XV, followed by treatment with diazomethane, resulted in a trimethyl ester which was selectively saponified, using two equivalents of base, to give XVI. Bis-decarboxylation of XVI with lead tetraacetate in pyridine resulted in keto-ester XVII. In order to protect the ketone function during the reduction of the A ring ester, the ketal of XVII was formed using ethylene glycol and p-toluenesulfonic acid[18]. Lithium aluminum hydride reduction of XVIII resulting in formation of ketal-alcohol XIX which was subsequently oxidized, using chromium trioxide in pyridine to form the aldehyde, XX.

Recrystallization of XX from ether-petroluem ether gave crystals which showed absorptions in the infrared for an aldehyde (2780, 2680, and 1723 cm^{-1}) and a double bond (1621 cm^{-1}). The nmr spectrum exhibited resonance signals δ 1.07 and δ 1.12 (tertiary methyl groups), δ 3.88 (the ethylene portions of the ketal), 6.04-6.10 (vinylic protons), and 9.26 (aldehyde). The mass spectrum of the compound showed the parent ion at $M^+ = 330$. The data is consistent with the structure XX[18] in Scheme 1.

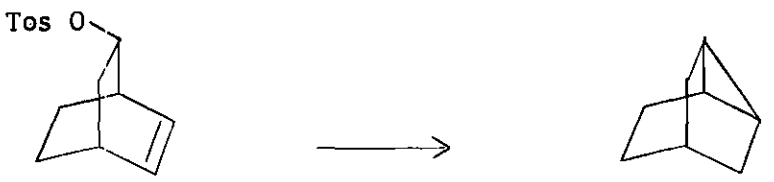
Reduction of XX, using the Huang-Minlon modification of the Wolff-Kishner method, resulted in the formation of XXI. Acid hydrolysis removed the ketal protecting group to give the unsaturated ketone, X, shown in Scheme 1, which had been prepared previously[10,18,19]

Treatment of X with methyl magnesium bromide at dry ice temperature led to the formation of essentially one product, as determined by glc and tlc. Recrystallization of the solid reaction product from petroleum ether gave crystalline XXII. The structure was assigned as follows: The infrared spectrum (Plate I) shows absorptions at 3330, 1370, and 1125 cm^{-1} as would be expected for a tertiary alcohol, and at 1615 cm^{-1} for the dou-

ble bond. The nmr spectrum (Plate II) showed two singlets at δ 0.83 and 0.85 for the two C-4 methyl groups, a singlet at δ 1.13 for the C-10 methyl group, which is deshielded due to the hydroxyl group[15], and a singlet at δ 1.18 for the C-14 tertiary methyl group. Moreover, the stereochemistry assigned was to be expected from steric arguments. Approach to C-14 from the side of ring A is inhibited by the proximity of the C-10 angular methyl group while approach from the side of the double bond presents little or no steric hindrance.

In a publication by McCrindle and co-workers[20], it was shown that tricyclo(3.2.1.$0^{2,7}$)octane (XXVI) can be formed by treating the bicyclic tosylate XXVII with lithium aluminum hydride (Scheme 5).

Scheme 5



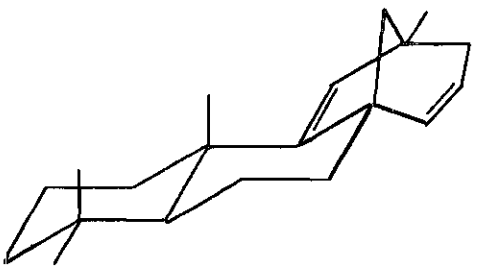
XXVI XXVII

Since XXII possessed a similar system, an attempt was made to form the tertiary p-nitrobenzoate which could then be treated with lithium aluminum hydride in the same manner to form the desired cyclopropane ring. Following the procedure given by Brown and co-workers[21] for the formation of p-nitrobenzoates of tertiary alcohols, XXII was treated with one equivalent of n-butyl lithium followed by the addition

of one equivalent of p-nitrobenzoyl chloride. The procedure was repeated several times, including the addition of excess reagents. The best result was the formation of 25 percent of a product which could not be separated from the starting material by recrystallization. Further investigation into the formation or separation of the product was terminated.

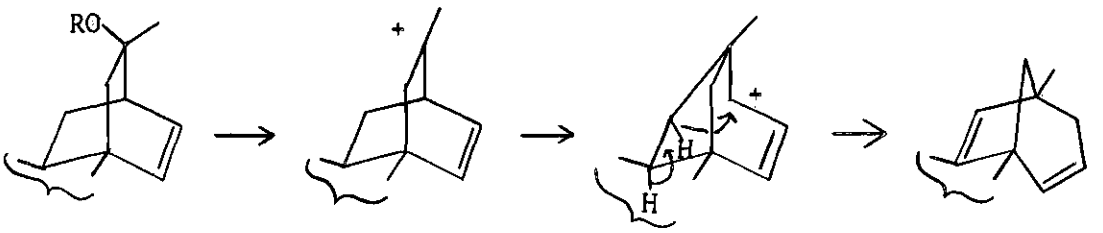
In light of the difficulty encountered in the attempted formation of the p-nitrobenzoate, a new route was sought to form the cyclopropane ring. It was thought that possibly a suitable complex could be formed using mixed hydride reduction which would lead to formation of the desired product.

With this in mind, an investigation of the mixed-hydride reduction of XXII was begun. Treatment of XXII with a 1:3 lithium aluminum hydride: aluminum chloride mixture led to the formation of a single product as determined by glc. Upon standing, the neat reaction product solidified to give crystalline XXIII. The infrared spectrum showed the absence of a hydroxyl band but the presence of unsaturation (1650 cm^{-1}). The nmr spectrum showed signals for two tertiary methyl groups at δ 0.87, one at δ 0.97 and one at δ 1.11. Three vinylic protons appeared in the range δ 5.1-5.6. The mass spectrum gave the parent ion at $M^+ = 270$. From the data, a tenative structure (which could arise from rearrangement of the bicyclic system as shown in Scheme 6) was assigned to XXIII.



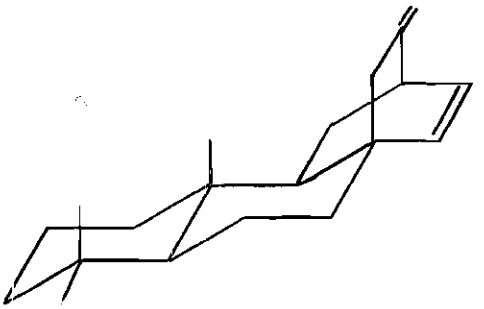
XXIII

Scheme 6



XXII XXIII

Treatment of XXII with a 1:1 lithium aluminum hydride:aluminum chloride mixture resulted in the formation of four products in the ratio of 16:20:22:42, as determined by glc. By mixed injection it was shown by glc that XXIII was not present in the mixture. The major component was isolated using preparative chromatography plates, and upon standing, XXIV crystallized. The infrared spectrum showed the absnece of a hydroxyl function but revealed the presence of unsaturation (1640, 875 cm^{-1}). The nmr spectrum showed three tertiary methyl groups at δ 0.85, δ 0.90, and δ 0.93, respectively; signals at δ 4.50 and δ 4.72 were due to two exomethylene protons. The mass spectrum showed the parent ion at M^+ = 270 (calculated for $C_{20}H_{30}$, M^+ = 270). These facts are consistent with the structure shown which arises from simple dehydration of XXII under the reaction conditions.



XXIV

When the preceding reaction was re-run on a five-times larger scale, two products were obtained in a 58:41 ratio as determined by glc. Mixed injection of a known sample revealed that XXIV was present in the reaction mixture as the minor component. Isolation of the major component using a preparative chromatography plate gave crystals of XXV. The infrared spectrum showed the absence of a hydroxyl group but the presence of unsaturation (1650, 1600 cm^{-1}). The nmr spectrum showed three tertiary methyl groups at δ 0.61, 0.85, and 0.93, respectively, and a doublet at δ 1.13 (J=1.5 cps) for a methyl on a double bond. Signals were also observed at δ 5.50 for a single vinylic proton and in the range of δ 5.90-6.30 for two vinylic protons. The signal at δ 0.61 was due to the C-10 angular methyl group which is shielded by the presence of the endocyclic Δ^{14}-double bond. The mass spectrum showed the parent ion at M^+ = 270 (Calcd. for $C_{20}H_{30}$, M^+ = 270) which is consistent with the structure assigned.

XXV

CHAPTER V

CONCLUSIONS

Optimum yields of ketonic products, XII and XIV, are obtained when maleopimaric acid ester (XI) is exposed to ozone for periods of less than 24 hours.

Mixed hydride treatment of the unsaturated tertiary alcohol XXII leads to rearrangement of the bicyclic system when a 1:3 lithium aluminum hydride:aluminum chloride mixture was employed.

Mixed hydride treatment of the unsaturated tertiary alcohol XXII leads to dehydration when a 1:1 lithium aluminum hydride:aluminum chloride mixture was employed.

CHAPTER VI

INTRODUCTION

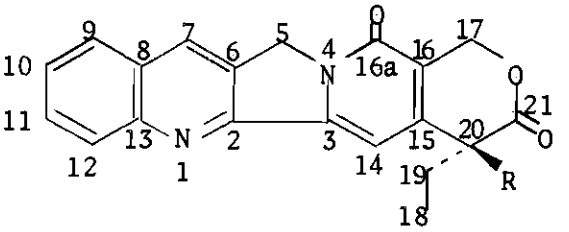
Camptothecin

Camptothecin (XXVIII) was isolated in 1966[22-25] from the stem wood of Camptotheca acuminata, Decaisne (Nyssaceae), a rare plant native to mainland China. Due to preliminary activity in Carcinoma 755, further testing was conducted which revealed that camptothecin was effective against lymphoid leukemia L-1210 in mice, giving life prolongation as high as 100 percent on a daily dose of 0.25 to 1.0 mg/kg[26]. Concentrations as low as 1.25 mg/kg gave significant inhibition of growth against Walker 256 (intramuscular) tumors in rats and moderate cytotoxicity was shown against KB cell culture, ED_{50} = 0.07 µg/ml. It was also found that the sodium salt of camptothecin has the same order of antileukemic activity as camptothecin[23].

Isolation and Structure of Camptothecin

The dried stem wood of Camptotheca acuminata was continuously extracted with a hot hexane-heptane solution followed by continuous extraction with hot 95 percent ethanol[22]. The concentrated ethanol extract was partitioned between chloroform and water. The methanol-insoluble portion of the chloroform extract was chromatographed on a silica gel column to give camptothecin which was recrystallized from methanol-acetonitrile to give pale yellow needles having a melting point of 264-267°C with decomposition. The molecular weight was determined

by mass spectrometer to be 348.1117 with a molecular formula of $C_{20}H_{16}N_2O_4$. The infrared spectrum showed absorptions at 3440 (hydroxyl), 1760-1745 (lactone), 1660 (lactam), and 1610, 1585 cm^{-1} (aromatic). Ultraviolet absorptions were observed at 220 mμ (ε 37,320), 254 mμ (29,230), 290 mμ (4,980), and 370 mμ (ε 19,900).



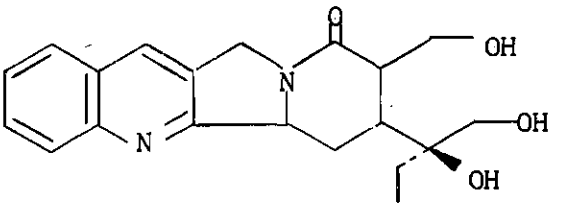
XXVIII R = OH

XXIX R = $OCOCH_3$

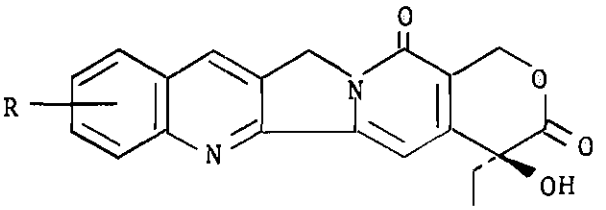
XXX R = Cl

XXXII R = $OCOCH_2I$

XXXIII R = $OCOCH_2Cl$



XXXI



XXXIV R = OH

XXXV R = OCH_3

The fact that the molecule possessed at least one asymmetric center was shown by the molecular rotation, $[\alpha]_D^{25}$ + 31.3° ($CHCL_3$ - MeOH, 8:2). The nmr spectrum of the compound in dimethyl sulfoxide-d_6 showed signals at δ 0.91 (3H, triplet) and δ 1.90 (2H, multiplet), indicating an ethyl side chain. Additional signals at δ 5.28 (2H) and δ 5.45 (2H) were assigned to a benzylamine- and a benzyether- type moiety, respectively.

It was found that camptothecin does not form stable salts with acids but prolonged treatment with acetic anhydride-pyridine at 25°C gives the acetate, XXIX (M^+ = 390.1217, $C_{22}H_{18}N_2O_5$, m.p. 271-274°C). The infrared spectrum gave absorption at 1770-1750 cm^{-1} (acetate and lactone) and the ultraviolet spectrum showed absorptions at 220 mμ (ε39,010), 254 (28,740), 290 (6160) and 360-370 (22,000). When treated with thionyl chloride and pyridine in benzene, camptothecin formed chlorocamptothecin (XXX), m.p. 248-250°C.

Exhaustive hydrogenation of camptothecin in acetic acid with Adams catalyst gave the dodecahydro derivative XXXI ($C_{20}H_{28}N_2O_4$, M^+ = 360). The infrared spectrum showed absorptions at 3460 and 3250 cm^{-1} (hydroxyls) and 1650 cm^{-1} (lactam). The nmr spectrum showed resonance signals at δ 5.25 for two benzylamine protons and at δ 7.20 for one aromatic proton.

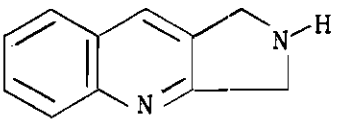
Conclusive proof of the structure was obtained from an X-ray analysis conducted on iodoacetate XXXII[22,23,27]. Camptothecin was treated with chloroacetic anhydride to form the chloroacetate XXXIII ($C_{22}H_{17}N_2O_5Cl$, m.p. 245-248°C, dec) which was then treated with sodium iodide in acetone to form XXXII ($C_{22}H_{17}N_2O_5I$, m.p. 238-240°C).

Additional compounds, XXXIV and XXXV, also possessing anti-tumor activity, have been isolated from Camptotheca acuminata[28].

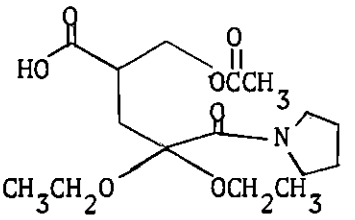
The numbering system given for camptothecin is based upon its probable biogenesis[29].

An approach to the Synthesis of Camptothecin

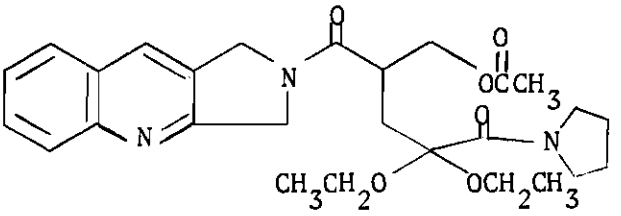
A synthetic approach by Wani, Kepler, and Wall[30], involved the condensation of the tricyclic compound, XXXVI, with the carboxylic acid, XXXVII, forming the amide linkage necessary to generate XXXVIII. Hydrolysis of the ketal in XXXVIII, followed by refluxing the ketone in triethylorthoformate and acetic anhydride was anticipated to give a key



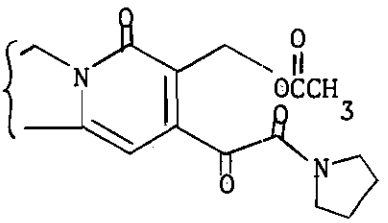
XXXVI



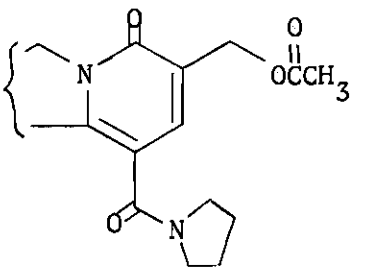
XXXVII



XXXVIII



XXXIX



XL

intermediate, XXXIX, necessary for the success of the synthesis; however, only XL was obtained. At this point, reinvestigation of the ring closure was begun.

Rationale to the Proposed Synthesis of Camptothecin

Due to the high level of leukemia and tumor inhibition shown by camptothecin and considering the difficulty of obtaining large quantities of plant material from mainland China, the interest in developing a synthetic sequence, capable of expension to a large scale, commercial process, hardly seems to need justification.

In the projected synthesis of camptothecin, as in any efficient and economical process, the intermediates should be readily obtainable in large quantities from commercially available starting materials. This qualification may be met by division of the synthesis into two parts, followed by condensation of the intermediates. In studying the molecule, it was determined that a natural division would separate the molecule into a nitrogen-containing portion and an oxygen-containing portion which could later be fused together to form the 3-14 and 4-16a bonds.

This section of the thesis deals with studies necessary for formation of a useful intermediate leading to the oxygen-containing portion.

CHAPTER VII

EXPERIMENTAL

Preparation of cis-1,2-Dibromocyclobutane-1,2-dicarboxylic Acid Dimethyl Ester, XLII

Following a published procedure[31], bromine (70 g) was added to a finely ground, ice-cooled mixture of trans-1,2-cyclobutanedicarboxylic acid, XLI, (10 g; Aldrich) and amorphous phosphorous (3 g). When addition was complete, the mixture was heated on a steam bath, causing great amounts of hydrogen bromide to be evolved; after four hours, the reaction vessel was cooled to ice-bath temperature and an additional 2.5 gm of amorphous phosphorous was added. Following the addition of another 70 g of bromine, the reaction vessel was again placed on the steam bath and allowed to heat for 15 hours and then allowed to cool to room temperature. The excess bromine was removed from the reaction vessel by blowing dry air through the mixture; the remaining material was then poured into excess methanol (800 ml). After the solution had cooled, the methanolic solution was concentrated by rotary evaporator to ca. 200 ml, some water was added, and the solution was extracted with ether. The ether solution was washed with water, a five percent sodium carbonate solution followed by a saturated brine solution, and finally dried over anhydrous magnesium sulfate. The recovered material, after removal of solvent, weighed 17.0 g and crystallized upon cooling to give XLII with m.p. 85-87°C (lit.[31] 88-89°C); ν_{max}^{KBr} 3030, 2990, 2950, 2850, 1740, 1310 cm^{-1}.

Preparation of Dimethyl Cyclobutene-1,2-dicarboxylate, XLIII

Potassium iodide (4 g) was added to a solution of XLII (1.9 g) in absolute ethanol (20 cc), then the mixture was heated at reflux for two hours using a steam bath and cooled to room temperature. Water (160 ml) was added to the black solution followed by extraction with five 50 ml portions of ether. The colored ether layer was washed with five percent sodium sulfite solution until both layers were colorless. The organic layer was then washed with fresh water followed by a saturated brine solution and finally dried over anhydrous magnesium sulfate. Following concentration by rotary evaporator, there remained a brown oil which could be crystallized using petroleum ether (30-60°C) to give 1 g of XLIII with m.p. 39-41°C (lit.[31] 44-46°C).

Attempted Thermal Rearrangement of XLIII

A solution of XLIII (0.300 g) in 15 ml of benzene was placed in a glass tube and sealed under a nitrogen atmosphere. After the sample had been heated at 170°C for 15 hours, the tube was opened and the contents were concentrated by the use of dry compressed air. Distillation of the residue resulted in 2 drops of viscous oil which distilled at an oil bath temperature of 175°C at 0.2 mm pressure; ν_{max}^{film} 2980, 2950, 2825, 1845, 1770, 1725, 1640 cm^{-1}. The nmr spectrum in deuterochloroform did not reveal exomethylene protons and the integration of the spectrum indicated that the sample was a mixture.

Formation of Dimethyl Itaconate, XLV

To a solution of commercial itaconic acid, XLIV (15 g; Eastman), in ether containing a small amount of methanol was added an ethereal

solution of diazomethane until the solution remained colored for ca. 5 seconds. The solution was then concentrated by rotary evaporator until a clear, colorless oil of low viscosity was all that remained. The last traces of solvent were removed under high vacuum and the remaining material was cooled to dry ice temperature. The solidified mass was allowed to warm to near room temperature and then filtered by vacuum to yield 10.3 g of white crystalline XLV with m.p. 33-34°C (lit.[32] 38°C); ν_{max}^{film} 2990, 2950, 2840, 1725, 1645 cm^{-1}. Glc of the product using a 6 ft by 1/8 in. glass column packed with 3 percent SE-30 on 100-110 mesh Gas Chrom Q at 110°C and a helium flow rate 88 ml/min gave one peak with a one minute retention time.

Attempted Formation of Fulgenic Acid Dimethyl Ester, XLVI

In the manner of Koelsh and Richter[32], a hot mixture of dimethyl itaconate, XLV (4.8 g; 0.03 mole), and paraformaldehyde (3g; 0.09 mole) was dropped, under a nitrogen atmosphere, into a flask containing dry sodium methoxide (formed by the action of metallic sodium (1.4 g) upon anhydrous methyl alcohol). The reaction mixture formed a black tarry mass which evolved a gas. After three hours of heating at steam bath temperature, a five percent sodium hydroxide solution was added. Following 12 hours at reflux, the basic solution was allowed to cool to room temperature and then extracted with chloroform and benzene to remove any neutral material. The remaining aqueous solution was made acidic using an ice-cold five percent hydrochloric acid solution followed by ether extraction with four portions of ether. The ether extracts were combined, washed with water, dried over anhydrous

sodium sulfate and finally concentrated to give a black oil (1 g). An nmr spectrum of this crude material gave no evidence of the desired material, XLVI (no exomethylene protons present).

Formation of sym-Tetraethyl Ethanetetracarboxylate, XLVII

Following a published procedure[33], an alcoholic solution of sodio-malonic ester (formed by the addition of 25 g of sodium to 190 g of Fisher purified ethyl malonate in 450 ml of ethyl alcohol) was formed in a five liter separatory funnel to which 1000 ml of anhydrous ether was added. The contents of the separatory funnel were treated with large portions of an ether solution of iodine (127 g of well-ground iodine in 600 ml of anhydrous ether) at such a rate that the temperature never rose above 30°C. After all of the iodine solution had been added, the reaction mixture was allowed to stand for two hours with periodic shaking. During this time, a large amount of sodium iodide precipitated out of the solution.

The contents of the separatory funnel were washed with 300 ml of water, followed by washing with 3 portions of 150 ml each of 20 percent sodium thiosulfate solution. The organic layer was then washed with a saturated brine solution, dried over anhydrous sodium sulfate and concentrated by rotary evaporator at 60°C to give ca. 450 ml of residual oil which formed cyrstals upon cooling in the refrigerator. The crystals were filtered under vacuum, washed with a 1:1 petroleum ether (30-60°): ether solution and then recrystallized from the same solvent system to give 133 g of white, crystalline XLVII with m.p. 73-75°C (lit.[33] 76°C); ν_{max}^{KBr} 2980, 2940, 1735, 1720 cm^{-1}.

Treatment of XLVII with Formaldehyde in the Presence of Base

To a mixture of XLVII (117 g; 0.37 mole), finely powdered paraformaldehyde(23 g; 0.77 mole), ethyl acetate (100 ml) and ethyl alcohol (40 ml) was added a catalytic amount of sodium ethoxide (0.03 mole formed by the action of metallic sodium (0.69 g) with 10 ml of absolute ethyl alcohol). The reaction mixture was maintained at 55°C for 3 hours and then allowed to cool to room temperature. The mixture was then acidified with 25 ml of 10 percent hydrochloric acid and mixed with three times its volume of ether. The mixture was then washed with two 30 ml portions of water, 30 ml of saturated brine solution, and finally dried over anhydrous sodium sulfate. Concentration by rotary evaporator gave an oil (crude XLVIII) weighing 116 g which was used in the next reaction without purification; ν_{max}^{film} 3640, 3550, 2980, 2945, 1775, 1750-1725 cm^{-1}; nmr (neat) δ 1.03 (9H,t, J = 6.5 cps), 3.6-4.8 (complex group of signals which corresponds to 11 H).

Formation of the Lactone of α-Hydroxymethyl-β-carboxyparaconic Acid, XLIX

To a solution of 25 percent hydrochloric acid (900 ml) was added 89 g of the crude XLVIII from the previous reaction. After heating at 60° ± 4°C for 55 hours, there remained a small amount of a green oil which was insoluble in the aqueous solution. Following decantation of the aqueous layer, the oil was discarded and the aqueous layer was concentrated by rotary evaporator at 60°C to give a viscous oil (ca. 65 g) which formed crystals upon standing. Removal of the crystals by vacuum filtration followed by washing with cold water (5 ml), methyl alcohol

(5 ml) and ethyl ether (20 ml) gave 7.1 g of XLIX with m.p. 182°-184°C (lit.[33] 178°C); ν_{max}^{KBr} 3480, 3010, 2630, 1780-1740 (broad); nmr (acetone-d_6) δ: 3.56 (doublet of doublets, J = 2.6, 5.8 cps, 1H), 4.02-4.13 (m, corresponds to 4H), 7.97 (S, 1H). The mother liquor was not investigated further (see Chapter VIII).

Formation of the Lactone of α-Hydroxymethylparaconic Acid, L

Crystals of XLIX (7 g) were heated using an oil bath at 185 ± 2°C under a nitrogen atmosphere for 15 minutes to give 5 g of crude material which solidified upon cooling. Recrystallization from an acetone-ether solution gave 3.7 g of L with m.p. 125-128° (lit.[33] 128°C; lit.[34] 138°C) ν_{max}^{KBr} 2980, 2930, 1775, 1760 cm^{-1}; nmr (acetone-d_6) δ: 3.65-3.90 (corresponds to 2H), 4.4-4.83 (corresponds to 4H). The mass spectrum gave a parent ion at M = 142 and the bas peak at 69 mass units. The ultraviolet spectrum gave absorption of 209 mμ (ε 84).

Attempted Oxidative Decarboxylation of XLIX Using Lead Tetraacetate

To a solution of XLIX (1.86 g) in 20 ml of anhydrous pyridine at 50°C, which had been degassed with dry nitrogen, was added lead tetraacetate (4.9 g). The mixture was heated to 70°C at which time gas evolution was noted. After 10 minutes at this temperature, the reaction mixture was removed from the heat source and the solvent was removed by rotary evaporator. To the thick residue was added an ice-cold 50 percent solution of nitric acid (20 ml). A white precipitate formed which would not melt below 360°C; it was discarded. The remaining acidic solution was neutralized with a 5 percent solution

of sodium carbonate until a pH of 6-7 was obtained as determined by pH paper. Removal of the water by rotary evaporator gave a residue which was washed with ethanol. The ethanol insoluble portion was discarded and the ethanol-soluble portion was subjected to glc analysis using a 6 foot by 1/8 in. glass column packed with 3 percent JXR on Gas Chrom Q at 135°C and a helium flow rate of 88 ml/min which gave peaks with retention times and percentages of 1.6 min (7%), 2.1 min (66%), 3 min (24%) and 3.5 min (3%). The compound with a retention time of 2.1 min corresponded to the dilactone, L, as determined by mixed injection.

Addition of ether to the ethanol-soluble portion resulted in the formation of a precipitate (0.96 g) which when redissolved in ethanol, gave the same glc analysis as reported above, using the same conditions. Further separation was not attempted.

Attempted Dehydrogenation of Dilactone L using 2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ)

To a solution of L (1.0 g) in 250 ml of dry dioxane was added solid DDQ (1.76 g). After a period of one hour at room temperature, the solution was heated to reflux. Glc analysis of the solution after 50 hours, using a 6 ft by 1/8 in. glass column packed with 3 percent JXR on Gas Chrom Q at 125° C and a helium flow rate of 88 ml/min, gave only one peak at a retention time of 2.8 minutes corresponding to L. An additional 1.8 g of DDQ was added and reflux temperature was maintained for a total of six days. A sample of the solution was analyzed by glc using a 6 ft by 1/8 in. glass column packed with 3 percent SE-30 on 100-120

mesh Gas Chrom Q at a temperature of 122°C and a helium flow rate of 88 ml/min. Only one peak appeared at a retention time of 4.4 minutes which corresponded to L as determined by mixed injection.

Attempted Dehydrogenation of Dilactone L with Palladium

An intimate mixture of L (0.142 g) and 10 percent palladium on carbon (0.250 g) under a nitrogen atmosphere was heated at 160 ± 4°C for one hour. Upon cooling, the solid material was washed with three 10 ml portions of ether. The combined ether extracts were subjected to glc analysis on both 3 percent SE-30 and 3 percent JXR columns, using the same condition given in the previous paragraph. In each analysis, only unreacted L was observed.

Attempted Dehydrogenation of Dilactone L with Palladium in p-Cymene

A well-ground mixture of L (0.142) and 10 percent palladium on carbon (0.250 g) in undistilled p-cymene (3 ml; Eastman) was heated at reflux under a nitrogen atmosphere for three hours. Glc analysis of the liquid portion of the misture, using a 3 percent SE-30 column at 122°C and the conditions given above, showed many peaks with a retention time of less than two minutes and were identified as being present in the freshly distilled solvent by mixed injection. The only additional peak present had a retention time of 4.4 minutes and was identified as unreacted L.

Epimerization of L with Aqueous Base

Following a published procedure[34], an aqueous solution of 2 N sodium hydroxide (42.5 ml) was added to L (6 g) followed by heating at

reflux for 30 minutes. Upon cooling in the refrigerator, crystals formed which were isolated by vacuum filtration to give a hydrated sodium salt[28].

After drying at 80°C under 20 mm vacuum for two hours, the crystals were suspended in ether while gaseous hydrogen chloride was bubbled through the suspension. The clear solution was decanted from the white precipitate and fresh ether was added to the solid. Again, gaseous hydrogen chloride was bubbled through the suspension. After repeating the process a third time no organic material was present on evaporation of the ether. The ether solutions were combined and concentrated by rotary evaporator to give solid LI weighing 2.3 g with m.p. 119-121°C (lit.[34] 122°); ν_{max}^{Nujol} 3480, 1765, 1720 cm^{-1}. The methyl ester, LII, formed by reaction LI with an ethereal solution of diazomethane, was not crystalline but gave the expected infrared spectrum ν_{max}^{film} 3450, 2950, 1765, 1725 cm^{-1}.

Attempted Oxidation of LI Using Chromic Acid

To a solution of LI (0.080 g) in acetone (2 ml) which was cooled to ice bath temperature was added 2 drops of Jones Reagent. After five minutes, during which time a green precipitate had formed, isopropyl alcohol was added to destroy the excess reagent. The solution was decanted from the precipitate and concentrated by rotary evaporator. The residue which remained was washed with several portions of ether which were combined and concentrated to give 0.060 g of unreacted LI as determined by the infrared spectrum and the melting point, 119-121°C.

The attempted oxidation was repeated using 0.060 g of LI in 2 ml

of acetone at room temperature. An excess of Jones reagent (4 drops) was added and the solution was allowed to stir at room temperature for one hour. Isopropyl alcohol was then added until excess reagent had been destroyed; the solvent was decanted from the precipitate and concentrated as above. The residue was washed with several portions of ether which were then combined and concentrated to give 0.050 g of an oily product which flowed freely at 40°C. Glc analysis of the oil using a 6 ft by 1/8 in. glass column packed with 3 percent SE-30 on 100/120 mesh Gas Chrom Q at 155° and a helium flow rate of 88 ml/min gave retention times and percentages of 1.1 min (72%), 2.1 min (2%) and 2.8, 3.0 and 3.4 min (unresolved peaks, total area corresponds to 26%). The peak with a retention time of 2.1 min corresponds to unreacted LI. The oil was soluble in ligroin and insoluble in ether. An attempt to form a 2.4-dinitrophenylhydrazone derivative failed and the oil was not further investigated.

Attempted Oxidation of LI Using Dimethyl Sulfoxide and N,N'-Dicyclohexylcarbodiimide

N,N-Dicyclohexylcarbodiimide (1.77 g, Eastman) and pyridinium phosphate* (0.26 g) were dissolved in a 1:1 dimethyl sulfoxide-benzene solution (8 ml).** After the resulting solution stood at room tempera-

*Prepared by adding 0.11 mole of anhydrous pyridine to 0.10 mole of 85 percent phosphoric acid (with cooling)[35a]. The resulting semi-solid was dried *in vacuo* at 60° for 4 days immediately prior to use.

**Prepared by drying a 1:1 solution of anhydrous benzene and dimethyl sulfoxide under a Dean-Stark trap for 4 days prior to use[35a].

ture for 30 minutes, LI (0.480 g) was added. The resulting solution changed through the colors of the spectrum, beginning with a light red and eventually turned black. After 15 minutes, the reaction vessel was placed in an ice bath. Isopropyl alcohol (19.4 ml) was added to the reaction mixture followed by warming to room temperature for four hours. The resulting solution was lyopholized at pressures below 150μ until a black semi-solid remained. This semi-solid was transferred to a continuous extractor and extracted with ether for three days. The only material obtained by concentration of the ether extract was pure N,N'-dicyclohexylurea (0.50 g) with m.p. 220-221 (lit.[35b] 222.5-223°C). The mass spectrum of N,N'-dicyclohexylurea gave M^+ = 224 (Calcd for $C_{15}H_{24}N_2O$, M^+ = 224).

Oxidation of LII With Dimethyl Sulfoxide and Acetic Anhydride

To a solution of ester LII (1.067 g, 88 percent pure) in 18.5 ml of dry dimethyl sulfoxide* was added 12 ml of acetic anhydride. The reaction mixture was allowed to stand at room temperature while the progress of the oxidation was followed by glc using a 4 ft by 1/8 in. glass column packed with 3.8 percent UC-W98 on 100-120 mesh Diatoport S at a temperature of 128°C and a helium flow rate of 88 ml/min. Under these conditions, the starting material gave two peaks with retention times and percentages of 2.1 min (12%) and 2.5 min (88%). After five hours, the solution had become blue and the glc analysis gave retention

*Obtained by removal of the benzene in vacuo from a solution of benzene-dimethyl sulfoxide which was dried as previously described.

times and percentages of 1.2 min (9%), 2.0 min (11%), 2.5 min (5%), 4.4 min (30%), 7.0 min (27%) and 10.9 min (18%). The peaks at 2.0 min and 2.5 min were identified as being present in the starting material. Following addition of isopropyl alcohol (15 ml), the reaction mixture was allowed to stand 12 hours. The solvents were then removed under a high vacuum on the steam bath. A check of the distillate by glc using the same conditions, revealed only the solvent peak. The residue (1.35 gm) contained solvent which could not be removed. A 0.35 g sample of the residue was separated by means of a 1 mm thick silica gel G (Mallinkcrodt) preparative chromatography plate using a solvent system of 90:10 benzene-acetone mixture which was allowed to develop for a distance of 20 cm. Visualization, was added by ultraviolet light, which indicated bands at R_f 0.65 and R_f 0.50 and a blue band between R_f 0.0 and R_f 0.35. The silica gel containing each band was removed separately, washed with ether and filtered. The solvent was then removed by rotary evaporator. From the band at R_f 0.65 was isolated 0.068 g of material which, when analyzed by glc using the conditions given above at a temperature of 125°C, gave one major peak with retention time of 13.4 minutes; ν_{max}^{film} 2950, 2910, 1780, 1735, 1430, 1175, 1075, 1010 cm^{-1}. No structure was assigned.

From the band at R_f 0.50 was isolated 0.157 g of material which was shown by glc, using the conditions given above at 125°C, to be a mixture of compounds with major peaks at 5.2 min and 8.4 min and minor peaks at 2.2, 2.5, 4.0 and 13.5 minutes, respectively; ν_{max}^{film} 2950, 2915, 1780, 1735, 1685 cm^{-1}. The nmr, which was taken on the neat oil, was

very complicated for the most part; however resonance signals were observed at δ 9.35 and 10.07, respectively, indicating possible aldehyde protons.

From the area of R_f 0.0-0.35 was isolated 0.086 g of material which was shown by glc to be a mixture of three compounds with retention times of 2.0 min, 5.2 min and 8.4 min, under the same conditions as given above 125°C.

Attempted Condensation of LIII with the Crude Aldehydic Reaction Material

From the preceding reaction, 0.450 g of the crude reaction oil was dissolved in one ml of acetic anhydride and to this solution was added 0.564 g of LIII*. The combined solution was heated at reflux for 14 hours and then allowed to cool to room temperature. Thin-layer chromatography of the reaction mixture on silica gel G (Mallinckrodt) for a distance of 14.5 cm using 90:10 benzene-acetone as the liquid phase, when visualized using Dragondorff's Reagent[36], revealed three spots at R_f 0.27, 0.45 and 0.55 respectively. No visualization was obtained by the use of a 2,4-dinitrophenylhydrazine spray followed by a 10% aqueous potassium hydroxide spray.

Following removal of the solvent in vacuo at 60°, a partial separation of 0.380 g of crude reaction material was obtained by the use of a preparative chromatography plate (1 mm) with silica gel G as the immobile phase and a 90:10 benzene-acetone solution as the mobile phase, developed for a distance of 16.5 centimeters. Visualiza-

*The author is indebted to Mr. J. B. Nabors for the sample of compound which was prepared by procedures similar to those given by G. Kempter and S. Hirschberg, Chem. Ber., 98, 419 (1965).

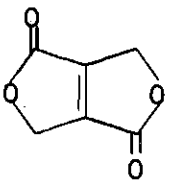
tion was obtained by spraying the plate with a 1.5 percent solution of methanolic berberine hydrochloride followed by viewing under ultraviolet light. In this manner bands were observed at R_f 0.91, 0.77, 0.61, 0.43 and 0.24, respectively. Removal of the silica gel in a band of R_f 0.85-0.70 followed by extraction with ether, filtration and finally removel of solvent gave 0.113 g of an oil which boiled at 85°C and 0.15 mm; ν^{CHCl_3} 2945, 2910, 2845, 1760 cm^{-1}; nmr ($CDCl_3$) and 1.38 (3H), 3.90 (3H) 4.92 (2H). Glc analysis of the oil, under the conditions given above, using a 3.8 percent UC-W98 column at 130°C, showed only one peak at 1.3 min. The mass spectrum gave M^+ = 156.0422 (Calcd. for $C_7H_8O_4$, M^+ = 156.0422). Structure LIV was tentatively assigned to this compound.

CHAPTER VIII

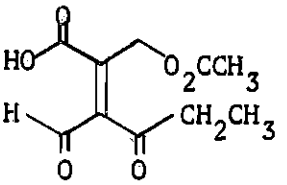
DISCUSSION OF RESULTS

As stated in Chapter I, the primary purpose of this work was to investigate means of synthesizing the oxygen-containing right half of camptothecin and suitable functionality for joining with the nitrogen-containing left half.

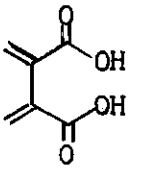
In an effort to generate LV, which, it was anticipated, can be transformed by suitable reactions into LVI, it was decided that a possible pathway might be the well-precedented iodolactonization[37] of a suitable di-β,γ-unsaturated acid; namely, fulgenic acid, an ester of which



LV



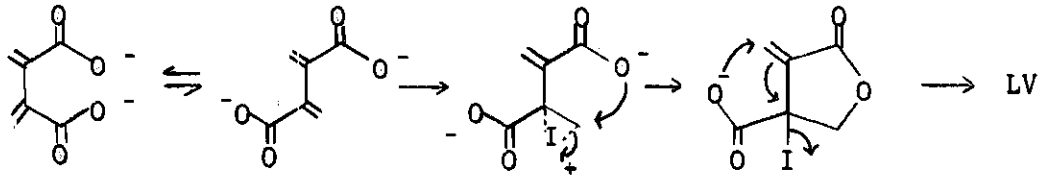
LVI



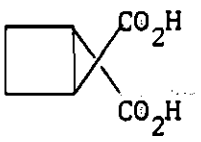
XLVI

is XLVI. Mechanistic considerations indicate that the iodolactonization should readily proceed by the method shown.

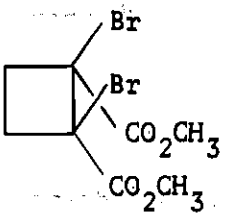
Scheme 6



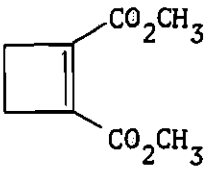
Dimethyl cyclobutene-1,2-dicarboxylate, reported by Perkin[31] in 1894, has been shown by Vogel[38] to give dimethyl fulgenate, trapped as the maleic anhydride adduct, in an 80 percent yield when heated at 160°C for 15 hours. Using the procedure reported by Perkin[31] for the formation of dimethyl cyclobutene-1,2-dicarboxylate (XLIII), commercially available trans-1,2-cyclobutane dicarboxylic acid (XLI) was treated with bromine in the presence of amorphous phosphorous. The resulting dibromide was reacted with methanol to give crystalline dimethyl cis-1,2-dibromocyclobutane-1,2-dicarboxylate (XLII), which exhibited the ester band at 1740 cm^{-1} in the infrared.



XLI



XLII

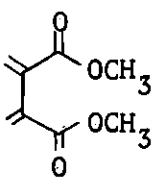


XLIII

Treatment of XLII with potassium iodide resulted in bis-halogenation to give dimethyl cyclobutene-1,2-dicarboxylate (XLIII), identified by its melting point and method of preparation.

In an attempt to form XLVI, the method of Vogel[38] was modified, omitting the trapping agent from the pyrolysis tube. The initial attempt at the pyrolysis resulted only in a black, granular solid, probably due to the presence of oxygen in the sealed tube. A repeated attempt, in

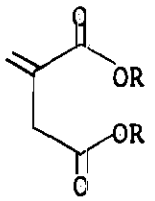
XLVI



which the atmosphere of the tube was displaced with dry nitrogen just prior to sealing, resulted in a viscous oil which gave a small amount of distillable product. The distillate, which was a mixture of products as evidenced by the nmr integration, gave nmr resonance signals for three different methoxyl groups in the region δ 3.6-3.9 with no indication of any exomethylene protons in the region δ 5.3-6.25, where normally expected. For this reason the reaction was not investigated further.

Compound XLVI, dimethyl fulgenate, is the dimethyl ester of the simplest member of a family of compounds. An extensive study of the substituted fulgides was conducted by Stobbe[39] and modifications of the original synthetic method for the preparation of fulgides have appeared[32,40]. It appeared feasible that dimethyl fulgenate might be generated by the addition of formaldehyde to easily accessible dimethyl itaconate, using a modification of the procedure of Kolsh and Richter[32].

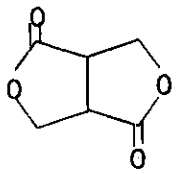
Dimethyl itaconate (XLV), formed by the addition of diazomethane to commercially available itaconic acid (XLIV), was treated with paraformaldehyde in the presence of sodium methoxide. A black tar resulted which was treated with a basic solution to hydrolyze the ester function followed by acidification. An nmr spectrum of the resulting black oil indicated that the double bond had migrated to the more substituted position, showing a resonance signal at δ 2.08 for a methyl group on a double bond and at δ 6.36 for a proton on a trisubstituted double bond. Investigation of this route was discontinued.



XLIV R = H

XLV R = CH_3

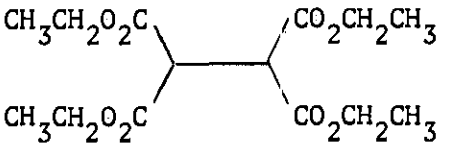
Due to the lack of success in the formation of fulgenic acid, another method was sought to form LV. It was found that the interesting compound, L, results as an acid-catalyzed degradation product of sesamolin and other closely related naturally occurring compounds[41]. It was anticipated that by the use of the proper dehydrogenating conditions, one could introduce a double bond and thus convert L into LV. Of further interest was the fact that the synthesis of L had been reported[34], in one instance, to occur in an overall yield of 64 percent from dimethyl malonate. Thus, it was determined to synthesize L and try to find conditions whereby LV could be generated.



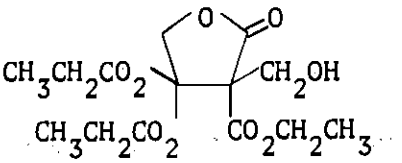
L

Following the procedure of Piskov[33], commercially available diethyl malonate was condensed to its dimer, sym-tetraethyl ethanetetracarboxylate (XLVII), by the formation of the sodium salt of diethyl malonate followed by treatment with iodine. Following the removal of the sodium

iodide which precipitated from the solution, a 71 percent yield of XLVII was obtained which exhibited two carbonyl bands in the infrared spectrum at 1735 and 1720 cm^{-1}, due to both symmetric and asymmetric stretching.



XLVII

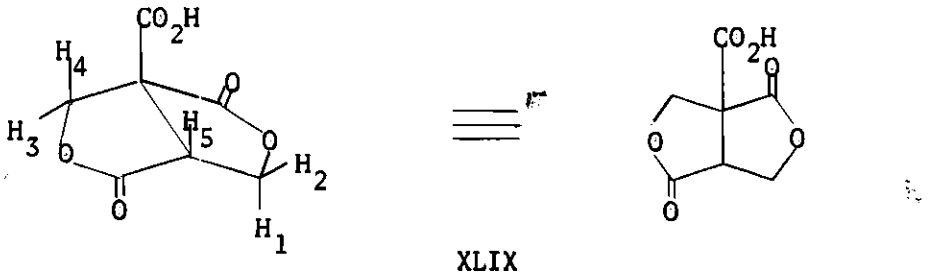


XLVIII

The addition of formaldehyde to XLVII in the presence of a catalytic amount of sodium ethoxide gave, after acidification, an oil which exhibited infrared bands at 3640 and 3550 cm^{-1}, due to hydroxyl absorptions, a sharp absorption at 1775 cm^{-1} (due to a γ-lactone) and a broad absorption between 1750 and 1725 cm^{-1} (due to ester functions). The nmr of the neat oil exhibited a triplet at δ 1.03 (J = 6.5 cps) which corresponded to 9 protons of the ethyl esters. A very complex group of signals in the range of δ 3.6-4.8 corresponded to eleven protons and was assigned, in general, to the remaining protons of the molecule. Since Piskov reported the yield of XLVIII as being 90 percent after distillation, and since the spectra corresponded to the expected product, the oil was used in the next step without further purification.

The oil mentioned above was heated in an acidic aqueous solution using a Thermowatch regulator which kept the temperature within a range of 56-64°C for 2 days. Vigorous stirring was applied to keep

the two-phase solution well mixed. At the end of the heating period, a small amount of a green oil remained, separated from the bulk of the solution as a heavier-than-water liquid. The aqueous portion was removed from the oil (which was discarded) and concentrated by rotary evaporator to give a viscous oil which partially crystallized upon standing. Separation of the crystals from the remaining oil, followed by a water wash (20 ml) gave the lactone of α-hydromethyl-β-carboxy-paraconic acid (11% by weight of viscous oil) which was identified as XLIX by its melting point (182-184°C; lit[33] 178°C) and infrared spectrum which showed a broad absorption at 3480 cm^{-1} for an acid and a broad, poorly resolved absorption in the range of 1780-1740 cm^{-1}.



XLIX

The nmr spectrum in acetone-d_6 exhibited a doublet or doublets at δ 3.56 due to H_5 which is split by both H_1 (J = 2.6 cps) and H_2 (J = 5.8 cps), a complex multiplet in the range δ 4.02-4.33 due to protons H_{1-4} and a singlet, which disappeared upon addition of deuterium oxide, at δ 7.97, due to the carboxylic acid proton.

Although the yield of XLIX was 11 percent, Piskov[33] reported a

yield of 84 percent for the same reaction using the same conditions. The reaction was repeated four times with ca. 10 percent yield of XLIX in each case. The mother liquor which remained after removal of the crystals was not immediately investigated but a partial investigation will be discussed later.

When heated above the melting point for 15 minutes, XLIX spontaneously decarboxylated, giving as the product the lactone of α-hydroxymethylparaconic acid (I) in a 69 percent yield. It was found that heating under a nitrogen atmosphere gave a slightly better yield with less coloration of the product. Recrystallization from an acetone-ether solution gave crystals which showed absorptions in the infrared spectrum at 1775 and 1760 cm^{-1}, due to symmetric and asymmetric carbonyl stretching. The nmr spectrum of the compound in acetone-d_6 exhibited a complex signal in the range of δ 3.65-3.90, assigned to the two bridge-head protons, and a complex signal in the range of δ 4.40-4.83 which was assigned to the four protons next to the oxygen. The complex spectral pattern is due to the rigidity of the conformation, creating complicated coupling patterns.

Since the oxidative decarboxylation of tertiary carboxylic acids using lead tetraacetate has been shown to introduce unsaturation into fused five-membered rings[42], it was thought that by decarboxylation of XLIX, the formation of LV could be achieved. Introduction of XLIX into the decarboxylating medium resulted in the evolution of a gas. When subjected to analysis by glc it was found that the major amount of the crude reaction mixture (66 percent) corresponded to the non-oxidative decarboxylation product, I, which previously had been obtained by

heating XLIX. The identification of the three other products was not pursued due to the fact that only one product (7%) had a shorter retention time (1.6 min) than L (2.1 min). It should be expected, considering polarity and, to a lesser extent, molecular weight, that LV would have a shorter retention time than L.

As previously stated, it was anticipated that L could be dehydrogenated, under suitable conditions, to yield LV. It was felt that the introduction of a double bond would be facilitated by the extended conjugation which would result. In this connection, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been used extensively in the dehydrogenation of carbonyl systems[43] moreover, saturated steroid δ-lactones have been converted to α,β-unsaturated lactones by prolonged exposure to DDQ in dioxane[44]. An attempt to dehydrogenate L with DDQ in a refluxing dioxane solution over a period of six days resulted in no reaction, glc analysis of the reaction solution showing only the presence of starting material.

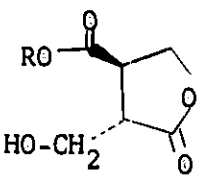
The lack of success in the dehydrogenation of L using DDQ can possibly be explained by the observation that in Δ^4-3-keto steroids, dehydrogenation occurs mainly by an ionic trans-diaxial loss of the 1α 2β-hydrogen atoms[45], although cases have been observed in which DDQ reacts to produce radicals[46]. An examination of a molecular model reveals that the molecule, L, must necessarily exist in the conformation shown. Thus the bridge-head hydrogens are cis and eclipsed with one another, a fact which should facilitate the removal of the hydrogens by a catalytic method.

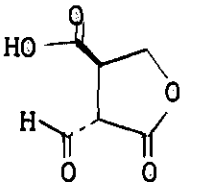
The dehydrogenation was thus attempted using 10 percent palladium on charcoal. In the initial attempt, solid catalyst and support was intimately mixed with solid L and then the mixture was heated under a nitrogen atmosphere. Upon extraction of the cooled solid mixture with

ether, it was determined by glc, using two different columns, that the only compound present was unreacted L. Due to the failure of the solid mixture to undergo dehydrogenation, it seemed advisable to use a solvent to obtain better mixing thus insuring better contact. A well-blended mixture of L and palladium on charcoal was refluxed in p-cymene for three hours. Analysis of the liquid portion by glc showed a great number of peaks whose retention times were less than four minutes. An analysis of the undistilled p-cymene also showed a large number of peaks whose retention times were less than four minutes. The reaction was repeated using freshly distilled p-cymene. Glc analysis after three hours showed three short-retention peaks and a peak corresponding to unreacted L. By mixed injection it was determined that the peaks with short-retention time were also present in the freshly distilled p-cymene. Thus it was determined that no reaction had occurred.

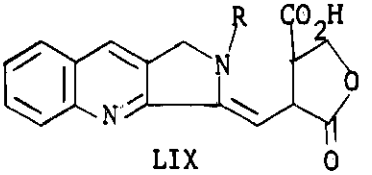
Following the unsuccessful attempts at dehydrogenation, it was decided that L could be epimerized, using the procedure of Michael and Ross[34], and anticipated that, by oxidation of the resulting trans alcohol-acid lactone, LI, aldehyde LVII could be obtained. It was hoped

LI R = H
LII R = CH_3





LVIII



LIX

R = $OCCH_3$

that LVIII could then be condensed with the nitrogen-containing portion, LIII, to form an intermediate, LIX, which could be converted into camptothecin. A condensation similar to this has been reported. (See Chapter VI.

Epimerization of L was obtained by refluxing in an aqueous basic solution. The crystals which formed upon cooling were previously identified by Michael and Ross[34] as being the octahydrate disodium salt of LI. After drying under vacuum, the salt was suspended in ether by means of rapid stirring and gaseous hydrogen chloride was bubbled through the suspension. Evaporation of the resulting ether solution resulted in crystals of LI which showed a broad infrared absorption around 3480 cm^{-1} for the alcohol and acid groups and carbonyl absorptions at 1765 (γ-lactone) and 1720 cm^{-1} (acid). It was found that acidification of the salt with concentrated hydrochloric acid solution resulted in a solution from which LI could not be extracted using ether, presumably due to the great solubility of LI in aqueous acid.

In an attempt to oxidize LI to LVII, Jones reagent was added to a cold, acetone solution of LI. Due to the precipitation of a green chromium salt within five minutes, the reaction was assumed to be complete. However, the material isolated from the solution was shown to be unreacted LI by virtue of the infrared spectrum and melting point. The procedure was repeated at room temperature for an hour. Again green chromium salts precipitated and were separated from the solution by decantation. Removal of the solvent gave an oil which, by glc analysis, contained five components. The major component (72%) had a retention

time of 1.1 minutes while the unreacted material was shown as only 2 percent of the total product with a retention time of 2.1 minutes. Three components appeared as three unresolved peaks at 2.8, 3.0 and 3.4 minutes retention time and an area of 26 percent of the total area of the products. In an attempt to determine the presence of an aldehyde, the oil was subjected to a 2,4-dinitrophenylhydrazine solution which gave no indication of the presence of an aldehyde. Investigation of the complex oil was terminated.

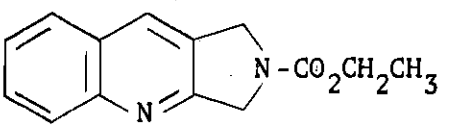
In 1963 Pfitzner and Moffatt[47] found that the addition of N,N'-dicyclohexylcarbodiimide to a solution containing pyridinium-phosphate, dimethyl sulfoxide and an alcohol resulted in selective oxidation of the alcohol to an aldehyde in high yield. McGonigal[48] used similar reaction conditions to oxidize an alcohol which resisted many of the classic oxidation methods. The oxidation of LI was attempted using the method reported by McGonigal in which freshly prepared pyridinium phosphate, N,N'-dicyclohexylcarbodiimide, and a 1:1 dimethyl sulfoxide-benzene mixture were combined. To this clear solution was added LI with the almost instantaneous formation of a red color. The color continued to become darker until, after a period of 15 minutes, the solution had become opaque and black. Following the addition of isopropyl alcohol to destroy the excess oxidant, the solution was concentrated by lyophilization until a black paste remained. In an attempt to obtain the product from the crude mixture, the viscous black material was distributed on the walls of a continuous extractor unit and continuously extracted with ether for three days. Removal of the solvent gave only pure N,N'-dicyclohexylurea which was identified by the melting point and the mass spectrum which gave M^+ =

224. Due to the fact that neither starting material nor oxidation product could be extracted, another method of oxidation was sought.

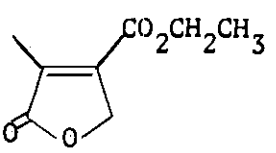
In the previous oxidation, it seemed possible that the presence of the pyridinium phosphate prevented the extraction of the reactant and/or the oxidation product. For this reason, a combination of acetic anhydride and dimethyl sulfoxide was selected as the oxidation medium[49]. The methyl ester, LII was introduced into the oxidation medium and the progress of the reaction was followed by glc analysis for a period of five hours using a 6 ft by 1/8 in glass column packed with 3 percent UC-W98 on 100-120 mesh Diatoport S at 128°C and a helium flow rate of 88 ml/min. Analysis of the starting reactant, methyl ester LII, showed two peaks with a retention time of 2.1 min (12%) and 2.5 min (88%). Immediately following the introduction of LII into the reaction solution, the glc indicated peaks with retention times of 1.2 min (14%), 2.1 min (9%), 2.6 min (43%), 4.5 min (30%) and 7.1 min (4%). The compounds with retention times of 1.2, 4.5 and 7.1 minutes were found to be present in a control solution of dimethyl sulfoxide-acetic anhydride. After a period of two hours, the reaction solution began to turn blue. Also, the glc of the crude solution indicated the formation of a new compound which had a retention time of 10.5 minutes. By comparison of the peak area of this new compound with the peak area at 2.6 minutes (due to LII) it was found that at 2, 3, 4, and 5 hours, the ratio of R_t2.6:R_t10.5 was 8:1, 7.7:1, 1:1 and 0.26:1, respectively. At the end of five hours, the oxidation was quenched by the addition of isopropyl alcohol. A sample of the residue which remained after removal of the solvent was partially separated on a thin-layer plate. Visualization with a spray-mist of 2,4-dinitrophenylhydrazine solution

revealed a diffuse spot which indicated the presence of an aldehyde. A partial separation of a portion of the residue by means of thin-layer chromatography resulted in three fractions, one of which had R_f 0.65 and was shown to be nearly pure by glc. The infrared spectrum of this fraction indicated the absence of a hydroxyl group but indicated that the γ-lactone (1780 cm^{-1}) and the ester (1735 cm^{-1}) were still present. An nmr spectrum of the impure oil obtained from the band at R_f 0.50 revealed several complex signals. However, signals were observed at δ 9.35 and δ 10.07 which indicated the possible presence of aldehyde protons.

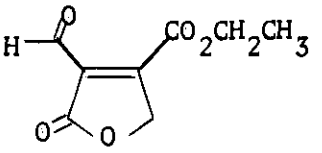
Due to the indicated presence of an aldehyde in the crude reaction material mentioned above, an attempt was made to condense the non-isolated aldehyde with LIII. The crude solution from the attempted condensation was separated by thin-layer chromatography and visualized using Dragondorff's Reagent which revealed three orange spots, indicative of the presence of alkaloids[36]. No visualization was obtained by spraying with a 2,4-dinitrophenylhydrazine solution, indicating the absence of an aldehyde. A partial separation of the crude mixture was obtained by the use of a preparative thin-layer chromatography plate. Separation of the plate into bands allowed the isolation of an oil which could be shown by glc give a single peak. The oil had a boiling point of 85°C at 0.15 mm and was assigned structure LIV due to the following observations. The mass spectrum gave a parent ion of M^+ = 156.0336 which is indicative of a molecular formula of $C_7H_8O_4$ (M = 156.0422). The infrared spectrum showed absorptions at 1760 cm^{-1}, indicating an α,β-unsaturated γ-lactone, and



LIII



LIV



LX

1725 cm^{-1}, indicating an α,β-unsaturated ester function. The nmr spectrum of the oil in chloroform-d revealed a triplet at δ 2.22 (3H,J= 2.5 cps) which was assigned to the methyl group on double bond with the splitting due to long range coupling with protons on the vinylic methylene group. A singlet at δ 3.90 (3H) was assigned to the methyl ester and a quartet at δ 4.92 (2H,Δν=4.5 cps, J=2.5 cps) was assigned to the vinylic methylene protons with the coupling due to long range splitting with the vinyl methyl group. The unsaturated lactone LIV undoubtedly arises by dehydration of LI during the attempted oxidation to LVIII.

Although the condensation was not attained, it was anticipated the oxidation of the vinyl methyl group of LIV to an aldehyde could yield LX, a desirable material which could then be condensed with LIII. However, an investigation[50] of the mother liquor from which XLIX was isolated, revealed that LIV was present in a 15-20 percent yield.

CHAPTER IX

CONCLUSIONS

Several systems were studied in an effort to produce a desirable intermediate for the formation of camptothecin.

The formation of the intermediate unsaturated lactone ester LIV was accomplished.

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15. Presented in part at the 19th Southeastern Regional Meeting of the American Chemical Society, November, 1967, Atlanta, Georgia. See also a) W. Herz, R. N. Mirrington, and H. Young, Tetrahedron Letters, 405 (1968); b) W. Herz, R. N. Mirrington, H. Young, and Y. Y. Lin, J. Org. Chem., 33, 4210 (1968).

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APPENDIX I

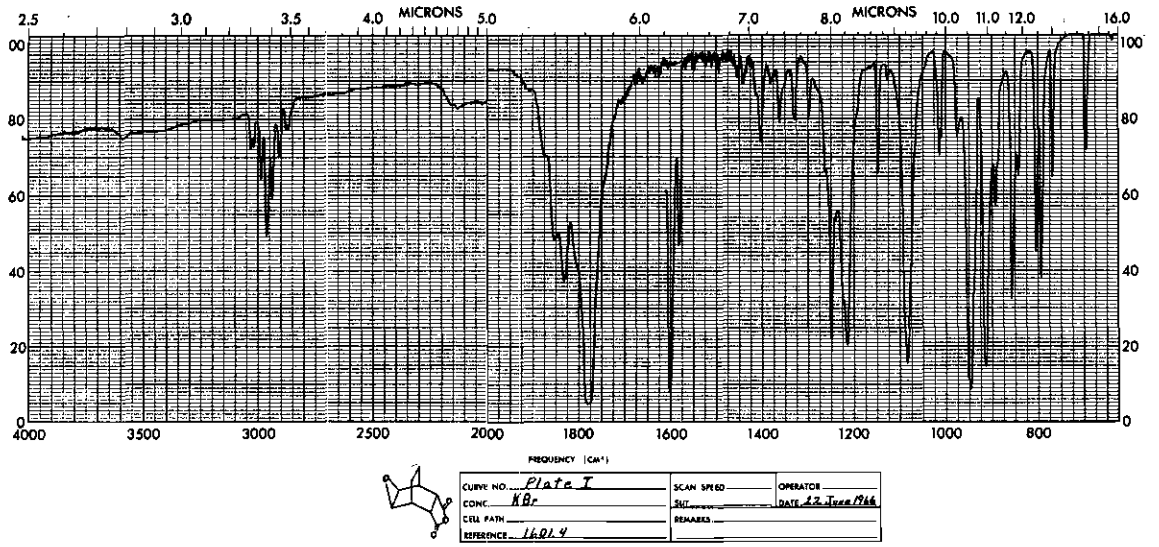

Plate I. Infrared Spectrum of 3-Oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic Anhydride (XX)

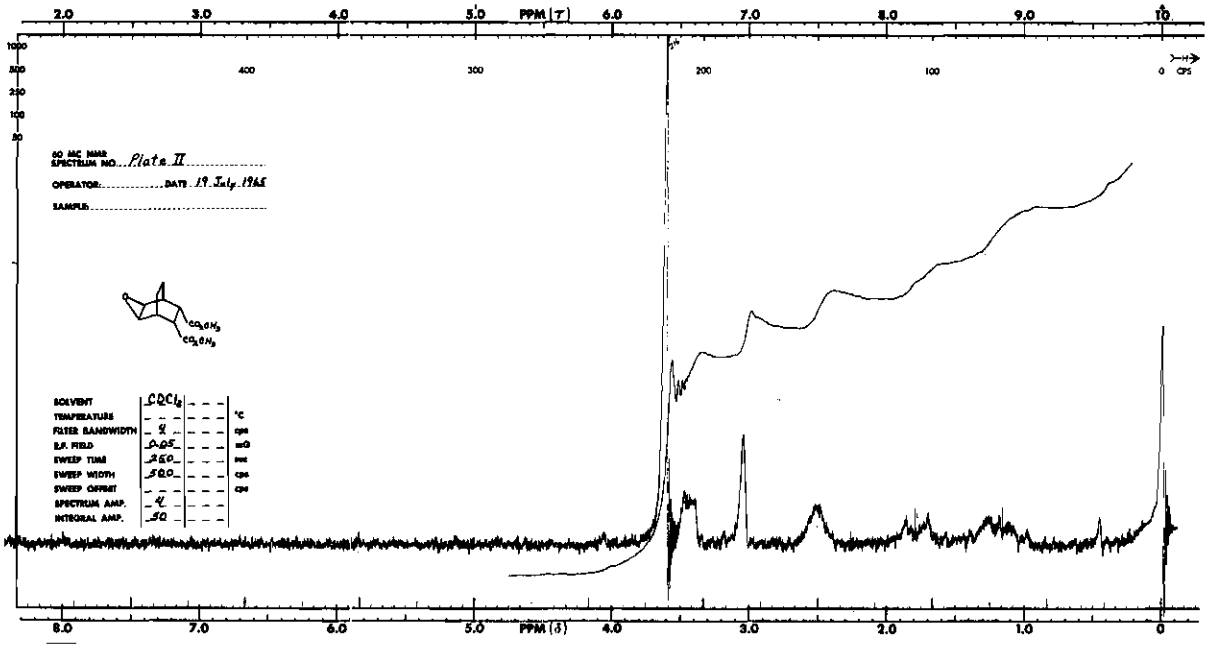

Plate II. Nmr Spectrum of 3-Oxatricyclo(3.2.2.$0^{2,4}$ exo)nonane-5,6-endo,cis-dicarboxylic Acid Dimethyl Ester (XXII)

APPENDIX I (Continued)

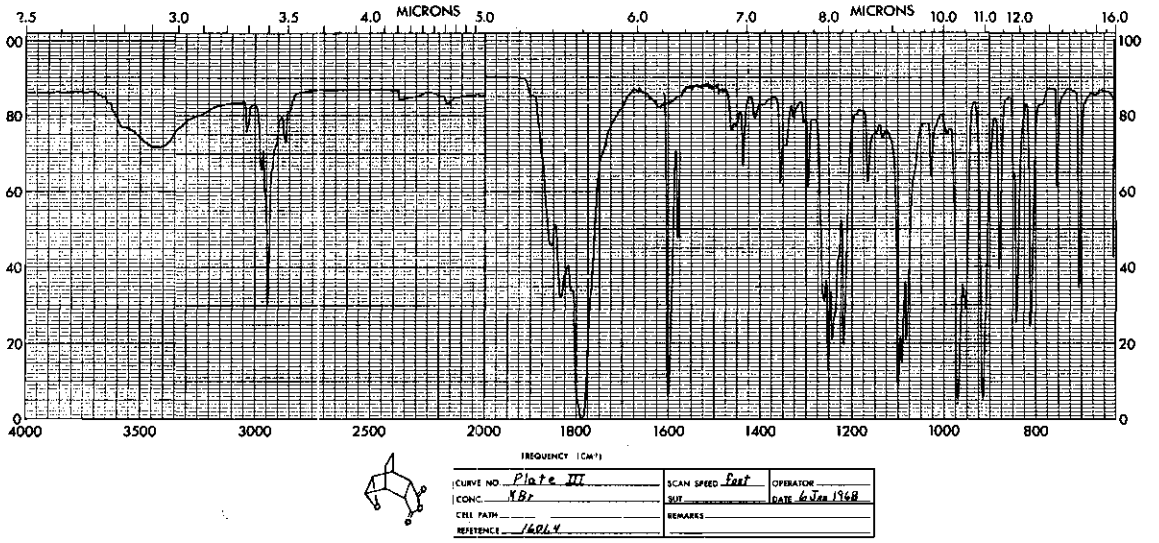

Plate III. Infrared Spectrum of 3-Oxatricyclo(3.2.2.0^{2,4} endo)nonane-5,6-endo,cis-dicarboxylic Anhydride (XXI)

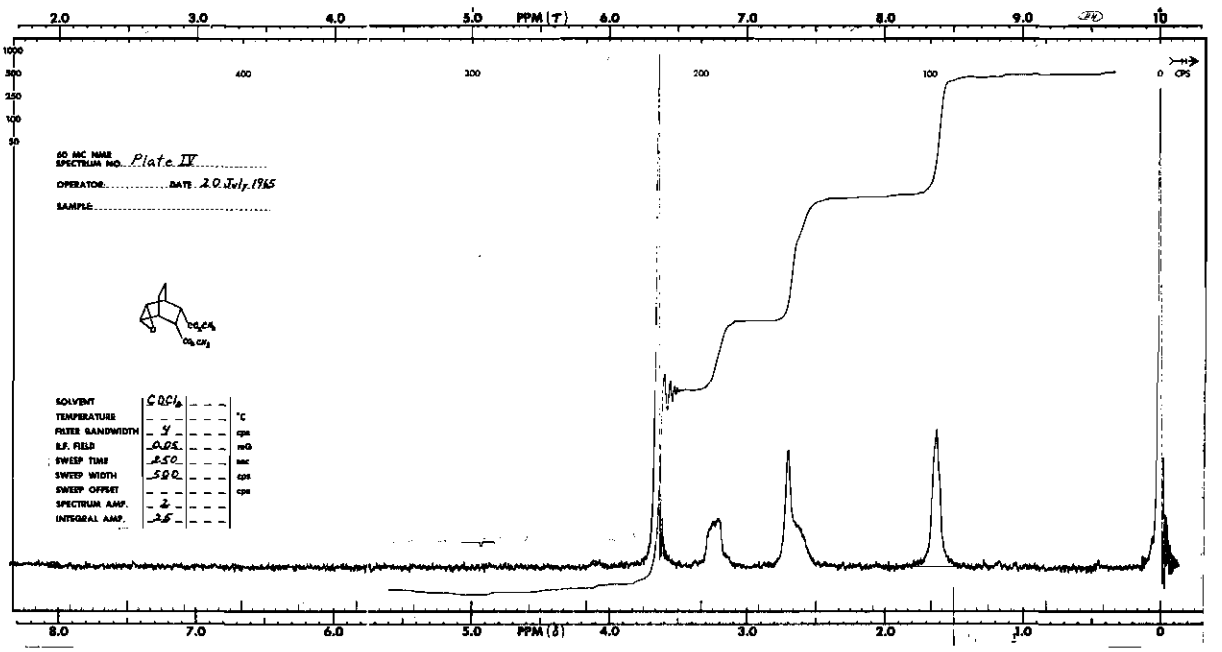

Plate IV. Nmr Spectrum of 3-Oxatricyclo(3.2.2.0^{2,4} endo)nonane-5,6-endo,cis-dicarboxylic Acid Dimethyl Ester (XXIII)

APPENDIX II

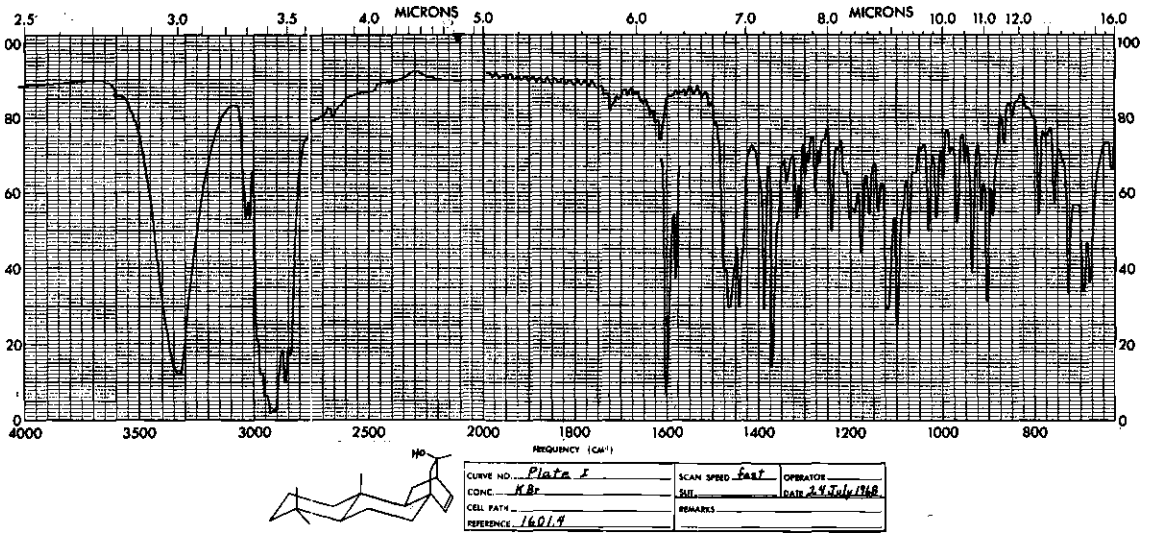

Plate I. Infrared Spectrum of Alcohol XXII

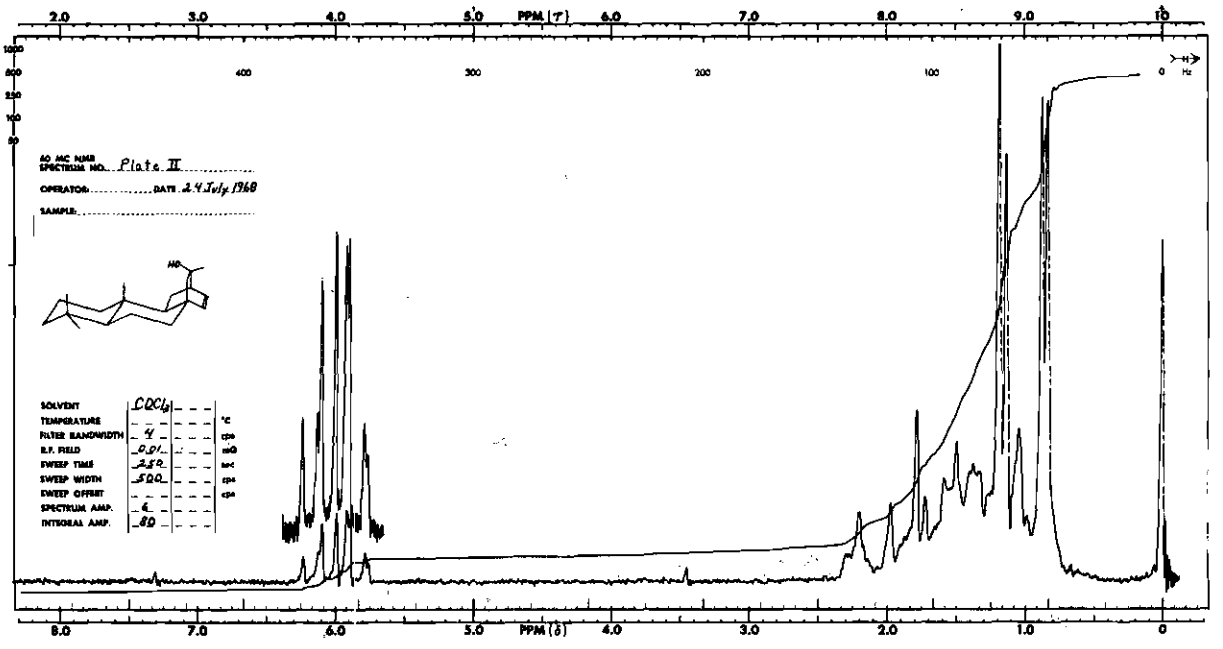

Plate II. Nmr Spectrum of Alcohol XXII

VITA

Sammy Karl Gabriel, son of Mr. and Mrs. Albert Gabriel, was born on August 9, 1942, near Hennessey, Oklahoma. He attended the Hennessey public schools, receiving his high school diploma in May, 1960. In September, 1960 he entered Oklahoma State University, Stillwater, Oklahoma and received the Bachelor of Science degree with a major in chemistry in June, 1964. Graduate work was begun at Oklahoma State University in September, 1964, under the direction of Dr. L. H. Zalkow.

In September, 1965 graduate work was continued at Georgia Institute of Technology under the direction of Dr. Zalkow.

In December 1968 he accepted a postdoctoral position with Dr. G. R. Pettit at Arizona State University, Tempe, Arizona.

He is married to the former Glenda Beth Gritz and has one daughter, Sami René Gabriel.