PART I -- APPROACHES TO THE SYNTHESIS OF ENDO TRIAZOLINES

PART II -- CHEMISTRY OF CAROTANE SESQUITERPENOIDS

A THESIS

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The Faculty of the Division of Graduate

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Marion Grove Clower, Jr.

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PART I -- APPROACHES TO THE SYNTHESIS OF ENDO TRIAZOLINES

PART II -- CHEMISTRY OF CAROTANE SESQUITERPENOIDS

Approved:

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J. C. Powers

Date approved by Chairman: 5/28/75

TO CHRIS AND CARRIE

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It is with pleasure that I express my appreciation to Dr. Leon H. Zalkow for his invaluable guidance and counsel during the course of this study and in the preparation of this dissertation. I wish also to thank Drs. D. S. Caine and J. C. Powers for serving as members of the committee.

To my wife, Becky, and children, Chris and Carrie, I wish to extend special gratitude for their patience and encouragement throughout this endeavor.

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GLOSSARY OF ABBREVIATIONS

bm	broad multiplet (NMR)
bs	broad singlet (NMR)
bp	boiling point
cc	cubic centimeter
cm^{-1}	wave numbers (IR)
Col	column
d	doublet (NMR)
g	gram
GC	gas chromatography
hr	hour
Hz	hertz (cycles per second)
IR	infrared
J	coupling constant (NMR)
l	liter
m	medium (IR)
m	multiplet (NMR)
m/e	mass to charge ratio
mg	milligram
ml	milliliter
min	minutes
mmol	millimoles
nm	nanometers
NMR	nuclear magnetic resonance

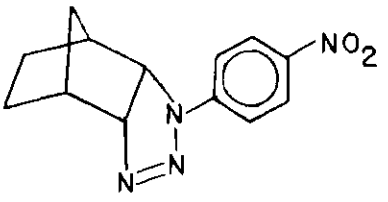
GLOSSARY OF ABBREVIATIONS (Continued)

ORD	optical rotatory dispersion
ppm	parts per million (NMR)
R_f	ratio of the distance a compound moves to the distance the solvent moves (TLC)
R_t	retention time (GC)
s	singlet (NMR)
s	strong (IR)
sec	second
sh	shoulder (IR)
TLC	thin layer chromatography
w	weak (IR)

SUMMARY

PART I

An investigation of the previously reported[7] synthetic sequence leading to endo triazolines (e.g. 10) has been carried out. The existing procedure for the preparation of the key intermediate in this sequence, chloroamine 13, has been modified, increasing the yield and purity of this compound.



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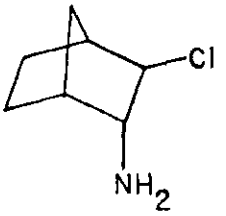

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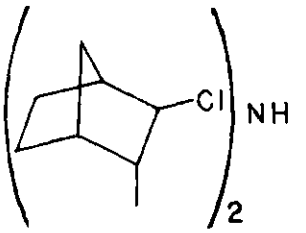

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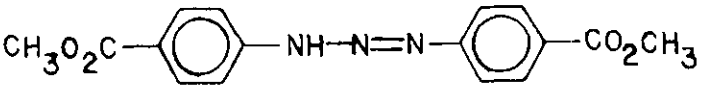
An alternate approach to chloroamine 13, reductive amination of 3-chloronorcamphor with sodium cyanoborohydride and ammonium acetate, was found to produce secondary amine 18 in addition to the desired chloroamine (13). The best separation of these amines achieved was unsuitable for large scale preparations.

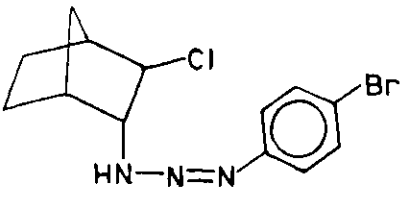
Coupling of chloroamine 13 with several diazonium salts was found in most cases to be an unsatisfactory method of preparing the required diazoamines. In the case of p-carbomethoxy compound, spectral evidence suggested the only solid isolated from this coupling reaction had struc-

ture 22.



22

Evidence suggesting successful formation of the desired diazoamine in the case of the p-bromo compound was obtained from spectral data of the product of the reaction of this diazoamine (25) with base. The ^{1}H-NMR spectrum of this product (26) was very similar to that obtained from the p-nitro endo triazoline (10) and supported the structure of the desired endo triazoline (26) as well as the structure of diazoamine 25.



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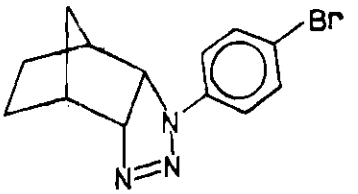

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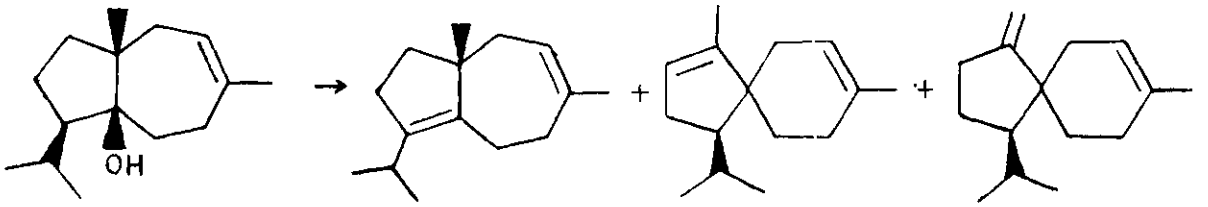
PART II

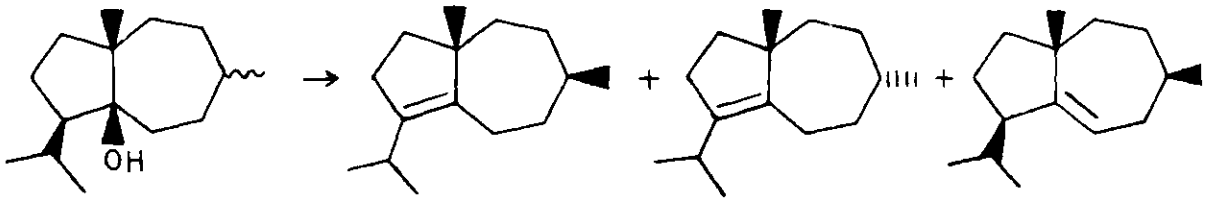
A reinvestigation of the dehydration of carotol (3) by thionyl chloride has shown the presence of two new products in addition to the previously reported daucene (5). These products have been isolated and identified as acoradienes 9 and 10. Acoradiene 9 is a known natural product found in the essential oil of Vetiveria zizanoides (Stapf).[27] Acoradiene 9 was shown to have the enantiomeric configuration to that reported,[27] by its formation by a stereochemically unambiguous means from

carotol (3), a compound of known absolute configuration.[7-9]



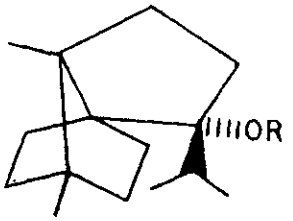
3 5 9 10

The importance of the double bond in the seven-membered ring in the dehydration of carotol (3) by thionyl chloride has been demonstrated by the absence of acorane products in the dehydration of dihydrocarotol (14).

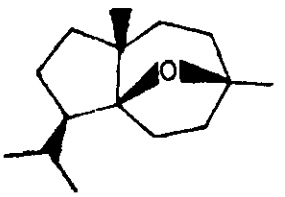


14 15 16 17

Upon prolonged treatment with formic acid, carotol (3) and daucene (5) gave the same mixture of five products. The structures of alcohol 25 and formate 26, which make up 80 percent of this mixture, were determined from spectral evidence, especially ^{13}C-NMR. Ether 24 was also isolated



25) R = H
26) R = COH



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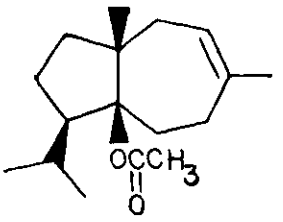
from the reaction mixture and identified by its spectral properties. A structure (22) was proposed for one of the two minor products of the reaction mixture. Preliminary studies of the composition of the mixture with time have shown the large amount of daucene (5) initially present rearranges rapidly to alcohol 25 and formate 26. Formate 26 was produced in larger quantities at first, but hydrolyzes with time to alcohol 25.

Carotol acetate (33) gave the same products as carotol (3) when treated with formic acid. Carotol acetate was found to rearrange on silica gel, whereas carotol does not. The major products of this rearrangement have been isolated and identified as daucene (5), acoradiene 9 and acoradiene 10.



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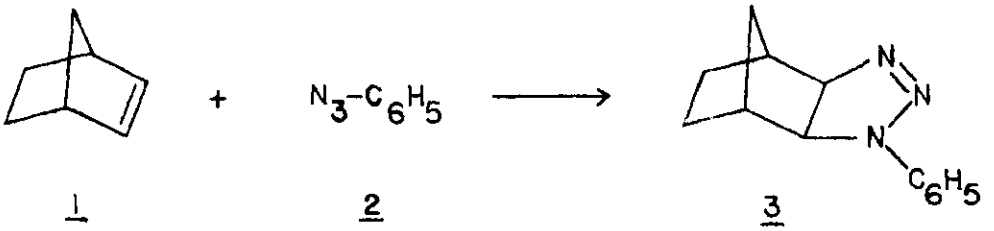
PART I

CHAPTER I

INTRODUCTION

Interest in Δ^2-1,2,3-triazolines (hereafter triazolines) arises from the fact that decomposition reactions (photolysis and thermolyses) lead in many cases to substituted aziridines. Aziridines are an interesting, useful group of compounds which have been studied extensively.[1] The biological properties and industrial uses of aziridines make any good synthetic pathway to this moiety important. Two of the most publicized uses of these heterocycles are as chemosterilants and anti-cancer drugs.[1]

The classical procedure for preparation of triazolines is the azide-olefin pathway, wherein an olefin (1), usually containing a strained double bond, and an aryl azide (2) undergo a 1,3-dipolar cycloaddition.[2]



1 2 3

Triazoline decomposition has been the subject of a recent excellent review.[2] The general results of thermal decomposition of triazolines are summarized in Figure 1. The usual course of thermolysis, Path A, involves expulsion of nitrogen; the remaining fragment is converted to aziridine and imine, as originally shown by Alder and Stein.[3] Cleavage

by Path B produces diazoalkane and imine and is a well established decomposition pathway in the reaction of arylsulfonyl azides with linear amines.[2,4]

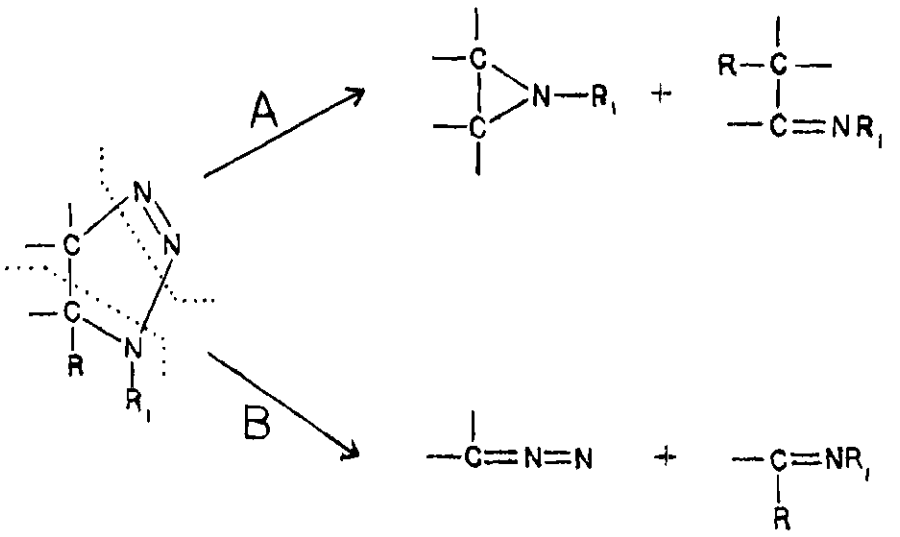
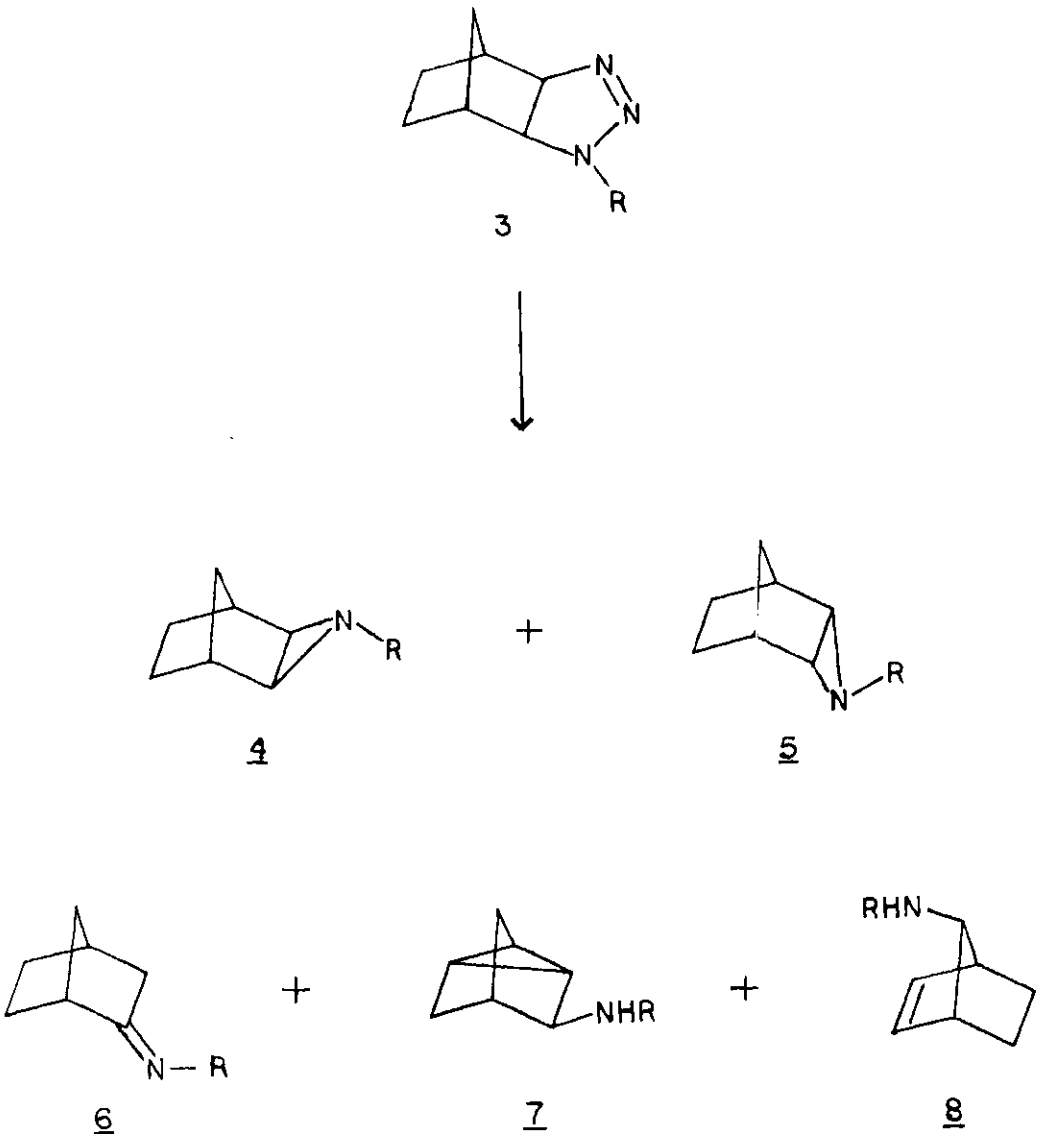


Figure 1. Generalized Thermal Decomposition of Triazolines

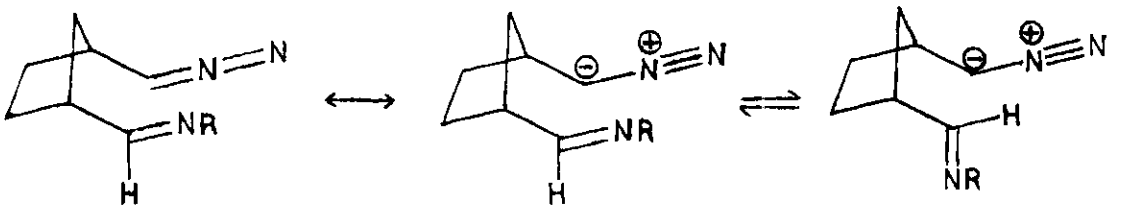
These pyrolyses are more complicated than originally assumed and their product distributions appear to be dependent on a number of structural and experimental factors. Figure 2 shows the products obtained in the reaction of norbornylene (1) with benzenesulfonyl azide, which gives substantial amounts of endo-aziridine (5b) and imine (6b) at elevated temperatures and in the presence of certain solvents and surfaces.[5] The intriguing formation of endo-aziridine 5b from the unstable and not isolated exo-triazoline 3b (hereafter triazoline-azidine inversion) was first reported in the reaction of cis-endo- and cis-exo-norbornene-5,6-dicarboxylic anhydride with benzene-sulfonyl azide in refluxing carbon tetrachloride.[6] In these cases, the endo-aziridine was the major product



Legend: a) R = C_6H_5, b) R = $SO_2C_6H_5$, c) R = p-NO_2-C_6H_4.

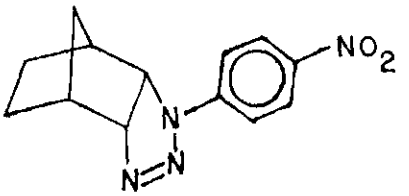
Figure 2. Generalized Thermolysis of a Triazoline

(68 to 76 percent). The only other product was the exo-aziridine. It was proposed that the endo-aziridine arose from exo-triazoline via diazoimine intermediates 9.[6]



9a 9b 9c

The exact mechanism of the formation of the diazoimine intermediate is uncertain. Previous reports from this laboratory have discussed an approach to this problem as well as the general nature of "trizaoline-aziridine inversion."[7] This work involved development of a synthetic route (Figure 3, p. 22) to the heretofore unknown bicyclic endo triazolines in order to determine if such an "inversion" would also occur in these isomeric compounds. An endo triazoline, 3-p-nitrophenyl-3,4,5-triazatricyclo[5.3.1.$0^{2,6\text{-endo}}$]dec-4-ene (10) was prepared and pyrolyzed.



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In addition to polymeric material (presumably due to the high pyrolysis

temperature), exo-aziridine 4c (7.3 percent), endo-aziridine (3.7 percent), and imine 6c (10.0 percent) were found.[7] These results, in particular the observation of the "triazoline-aziridine inversion," added further support to the postulation of diazoimine intermediate 9.[7]

The purpose of the present work, then, was to further develop the synthetic route to endo triazolines allowing preparation of a variety of compounds. The pyrolyses of these endo triazolines could then be compared with those of the readily available exo triazolines.[2] The variables which are responsible for the product distribution on thermolysis of both endo and exo triazolines could then be studied in order to gain a greater understanding of the mechanism(s) of these decompositions. This would also allow an opportunity to study the chemistry of the little known endo aziridines, as well as supply a broad range of structurally related triazolines and aziridines for biological testing.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Removal of solvents *in vacuo* was done using a Buchler Instruments rotary evaporator at water aspirator pressure. Infrared spectra were recorded using a Perkin-Elmer 237B spectrophotometer with solids in the form of potassium bromide pellets and liquids in the form of thin films between sodium chloride plates or in CCl_4 solution. The band at 1601 cm^{-1} of polystyrene film was used as a reference.

All ^{1}H-NMR spectra were obtained, with solutions containing tetramethyl silane as an internal standard, using a Varian Associates A-60D spectrometer. Mass spectra were obtained using a Varian Associates Model M-66 mass spectrometer.

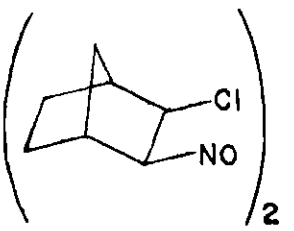
All thin layer chromatography was carried out using plates precoated with Silica Gel-G. Analytical plates (Brinkman 661412-09) were 5 cm by 20 cm with absorbant 0.25 mm thick. Preparative plates (Brinkman 661000-09) were 20 cm by 20 cm with absorbant 1 mm thick.

CHAPTER III

EXPERIMENTAL

2-Nitroso-3-chloronorbornane (11)

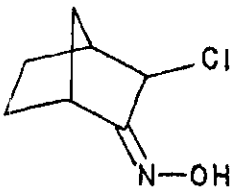
This compound was prepared by addition of NOCl gas to norbornylene according to the procedure of Zalkow and Hill.[7] The yield and spectral properties of the product were identical to the reported values.[7]



11

3-Chloronorcamphor Oxime (12a)

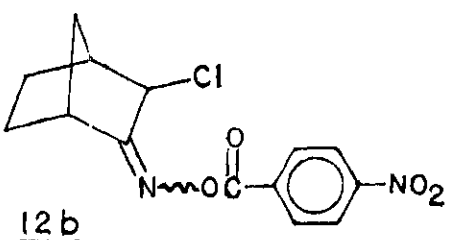
Isomerization of 2-nitroso-3-chloronorbornane to 3-chloronorcamphor oxime was accomplished by refluxing the former in urea as previously described.[7] The yield and spectral properties of the oxime were identical to the reported values.[7]



12a

3-Chloronorcamphor Oxime p-Nitrobenzoate (12b)

Esterification of the oxime (12a) was carried out by reaction with p-nitrobenzoyl chloride in ether as previously described.[7] When the product had been

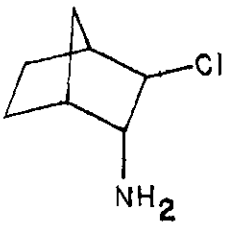


12b

recrystallized from 95 percent ethanol, the yield and spectral properties were the same as those previously reported.[7] This compound is a powerful vesicant and should be handled with due caution.

2-Endo-amino-3-exo-chloronorbornane (13)[7]

Preparation of this amine as its hydrochloride salt following the procedure of Zalkow and Hill[7] gave the variable results in yield and purity reported. When the method of Feuer and Braunstein[8] and a commercially prepared solution of borane in THF was used the yield and quality of the product were greatly increased.



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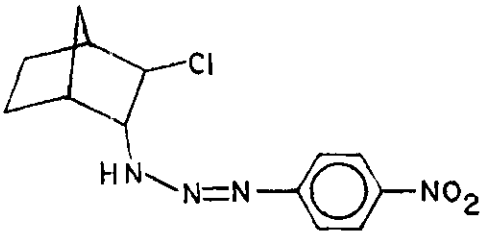
To a chilled (ice bath) solution of p-nitrobenzoate 12b (13.8 g, 45 mmol) in THF (500 ml) freshly distilled from $LiAlH_4$ was added 130 ml (60 mmol) of a 1.3 M solution of borane in THF (Ventron 35117). The apparatus was connected to a gas trap containing Hg and acetone. The solution was allowed to warm to room temperature and stirred for two days. The solution was then chilled in an ice bath and small pieces of ice cautiously added to destroy excess borane. The THF was removed in vacuo and concentrated HCl added to the residue until the pH was two. The solution was refluxed 1.5 hours, cooled to room temperature and continuously extracted with ether for 48 hours. The aqueous layer was separated, basified (pH 8) with 6 M KOH, and continuously extracted with ether for 48 hours. The ether extracts were collected, dried over $MgSO_4$, and filtered. Addition of HCl gas (through a fritted glass tube) yielded a

white precipitate (7.56 g, 93%) which was collected by filtration. Recrystallization of this solid (14) from 95 percent ethanol gave white crystals, mp 256-257° (reported[7] 254-255°), showing spectral properties identical to those reported.[7]

Coupling of p-Nitrobenzene Diazonium Chloride with 2-Endo-amino-3-exo-chloronorbornane (15)

Recrystallized (from water) p-nitroaniline (691 mg, 48.2 mmol) in 1.5 ml of water and 0.75 ml of concentrated HCl was cooled to 0°C in an ice bath. This solution was stirred half an hour at 0°C maintaining temperature by direct addition of ice to the flask. The solution was filtered onto ice (10 g) and then added to 10 ml of cooled saturated sodium acetate solution. The pH of this solution was above 5.5 and less than 6.5 by pH paper. (A standard buffer solution of pH 6 ± 0.01 also appeared to have a pH of 6.5 on the pH paper.) Over a 40 minute period the salt solution was added several milliliters at a time to a solution of free chloroamine amine (1.38 mmol) in ice water (25 ml). A yellow precipitate was observed after the first several milliliters had been added. Sodium chloride (10 g) was then added and the reaction stirred on hour at 0°C. Stirring was continued while the mixture warmed to room temperature overnight. Filtration removed 43 mg (22%) of a dark yellow solid, mp 110-112°C (reported[7] 112-115°C). This material was used without further purification or analysis.



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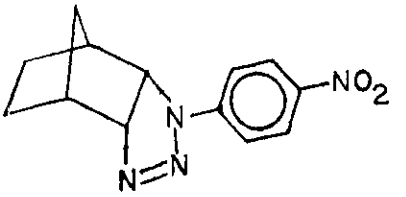
IR: ν_{KBr} (cm^{-1}): 3400 (N-H); 1600 (N=N).

3-p-Nitrophenyl-3,4,5-endo-triazotricyclo [5.2.1.$0^{2,6}$] dec-4-ene (10)[7]



10

Diazoamine 15 (42.5 mg, 0.14 mmol) in absolute ethanol (10 ml) was heated at 55°C with a hot water bath for one half hour. Sodium ethoxide (42.5 mg, 138 µl of a 1.04 M solution) was added using a 500 µl syringe. The pale yellow solution immediately turned wine red. The temperature was maintained at 60°C for an additional half hour. A solution of silver nitrate (25 mg in 7.5 ml of absolute ethanol) was then added by pipet. Appearance of a very fine brown precipitate obscured the red color of the solution. After stirring 10 minutes, the solution was filtered, the precipitate washed with ethanol and discarded. The solution was then reduced to dryness in vacuo. The residue was taken up in $CHCl_3$ and filtered again. The $CHCl_3$ was removed in vacuo leaving a red-brown residue which was taken up in CCl_4 and filtered. The CCl_4 was removed in vacuo leaving a small amount of red oil which partially crystallized upon standing overnight. The IR spectrum of this oil was identical to that of authentic triazoline, but no further characterization was possible due to the small amount of material produced.

IR: ν_{neat} (cm^{-1}): 1595, 1500, 1378, 1320.

Reductive Amination of 3-Chloronorcamphor (16) with $NaBH_3CN$

A solution of ammonium acetate (7.7 g, 100 mmol) and $NaBH_3CN$ (0.44 g, 7 mmol) in freshly distilled anhydrous methanol (30 ml) containing several grams of 3A molecular sieves was stirred at room temperature in a flask fitted with condensor and drying tube. Neat 3-chloronorcamphor (1.13 g, 0.96 ml, 10 mmol) was added via syringe and the solution stirred for 48 hours. Concentrated HCl was added until the pH of the solution was less than two and the solution reduced *in vacuo* to constant volume. The residue was taken up in water (10 ml) and extracted with $CHCl_3$. The aqueous layer was then brought to pH 10 by addition of solid NaOH and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, filtered, and hydrogen chloride gas added until no more precipitate appeared. This white precipitate (0.58 g, 41% based on desired amine salt 14) was collected by filtration, washed with ether, and air dried overnight. This material was spotted on a precoated silica gel plate and developed with acetone. Two spots were detected by iodine vapor: R_f = 0.59 (same value as authentic amine salt 14), and R_f = 0.23. The following spectral properties were observed for this mixture.

IR: ν_{KBr} (cm^{-1}): 3400 (b), 1585 (m), 1555 (m), 1490 (m), 1470 (m), 1375 (w), 1300 (w), 1130 (w), 1025 (w), 945 (w), 930 (w), 815 (w).

^{1}H-NMR (δ, CF_3CO_2H-$CDCl_3$): 1.0-2.0 (6H, complex); 2.32 (1H, m); 2.50 (1H, m); 3.63 (2H, m); 7.3 (2.5H, m).

Mass Spectrum: M^+_{found} = 273 (30%), calculated ($C_7H_{13}Cl_2N$-HCl) = 145; base peak m/e = 238.

Reductive Amination of 3-Chloronorcamphor (16) with $NaBH_3CN$ Using Excess Ammonium Acetate

A solution of 3-chloronorcamphor (0.74 g, 0.63 ml, 5 mmol) in freshly distilled anhydrous methanol (11 ml) was added dropwise to a previously prepared stirred solution of ammonium acetate (30.8 g, 400 mmol), $NaBH_3CN$ (0.44 g, 7 mmol), and several grams of Davidson 3A molecular sieves. The solution was stirred an additional 20 minutes after addition was complete. The solution was filtered to remove the sieves and concentrated HCl added until the pH was two. The solution was then reduced *in vacuo* to dryness and the residue taken up in a minimum amount of water. The solution was then extracted with $CHCl_3$ to remove starting material, the pH raised to 10 by addition of solid KOH, and extracted with ether. The extracts were combined, dried over $MgSO_4$ for one hour, and filtered. Hydrogen chloride gas was added via fritted glass tube until precipitation ceased. The white precipitate thus formed was collected by filtration, washed with anhydrous ether, and air dried overnight. TLC analysis (precoated silica gel plates developed with acetone) of this solid showed two spots: $R_f = 0.59$ (same value as authentic amine salt 14) and $R_f = 0.23$ (presumably secondary amine salt 17). The size and intensity of the spots (as detected by iodine vapor) suggested that nearly equal amounts of each compound were present in the mixture.

Attempted Separation of Amine Salts 14 and 17

The best separation of primary amine hydrochloride 14 and secondary amine hydrochloride 17 from the reductive amination of 3-chloronorcamphor with $NaBH_3CN$ was achieved by thin layer chromatography. A precoated

silica gel plate developed with acetone gave amine salt 14 an R_f of 0.59 and amine salt 17 an R_f of 0.23. When acetone was used to develop a preparative TLC plate, useful separation was obtained only if less than 40 mg of mixture was applied to the plate. TLC was therefore judged impractical for large scale separations of this mixture.

Column chromatography on acid washed alumina and on silica gel using a series of solvents was also found to be unsatisfactory for separation of the two compounds in this mixture. In all cases the mixture applied to the column was eluted without separation. The solvents used in these attempted separations were hexane, benzene, methylene chloride, chloroform, ethyl acetate, isopropanol, and acetone.

Reductive Amination of 3-Chloronorcamphor (16) with $NaBH_3CN$ and NH_3

A slow stream of ammonia gas was bubbled through a refluxing solution of ammonium acetate (15.4 g, 200 mmol) and 3-chloronorcamphor (1.13 g, 0.96 ml, 7.5 mmol) in freshly distilled methanol (175 ml) contained in a flask connected to a soxhlet extractor containing 3A molecular sieves. $NaBH_3CN$ (0.44 g, 7 mmol) was added and refluxing continued two hours. The solution was then cooled to room temperature and stirring continued three hours. The stream of ammonia was then cut off and the reaction worked up. Concentrated HCl was added until the pH was less than two and the solvent removed *in vacuo*. The residue was dissolved in a minimum amount of water and extracted with $CHCl_3$. The aqueous layer was then basified to pH 10 with solid KOH and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, and filtered. Hydrogen chloride

gas was added to the ether solution *via* a fritted glass tube. The white precipitate initially produced disappeared after several minutes forming a gummy tan residue which was collected by filtration. The $CHCl_3$ extracts, from above, and the tan gum were analyzed by TLC (precoated silica gel plates developed with acetone). The $CHCl_3$ extracts showed only one spot (R_f = 0.93) with an R_f identical to authentic starting material. The tan gum showed two spots: R_f = 0.59 (the same value as desired amine salt 14), and R_f = 0.23 (presumably amine salt 17). The intensity and size of these spots, as detected by iodine vapor, suggested the major product was the secondary amine salt (17).

Reaction of Benzenediazonium Chloride with Chloroamine 13

Benzenediazonium chloride solution was prepared by mixing chilled (ice bath) solutions of $NaNO_2$ (48.5 mg, 0.70 mmol) in 1.0 ml of H_2O and aniline hydrochloride (84.5 mg, 0.65 mmol) in 1.5 ml of H_2O containing concentrated HCl (0.5 ml, 9.07 mmol). This diazonium salt solution was stirred 15 minutes in an ice bath then added to 10 ml of a chilled (ice bath) saturated sodium acetate solution. The pH of this solution was six as determined by specific range pH paper. A small amount of yellow precipitate appeared upon addition of this buffered diazonium salt solution to a solution of free chloroamine 13 (generated from 250 mg, 1.38 mmol, of hydrochloride salt[9]) in 10 g of ice and several milliliters of H_2O. No visible precipitate was present the next day in the darkened solution. A yellow residue on the sides of the flask was taken up in ethanol and recrystallization attempted. No crystals were obtained. The ethanol was removed *in vacuo* and several milliliters of ether added. A portion of

the ether solution was allowed to evaporate on a NaCl plate and an IR spectrum obtained.

IR: ν_{neat} (cm^{-1}): 1600 (s), 1500 (w), 1275 (m), 1225 (m), 1140 (s), 845 (m), 765 (m), 690 (m).

This procedure was repeated with the following modifications: (1) the diazonium salt solution was stirred two hours at 0°C to insure complete reaction, and (2) only enough saturated sodium acetate solution (1.5 ml) was added to raise the pH of the diazonium salt solution to six. A visible bright yellow precipitate appeared as the coupling reaction was carried out. After complete addition, the mixture was stirred at 0°C for one hour, then 10 g of NaCl was added. The solution darkened overnight. The aqueous solution was extracted with ether (6 x 25 ml), and the combined extracts washed with H_2O then dried over $MgSO_4$ and filtered. Removal of the ether in vacuo from the bright yellow solution gave a red-brown oil (40 mg). The residue remaining on the sides of the reaction vessel was worked up in a similar manner to give a red-brown oil (70 mg). Both of these product mixtures were analyzed by TLC on precoated silica gel plates developing with $CHCl_3$. The only identifiable spot (R_f = 0.66) was 2-chloronorcamphor. Five other spots were observed by iodine detection: R_f = 0.16, 0.22, 0.35, 0.74, 0.81. No further analysis of this complex mixture was attempted.

Reaction of p-Carbomethoxybenzenediazonium Chloride with Chloroamine 13

To a previously chilled (ice bath) solution of p-carbomethoxyaniline (99 mg, 0.65 mmol) in 1.5 ml of water containing concentrated HCl (0.75

ml, 9.1 mmol) was added a chilled solution of $NaNO_2$ (48.3 mg, 0.65 mmol) in 1.0 ml of water. This diazonium salt solution was stirred in an ice bath one half hour, then chilled saturated sodium acetate solution added until the pH of the salt solution was 6 as determined by specific range pH paper. This buffered diazonium salt solution was then added several milliliters at a time to a previously chilled solution of free chloroamine 13 (generated from 250 mg, 1.38 mmol, of hydrochloride salt[9]) in water. When this addition was complete, NaCl (10 g) was added and the solution stirred at 0°C one hour, then allowed to come to room temperature overnight. A fluffy, orange solid (40 mg) was recovered by filtration and recrystallized from chloroform-hexane. An additional 20 mg of solid appeared in the mother liquor and was recrystallized in a like manner. Two additional crops of crystals were obtained from the mother liquor (total weight obtained was 70 mg). The spectral properties of this yellow solid, mp 210-212°C with bubbling, indicated it was not the desired p-carbomethoxydiazoamine.

IR: ν_{KBr} (cm^{-1}): 3400 (bm), 3245 (m), 1700 (s), 1610 (s), 1285 (s), 1250 (s), 1170 (s), 1110 (m), 850 (w), 765 (w), 695 (w).

^{1}H-NMR (δ, $CDCl_3$): 3.14 (6H, s); 7.04 (4H, d, J = 8 Hz); 7.57 (4H, d, J = 8 Hz).

Mass Spectrum: M^+_{found} = 313 (1%); calculated for desired diazoamine = 307; base peak m/e = 135.

Reaction of p-Methoxybenzenediaznonium Chloride with Chloroamine 13

A chilled solution (ice bath) of $NaNO_2$ (48 mg, 0.70 mmol) in 1.0

ml of H_2O was added to a chilled solution (ice bath) of p-methoxyaniline (80 mg, 0.65 mmol) in 1.0 ml of H_2O containing 0.1 ml of concentrated HCl. The resulting lavender colored solution became orange after stirring several minutes. The diazonium salt solution was stirred 20 minutes, filtered onto 10 g of ice and replaced in the ice bath. A solution of free chloroamine 13 (generated from 200 mg, 1.1 mmol, of hydrochloride salt 14) in 7 ml of ice water was added in 1.5 ml portions over a period of 10 minutes to the diazonium salt solution (the pH of the salt solution had been adjusted to 5.5-6.0 by addition of saturated sodium acetate solution). This reaction mixture was stirred 15 minutes, NaCl (10 g) added, and then placed in the refrigerator overnight. The cloudy aqueous solution was filtered and the flask and filter rinsed with $CHCl_3$. The $CHCl_3$ rinsings were combined, dried over $MgSO_4$, filtered, and solvent removed *in vacuo*. The IR and ^{1}H-NMR spectra of the tan solid (100 mg) obtained support the structure of the desired diazoamine 23. This material was used without further purification.

IR: ν_{CCl_4} (cm^{-1}): 3400 (w), 3300 (w), 1600 (s), 1505 (sh), 1500 (s), 1460 (m), 1440 (m), 1400 (m), 1300 (m), 1250 (s), 1230 (s), 1175 (s), 1040 (s), 830 (s).

^{1}H-NMR (δ, $CDCl_3$): 1.1-2.1 (6H, complex); 2.5 (2H, m); 3.70 (1H, m); 3.80 (3H, s); 4.30 (1H, m); 6.90 (2H, d, J = 8 Hz); 7.35 (2H, d, J = 8 Hz).

This reaction was repeated using diazonium salt solution prepared from p-methoxyaniline (160 mg, 1.3 mmol), $NaNO_2$ (97 mg, 1.4 mmol) and concentrated HCl (0.2 ml) in 2 ml of H_2O. This solution was stirred 3.0 hours in an ice bath. The pH of this diazonium salt solution was then

adjusted to 5.5-6.0 by addition of saturated sodium acetate solution. A chilled solution of free chloroamine 13 (1.3 mmol) in 3 ml of ice water was then added to this buffered diazonium salt solution and the mixture stirred in the ice bath one hour then placed in the refrigerator overnight. No precipitate or oil was visible in the solution the next day.

Reaction of Crude p-Methoxydiazoamine 23 with Potassium t-Butoxide

A solution of crude p-methoxydiazoamine 23 (100 mg, 0.29 mmol) in t-butyl alcohol (15 ml) was stirred in a hot water bath until dissolved, and added to a solution of potassium t-butoxide (56 mg, 0.5 mmol) in t-butyl alcohol (8 ml) prepared in a similar manner. The resulting deep orange solution was stirred at 60°C for 30 minutes. To this solution was added $AgNO_3$ (51 mg, 0.30 mmol) in absolute ethanol (11 ml). A dark green precipitate formed immediately. After heating an additional 15 minutes, the solution was allowed to cool to room temperature, filtered and the solvent removed in vacuo. The residue was taken up in CCl_4, filtered, and the CCl_4 removed in vacuo. A pale yellow oil (55 mg) showing the following spectral properties was obtained.

IR: ν_{CCl_4} (cm^{-1}): 3400 (bw), 1600 (m), 1505 (sh), 1500 (s), 1460 (m), 1440 (m), 1290 (m), 1240 (s), 1175 (m), 1040 (s), 830 (m).

Reaction of p-Bromobenzenediazonium Chloride with Chloroamine 13

To a previously chilled (ice bath) solution of p-bromoaniline (112 mg, 0.65 mmol) in 1.0 ml of H_2O containing concentrated HCl (0.1 ml, 1.17 mmol) was added a chilled solution of $NaNO_2$ (48.5 mg, 0.7 mmol) in 1.0 ml

of H_2O. This diazonium salt solution was stirred in an ice bath 15 minutes, then chilled saturated sodium acetate solution added until the pH of the resulting solution was 6 as determined by specific range pH paper. This buffered diazonium salt solution was then added several milliliters at a time to a chilled solution of free chloroamine (generated from 250 mg, 1.38 mmol, of hydrochloride salt[7]) in water. The chloroamine solution became cloudy yellow upon addition of the first portion of diazonium salt. After addition was complete, the solution was placed in a refrigerator overnight. A yellow precipitate was collected by filtration, taken up in $CHCl_3$, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave 50 mg of a yellow solid. The IR and ^{1}H-NMR spectra indicated this solid contained the desired diazoamine 25. This material was used without further purification.

IR: ν_{CCl_4} (cm^{-1}): 3420 (w), 3315 (w), 1600 (m), 1500 (s), 1475 (m, sh), 1235 (s), 1170 (s), 1075 (m).

^{1}H-NMR (δ, $CDCl_3$): 1.1-2.2 (6H, complex); 2.52 (2H, m); 3.83 (1H, t, J = 4 Hz); 4.28 (1H, m); 7.15 (2H, d, J = 8 Hz); 7.48 (2H, d, J = 8 Hz).

This reaction was repeated and carried out in a cold room (3°C). A dark yellow precipitate appeared overnight as before, and was collected by filtration, taken up in $CHCl_3$, dried over $MgSO_4$, and the solution filtered. The solvent was removed in vacuo leaving 62 mg of yellow solid. The ^{1}H-NMR spectrum of this solid showed signals only in the aromatic region of the spectrum, indicating diazoamine 25 was not present.

^{1}H-NMR (δ, $CDCl_3$): 7.15 (d, J = 8 Hz); 7.48 (d, J = 8 Hz).

Reaction of Diazoamine 25 with Base

Several milligrams of diazoamine 25 were added to a small amount of 1.04 M sodium ethoxide in ethanol. No change in the yellow color of the diazoamine was observed. A stronger base was apparently required. A solution of potassium t-butoxide (22.4 mg, 0.20 mmol) in t-butyl alcohol (8 ml) was added dropwise to a solution of diazoamine 25 (50 mg, 0.15 mmol) in t-butyl alcohol (3 ml). The initially yellow solution became darker, then lightened as a white precipitate formed in the flask. An additional 20 mg of base was added and the solution heated to 55°C. After stirring one half hour, a solution of $AgNO_3$ (25.5 mg, 0.15 mmol) in absolute ethanol (8 ml) was added causing formation of a dark green precipitate which obscured the color of the solution. This solution was stirred 10 minutes, filtered through a fritted glass funnel, the solvent removed in vacuo, and the dark residue taken up in $CHCl_3$ (10 ml). This solution was filtered three times using a Buchner funnel, the solvent removed in vacuo and the residue taken up in CCl_4 (10 ml). Filtration of this solution through a Celite 545 pad produced a yellow filtrate. The solvent was again removed in vacuo and the yellow residue recrystallized from hexane. A small amount of bright yellow crystals was obtained, mp 135-136°C with bubbling. The spectral properties exhibited by this solid support the structure of the desired endo triazoline 26.

IR: ν_{KBr} (cm^{-1}): 3455 (bm), 1595 (m), 1480 (s), 1465 (sh), 1365 (m), 1135 (w), 1120 (m), 1100 (m), 1085 (m), 1075 (w), 990 (sh), 985 (m), 820 (w), 805 (m).

^{1}H-NMR (δ, $CDCl_3$): 1.2-1.6 (6H, complex); 2.75 (1H, m); 2.95 (1H, m); 4.03 (1H, d of d, J = 5.0, 12 Hz); 5.08 (1H, d of d, J = 4.5, 12 Hz), 7.18 (2H, d, J = 8.5 Hz); 7.46 (2H, d, J = 8.5 Hz).

CHAPTER IV

DISCUSSION OF RESULTS

As stated in the introduction section, the purpose of this research was to determine the general synthetic utility of the endo triazoline synthesis previously developed in this laboratory.[7] The preparation of the endo-p-nitrophenyltriazoline 10 by this synthesis is illustrated in Figure 3. The nitrosyl chloride dimer (11) was prepared and smoothly isomerized to the 3-chloronorcamphor oxime (12a) as reported.[7] The p-nitrobenzoate (12b) of this oxime was easily prepared by reaction of the oxime with p-nitrobenzoyl chloride.[7] The benzoate 12b is a powerful vesicant and produced severe allergic reactions in all individuals who came into contact with it. Reduction of 12b with diborane yielded chloroamine 13, isolated as its hydrochloride salt (14) in 40 percent yield as reported.[7] The free chloroamine 13 was prepared[9] and coupled with p-nitrobenzene diazonium chloride to give the p-nitrodiazoamine 15 in 22 percent yield. A yield of 62 percent was previously reported.[7] In spite of the low yield in the present case, the IR spectrum and melting point of the product were identical to those of an authentic sample. The endo triazoline 10 was then prepared by treatment of diazoamine 15 with sodium ethoxide in absolute ethanol, forming a deep red colored solution, and addition of silver nitrate, causing a dark precipitate of silver chloride to form. The IR spectrum of the product was identical to that of authentic endo triazoline 10.

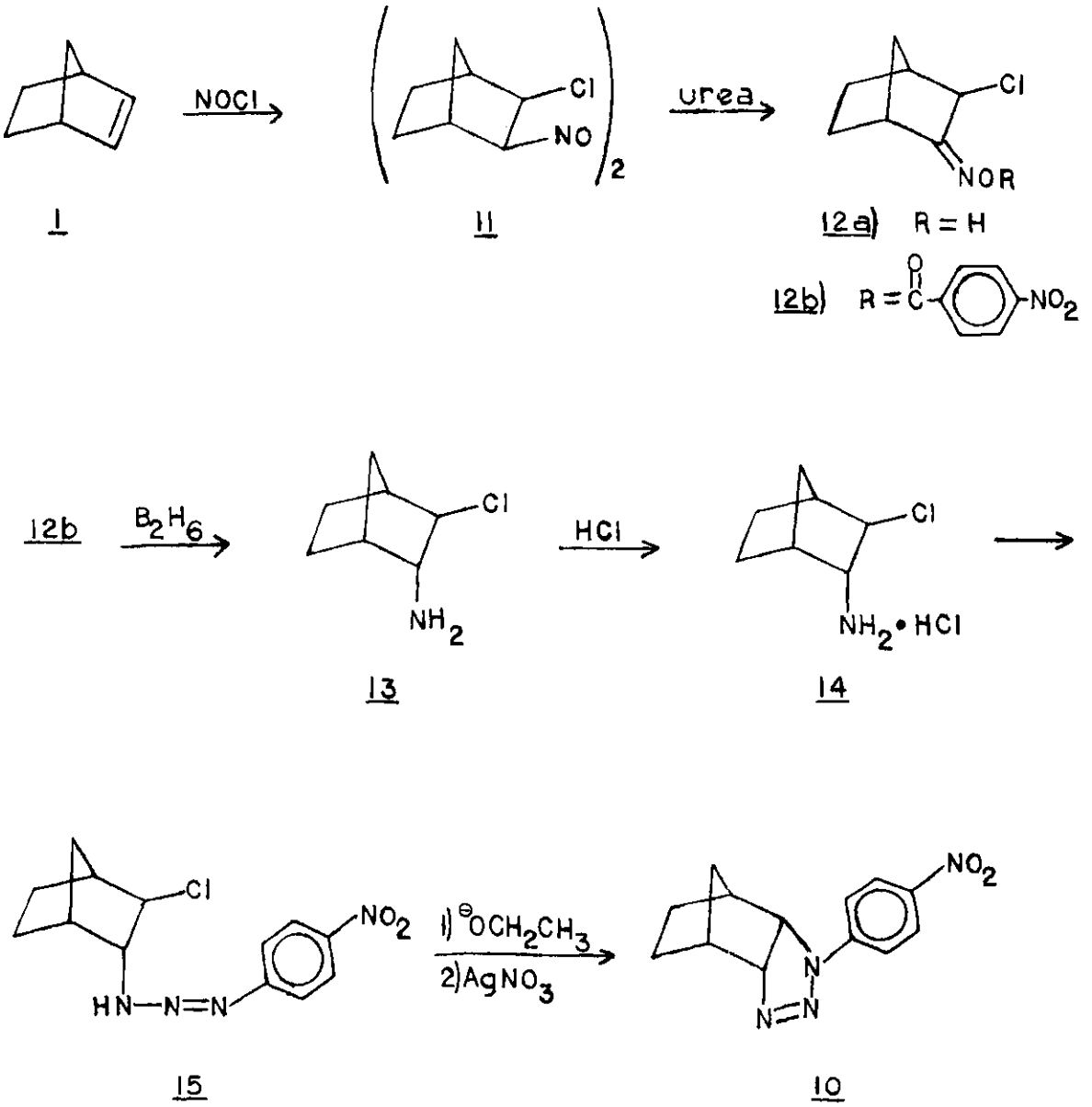
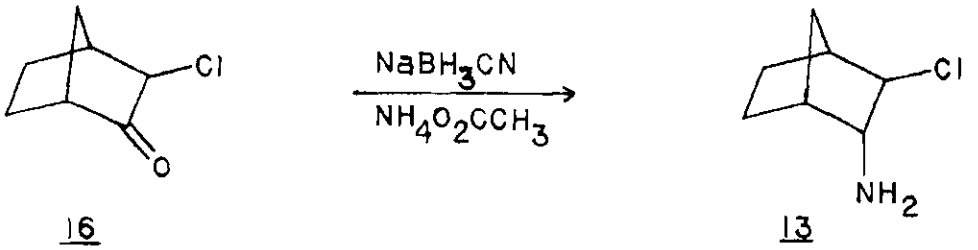


Figure 3. Synthesis of Endo p-Nitrophenyl Triazoline

Since preparation of the endo triazoline 10 was carried out with crude diazoamine 15, the low yield obtained was not surprising. The major problem with this sequence then appeared to be the variable yield and purity of chloroamine 13 obtained in the hydroboration of p-nitrobenzoate 12b. Although this reaction does give the desired product, the yield is only moderate and attempts to scale up the reaction were unsuccessful.[7]

A possible alternative approach to chloroamine 13 was found in the reported reductive amination of the closely related norcamphor with sodium cyanoborohydride in the presence of sodium acetate in anhydrous methanol.[10] A 68 percent yield of endo-norbornyl amine was reported.[10] Reductive amination of the readily available 3-chloronorcamphor (16) would produce chloroamine 13 with the desired stereochemistry. This reaction was carried out according to the procedure reported for norcamphor,



16 13

and the product isolated as the hydrochloride salt in 41 percent yield. The IR spectrum of this product, although similar to that of the desired chloroamine salt (14) showed broad absorption in the N-H stretching region of the spectrum. The ^{1}H-NMR spectrum appeared identical to that of the desired material, but integration showed 2.5 protons in the N-H multiplet of the spectrum. Analysis of this product by TLC showed an extra spot as

well as the spot corresponding to the desired chloroamine salt (14). The nature of this mixture was determined from the mass spectrum which showed a molecular ion of m/e 309, instead of m/e 145 expected after loss of HCl from the hydrochloride salt of chloroamine 13. A molecular ion of m/e 309 requires a formula of $C_{14}H_{22}Cl_3N$, which corresponds to a bicyclic secondary amine hydrochloride (17). Loss of HCl from the molecular ion gives rise to a set of peaks confirming the presence of two chlorine atoms in the molecule in addition to the hydrochloride. Table 1 lists the observed and calculated[12] intensities of isotope peaks for an ion containing one and two chlorine atoms.

Table 1. Intensities of Isotope Peaks Due to Chlorine

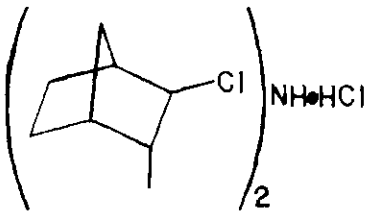
	P	P+2	P+4
Cl (calc)	100	32.6	--
Cl (obs)†	100	30	--
Cl_2 (calc)	100	65.3	10.6
Cl_2 (obs)‡	100	64	11

†P = m/e 238; ‡P = m/e 273

The set of peaks at m/e 273, 275, 277 has intensities corresponding to the presence of two chlorine atoms (structure 18), and the set at m/e 238 (the base peak) and 240 corresponding to the presence of one chlorine atom (structure 19). A peak (m/e 145, 34 percent of the base peak) corresponding to loss of HCl from the molecular ion of the desired chloroamine salt (14) was also present in the spectrum.

The presence of secondary amine 18 in the product mixture suggests

that formation of an imine from 3-chloronorcamphor and ammonia (produced from ammonium acetate) is slow when compared with formation of an imine from 3-chloronorcamphor and bicycloamine (or amine-cyanoborohydride complex).



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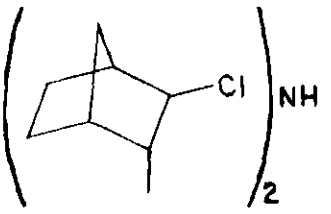

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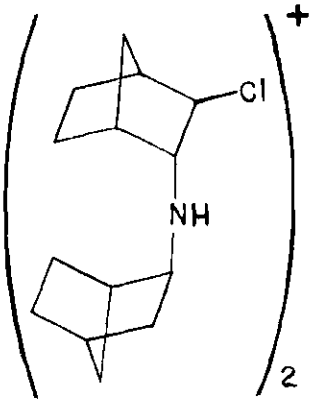

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In order to decrease formation of the secondary amine (18) the reaction was repeated with the following modifications: (1) the reaction was carried out in the presence of 3A molecular sieves, (2) an eight-fold excess of ammonium acetate was used to increase the rate of formation and concentration of the desired imine, (3) a two-fold excess of sodium cyanoborohydride was used to increase the rate of reduction of the imine, and (4) the volume of the solution used was doubled. In addition, 3-chloronorcamphor in methanol was added dropwise to a solution of the other reagents, reducing the concentration of unreacted ketone in the mixture and decreasing the probability of imine formation from ketone and reduced imine (or reduced ketone-cyanoborohydride complex) which would lead to formation of the secondary amine salt (18). Analysis by TLC of the product from this reaction again showed the presence of both primary amine salt (14) and secondary amine salt (17). The size and intensity of the

spots, as detected by iodine vapor, suggested that nearly equal amounts of each compound were present.

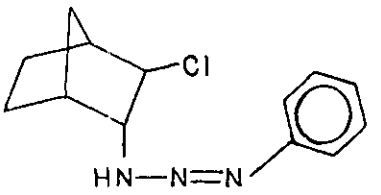
A successful separation of these two amine salts was achieved using preparatory TLC, but the small amount of material obtained from each separation made this method impractical on a large scale. Column chromatography on acid washed alumina and on silica gel using a wide variety of solvents also proved unsatisfactory.

A final attempt was made in eliminating secondary amine produced in this reaction by using ammonia gas in addition to ammonium acetate. A stream of ammonia was bubbled through a dilute solution of ammonium acetate and 3-chloronorcamphor (16) in anhydrous methanol. The apparatus was connected to a soxhlet extractor containing 3A molecular sieves to remove water produced in imine formation. After two hours, the solution was cooled to room temperature, sodium cyanoborohydride added, stirred three hours, then worked up in the usual manner. Addition of hydrogen chloride gas in an ether solution of the product produced a white precipitate which immediately became a tan gum. Analysis of this gum showed the two spots corresponding to both primary and secondary amine salts. The intensity and size of the spots as detected by iodine vapor, suggested the undesired secondary salt (17) was the major product.

These results forced a return to the original method of preparation of chloroamine 13. The major faults of this procedure were the complicated apparatus required for generation of the diborane, and the variable quantity and quality of the product.[7] The first difficulty was eliminated by use of a commercially prepared solution of borane in tetrahydrofuran.

A search of the literature revealed the use of continuous ether extractions in the work-up procedure.[8] When these modifications were implemented excellent yields (as great as 93 percent) of chloroamine salt 14 were obtained with even large scale reactions. Recrystallization of the product from 95 percent ethanol gave beautifully crystalline sharp melting crystals, exhibiting spectral properties identical to those of authentic material.

Now that the key intermediate in this synthesis of endo triazolines was available in high purity and large quantities, the coupling reactions of this intermediate as well as triazoline formation itself could be investigated. It was decided to prepare the parent compound in the series, phenyldiazoamine 20. The procedure used was that reported in the literature for the p-nitro compound (15).



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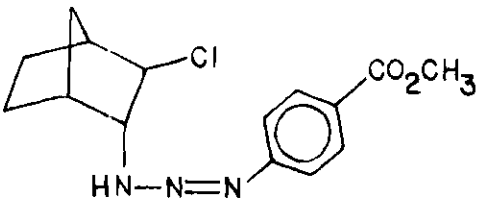
No visible precipitate was obtained on work up of this reaction. A yellow residue found on the sides of the flask was collected and an IR spectrum obtained. The overall appearance of this spectrum was similar to that obtained for the p-nitrophenyldiazoamine (15) when the absorptions due to the nitro group were neglected. The procedure was repeated with the following modifications: (1) the diazonium salt solution was stirred two hours to insure complete formation of the salt, and (2) only enough buffer (saturated sodium acetate solution) was added to raise the pH of the diazonium salt solution to six. When the solution prepared in this manner was added to a solution of chloroamine 13 a visible bright yellow precipitate appeared. The solu-

tion darkened overnight, however, and the dark red oil obtained on work up was shown by TLC to contain six products. No further analysis of this complex mixture was attempted.

It was then decided to attempt preparation of p-carbomethoxy diazoamine (21), which, with the electron withdrawing para substituent, should be similar in nature to the previously prepared[7] p-nitro compound (15). The published procedure[7] was followed and a yellow solid (mp 210-212°C with bubbling) was isolated. The IR spectrum of this solid showed the expected strong absorption at 1700 cm^{-1} for the ester carbonyl, but also showed a broad medium intensity absorption at 3400 cm^{-1}.



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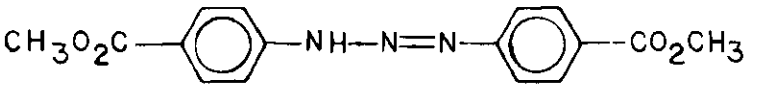
The ^{1}H-NMR spectrum showed the expected signals for the p-carbomethoxyphenyl moiety, but no signals were observed for the bicyclic portion of the desired product. The evolution of a gas upon melting this solid, and the absence of signals in the aliphatic region of the ^{1}H-NMR spectrum indicated the diazonium salt had coupled, but not with the chloroamine (13). The mass spectrum of this solid suggested coupling of the diazonium salt with undiazotized p-carbomethoxyaniline had occurred and that the structure of the product was that shown in 22. None of the peaks in the mass spectrum showed isotope intensities requiring the presence of chlorine. A molecular ion was barely detectable at m/e 313, corresponding to a formula of $C_{16}H_{15}N_3O_4$. Loss of nitrogen from this molecular ion gave a peak

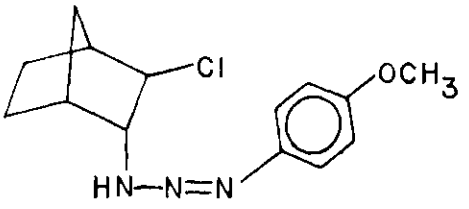


22

at m/e 285 (13 percent of the base peak). Loss of nitrogen and a methoxy group from the molecular ion gave a peak at m/e 254 (12 percent of the base peak). The base peak at m/e 135 corresponded to a carbomethoxyphenyl ion. No peaks were observed for the molecular ion, or molecular ion less nitrogen, of the desired diazoamine (19).

The yield of 22 obtained corresponds to over two-thirds of the p-carbomethoxyaniline used in the reaction. It appears that diazotization was incomplete, and the coupling reaction much faster with the aniline than with chloroamine 13.

In another attempt at preparing a diazoamine suitable for closure to an endo triazoline, p-methoxyaniline was used. The reported procedure[7] was followed and the spectral properties (see experimental section) of the tan solid isolated supported the structure of the desired p-methoxyphenyl diazoamine (23). The procedure was repeated on three times this scale and the diazonium salt solution stirred three hours to insure complete diazotization, but no precipitate or oil was observed in the aqueous solution when the reaction was worked up.



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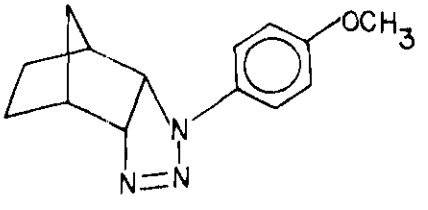

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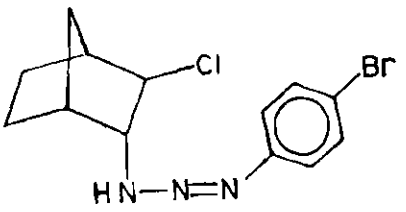
An attempt to form the endo triazoline (24) with the crude diazoamine (23) produced earlier using the procedure described below for the p-bromodiazoamine (25) resulted in the isolation of a pale yellow oil. This IR spectrum of this oil was essentially the same as that of the starting material (23).

A final attempt at obtaining a bicyclic diazoamine was made with p-bromoaniline. The reaction was carried out as before and a yellow precipitate collected. The spectral properties of this solid indicated it was the desired diazoamine (25). The IR spectrum was similar to that of the p-nitrodiazoamine (15), but also showed the presence of some primary amine (presumably p-bromoaniline) by very weak absorptions at 3420 and 3315 cm^{-1} in the N-H stretching region of the spectrum. The ^{1}H-NMR spectrum showed two doublets (J = 8 Hz) corresponding to the aromatic protons at δ 7.15 and 7.48 ppm. A complex six proton signal was observed at δ 1.1-2.2 ppm. A two proton multiplet (presumably the bridgehead protons[7c]) was observed at δ 2.52 ppm. Multiplets observed at δ 3.83 and 4.28 ppm were assigned to the protons alpha to the chloro and amino functions.

This reaction was repeated in an attempt to obtain more material, but the ^{1}H-NMR spectrum of the solid isolated showed signals only in the aromatic region of the spectrum.



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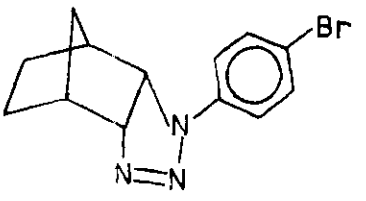

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The p-bromodiazoamine (25) obtained earlier was dissolved in sodium ethoxide in absolute ethanol preparatory to addition of silver nitrate and ring closure to the endo triazoline. No change in the yellow color of the solution was observed, indicating a stronger base may be required to form the anion needed for displacement of the chlorine. When the diazoamine was dissolved in t-butyl alcohol and potassium t-butoxide in t-butyl alcohol added, the light yellow solution became darker. This solution was then heated and silver nitrate added following the reported procedure.[7] The spectral properties of the sharp melting (with bubbling) bright yellow crystals obtained from this reaction support the structure of the desired endo triazoline (26). The ^{1}H-NMR spectrum, in particular, gave dramatic evidence to this effect. The expected bicyclic and aromatic signals were observed (see experimental section), but more importantly, the protons on the carbon atoms in the triazoline ring each appeared as a doublet of doublets at δ 4.03 ppm with J = 4.5 and 12 Hz and at δ 5.08 ppm with J = 5.0 and 12 Hz. These are essentially the same chemical shifts and coupling constants observed in the ^{1}H-NMR spectrum of the p-nitro endo triazoline (10).[7] Based on this previous work, these multiplets were assigned to the protons on C_3 and C_2, respectively, the larger coupling of 12 Hz corresponding to $J_{2,3}$, and the smaller coupling corresponding to $J_{1,2}$ of 5.0 Hz and $J_{3,4}$ of 4.5 Hz.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

An investigation of the previously reported[7] synthetic sequence leading to endo triazolines has been carried out. The existing procedure for the preparation of the key intermediate in this sequence, chloroamine 13 , has been modified. The yield and purity of 13 obtained have been greatly increased.

An alternate approach to this chloroamine (13), reductive amination of 3-chloronorcamphor (16) with sodium cyanoborohydride and ammonium acetate, was found to produce secondary amine 18 in addition to the desired chloroamine (13). The best separation of these amine salts achieved was unsuitable for large scale preparations.

Coupling of chloroamine 13 with several diazonium salts was found in most cases to be an unsatisfactory method of preparing the diazoamines required in this sequence. Spectral evidence suggested coupling of p-carbomethoxybenzenediazonium chloride with undiazotized p-carbomethoxyaniline had occurred. Evidence suggesting successful formation of the desired diazoamine in the case of the p-bromo compound was obtained from spectral data of the product of the reaction of this diazoamine (25) with base. The ^{1}H-NMR spectrum of this product (26) was very similar to that obtained from the p-nitro endo triazoline (10) and supported the structure of the desired endo triazoline 26.

This sequence, then, would be satisfactory as a general synthesis

of endo triazolines only if difficulties in the preparation of the required diazoamines could be solved.

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7. a) L. H. Zalkow and R. H. Hill, Tetrahedron Lett., 2819 (1972).
   b) L. H. Zalkow and R. H. Hill, Tetrahedron, 31, 831 (1975).
   c) Robert Howard Hill, Ph.D. Thesis, Georgia Institute of Technology, 1972.

8. H. Feuer and D. M. Braunstein, J. Org. Chem., 34, 1817 (1969).

9. Free chloroamine 13 was generated from the hydrochloride salt (14) by basification of an aqueous solution of the salt with KOH, extracting with ether, washing the combined ether extracts with water, and removal of the ether in vacuo.

10. a) R. F. Borch, M. D. Berstein, and H. D. Durst, J. Amer. Chem. Soc., 93, 2897 (1971).
    b) Sodium Cyanoborohydride, obtained from Alfa Inorganics (87839) was used without further purification.

11. 3-Chloronorcamphor (16) was obtained from Aldrich (C6243).

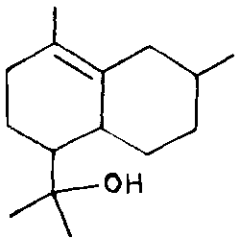
12. R. M. Silverstein and G. C. Bassler, Spectrometric Identification of Organic Compounds, Wiley-Interscience, New York, 1967, p. 29.

PART II

CHAPTER I

INTRODUCTION

The major component of the essential oil derived from the seeds of the Indian Black Carrot (Daucus carota L.) has been found to be carotol, a sesquiterpene alcohol of formula $C_{15}H_{26}O$. Isolation of carotol was first accomplished by Asahina and Tuskamoto in 1925.[1] Sorm and Urbanek originally proposed carotol had structure 1 in 1948.[2] Eleven years later, Chuirdoglu and Descamps offered evidence in support of structure 2.[3] At the time of this report, Sorm and co-workers proposed structure 3 on the basis of new degradation studies.[4] Convincing NMR evidence in support of 3 was put forth by Zalkow et al. in 1960.[5]



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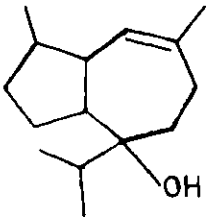

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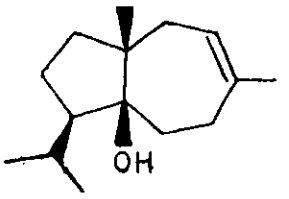

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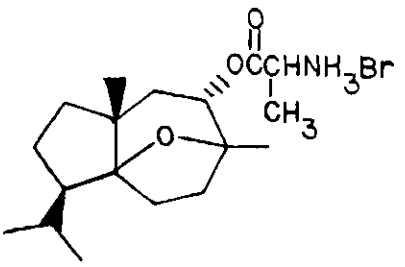
This structure was finally confirmed by an x-ray crystallographic study of daucyl D,L-alaninate hydrobromide (4).[6] Daucol, which co-occurs with carotol in the essential oil, is easily obtained from carotol on oxidation with peracids.[4] Levisalles et al., who proposed the stereochemistry shown in 3,[7] published a synthesis of carotol from carvone in 1972.[8,9,10]

The carotane class of sesquiterpenes, of which carotol (3) is the

principal member is a small group of compounds containing the cis-fused five-seven membered ring structure of carotol. Relatively little is known of the chemistry of this interesting class of compounds. Levisalles et al., for example, in their conversion of daucene (5) into carotol (3), have made a detailed study of the properties of the various epoxides and epoxyalcohols available from these compounds.[10] No attempt was made, however, to investigate the chemistry of these compounds or their derivatives. In addition to Levisalles' synthesis, two additional pathways to



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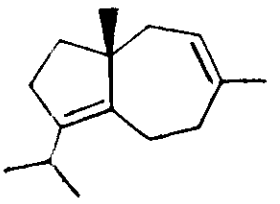

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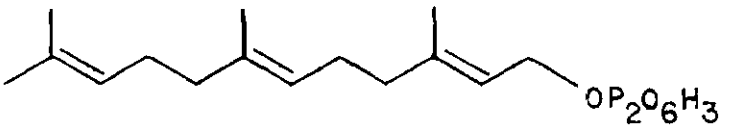
daucene have been published, but here again, no attempt was made to investigate the chemistry of the compound itself.[11,12] The earlier studies on carotol were carried out in order to elucidate the structure and stereochemistry of that compound and not to investigate its chemistry. The reaction sequences involved in all of these studies were, of necessity, known reactions whose products were well documented.

It is not surprising then, that in addition to the lack of knowledge of the chemistry of the carotanes, the biogenesis of these compounds is also not well understood. A typical study of the biogenesis of sesquiterpenes (and terpenes in general) involves examination of postulated biogenetic pathways, followed by "in vitro" experiments to simulate these postulations. The rationale usually involves illustrating how a new

skeletal type could arise by mechanistically and stereochemically sound means from a previously known skeletal type.

Sesquiterpenes are thought to be biosynthesized in some way from farnesol, the biogenetic equivalent of which is farnesyl pyrophospahate (6).[13] The process is envisaged as removal of the pyrophosphate anion and participation of the central or terminal double bonds and cyclization of the resulting cation to the desired sesquiterpene skeleton.



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Soucek envisioned two possible modes of cyclization of the farnesyl cation which could produce the carotane skeleton (Figure 1).[14] Path A supposed direct cyclization to the carotane skeleton, while Path B required cyclization to a ten-membered intermediate and subsequent shift of a methyl group. Incorporation of labeled sodium acetate (1-^{14}C) into the carrot plant, extraction of the essential oil, isolation of the radioactive carotol followed by degradation showed C_6 and its attached methyl group to have one-sixth of the total incorporated activity. This finding is consistent with Path A, involving direct cyclization to the carotane skeleton.

From the preceding discussion, it is obvious that a thorough investigation of the carotane sesquiterpenes was in order. The purpose of this research, then, was to begin such an investigation. Such a small class of natural products may be related to another larger class of

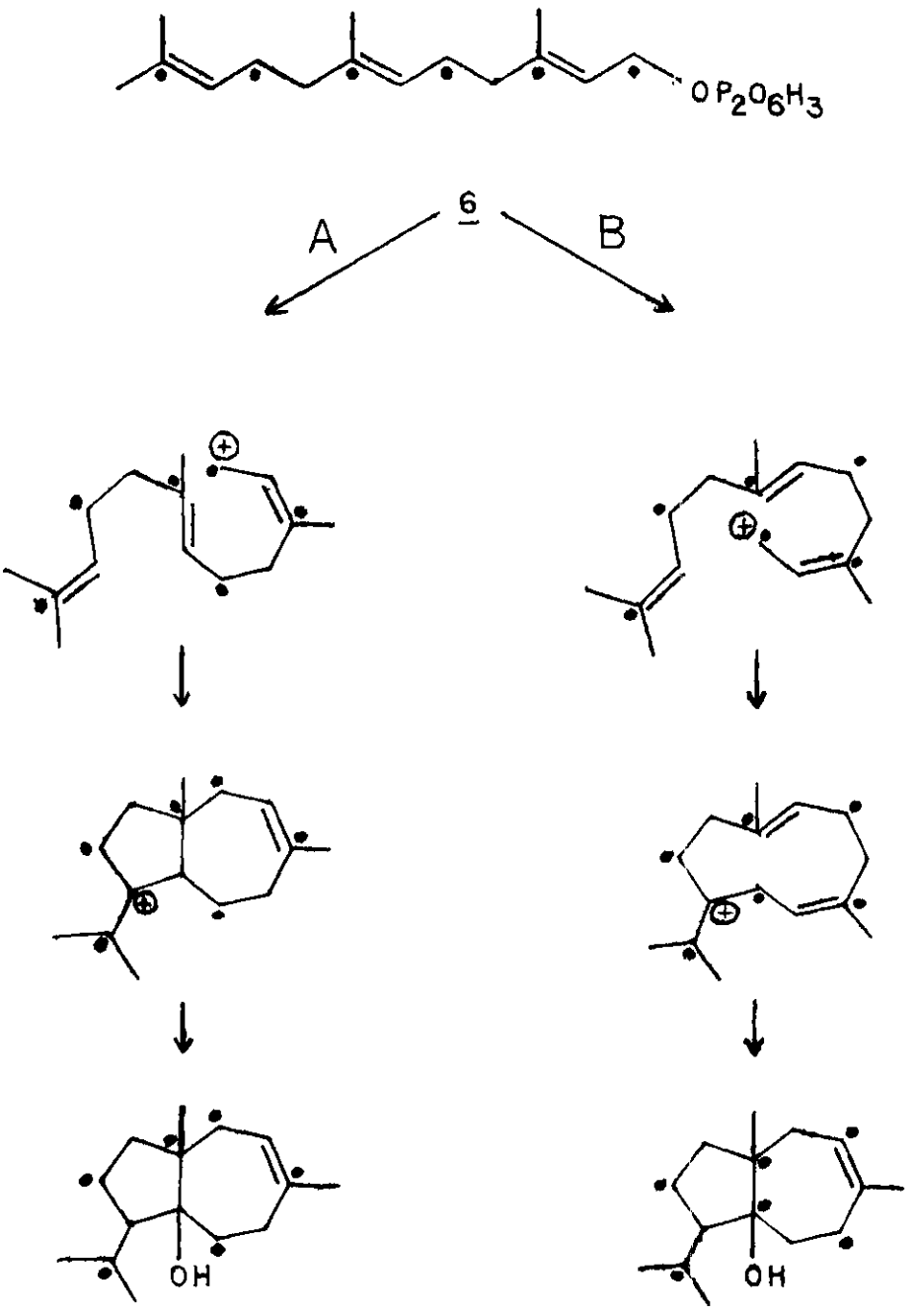
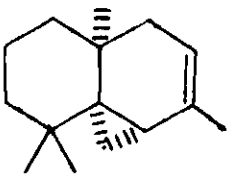


Figure 1. Postulated Biogenesis of Carotol[14]

naturally occurring compounds. Biogenesis may occur via some cyclized sesquiterpene skeleton instead of directly from farnesyl pyrophosphate as proposed by Soucek.[14] Alternately, the carotane sesquiterpenes could be an intermediate class between farnesyl pyrophosphate and another group of sesquiterpenes. Perhaps a simple biogenetic-type synthesis could be devised.

Only recently has an investigation of this type been carried out on thujopsene (7).[15-18] Thernodynamic stabilities and cation solvation in different acidic media can dramatically influence reaction pathways. A number of the compounds obtained in these studies had already been found to be natural products.[19]



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Reaction of carotane sesquiterpenes under conditions known to produce carbonium ions would most probably lead to an interesting chemical investigation of this atypical sesquiterpene skeleton. More importantly, additional light may be shed on the biogenesis of these compounds as well as their relationships with other sesquiterpenes.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Removal of solvents *in vacuo* was done using a Buchler Instruments rotary evaporator at water aspirator pressure. Low pressure hydrogenations were carried out on a Parr hydrogenation apparatus. Atmospheric hydrogenations were carried out using an apparatus similar to that described by Augustine.[20] Gas chromatographs were obtained on a Hewlett-Packard Model 402 gas chromatograph using a flame ionization detector. Preparative gas chromatography was performed on an F and M Model 400 gas chromatograph fitted with a glass capillary stream splitter. The following GC columns (glass bent into a U-shape) were used:

Column Number	Liquid Phase	Support	Column Size
I	3% SE-30	100/120 Gas Chrom Q	4' x 1/4"
II	3% SE-30	100/120 Gas Chrom Q	6' x 1/4"
III	10% XE-60	60/80 Gas Chrom Q	6' x 1/4"
IV	20% XF-1150	100/120 Chromasorb W	6' x 1/4"

Infrared spectra were recorded using a Perkin-Elmer 237B spectrophotometer with solids in the form of potassium bromide pellets (approximately 3% by weight) and liquids in the form of thin films between sodium chloride plates or in CCl_4 solution. The band at 1601 cm^{-1} of polystyrene film was used as a reference.

All nuclear magnetic resonance spectra were obtained using solutions containing tetramethyl silane as an internal standard. ^{1}H-NMR spectra were obtained using Varian Associates A-60D or T-60A spectrometers. ^{13}C-NMR spectra were obtained using a JEOL PFT-100 Fourier transform spectrometer, and are broad band proton decoupled unless specifically described as off resonance proton decoupled spectra.[21]

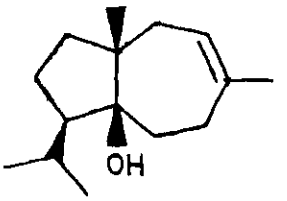
Optical rotatory dispersion curves were obtained using a JASCO ORD/UV-5 spectrophotometer.

CHAPTER III

EXPERIMENTAL

Purification of Carotol (3)

The carotol used in this work was obtained from two sources. A ninety percent pure carotol fraction (bp 80-94/0.1 mm) of carrot seed oil obtained from Magnus, Mabee, and Reynard, Inc., New York, N. Y. was further purified by chromatography on silica gel.



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When all impurities were eluted with hexane (as detected by GC, Col III, 170°C), gas chromatographically pure carotol was obtained in the 25 percent benzene in hexane eluent.

A second batch of carrot seed oil (P. Robertet and Co., Grasse, France) was distilled on a Nester-Faust 36 inch stainless steel spinning band column and the carotol fraction (bp 65-85°C/0.5 mm) redistilled to give pure carotol (bp 73-74°C/0.35 mm).

IR: ν_{neat} (cm^{-1}): 3600, 3500 (O-H).

^{1}H-NMR (δ, $CDCl_3$): 0.95 (1H, s, tertiary methyl); 0.96 (3H, d, J = 6 Hz, isopropyl methyl); 1.02 (3H, d, J = 6 Hz, isopropyl methyl); 1.18 (1H, s, hydroxyl proton); 1.65 (3H, s, olefinic methyl); 5.40 (1H, bm, olefinic proton).

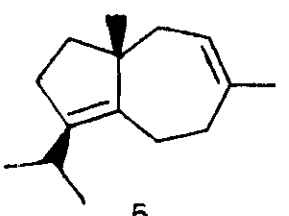
^{13}C-NMR (δ, $CDCl_3$): 84.3 (hydroxyl carbon); 122.2, 138.3 (olefinic carbons).

Mass Spectrum: M^+_{found} = 222 (2%), calculated ($C_{15}H_{26}O$) = 222; base peak m/e = 161.

ORD (c = 3.02, $CDCl_3$): $[\emptyset]_{700}$ = 29.3, $[\emptyset]_{600}$ = 58.3, $[\emptyset]_{589}$ = 74.6 ($[\alpha]^{25}_{589}$ = 33.6), $[\emptyset]_{500}$ = 91.9, $[\emptyset]_{400}$ = 172.7, $[\emptyset]_{350}$ = 246.2, $[\emptyset]_{300}$ = 389.6.

Dehydration of Carotol with $SOCl_2$

A solution of carotol (1.00 g, 4.54 mmol) in dry pyridine (16 ml) was chilled with an ice bath for 15 minutes. To this solution $SOCl_2$ (1.2 ml, 1.9 g, 16.3 mmol) in dry pyridine (16 ml) was added over a period of 10 minutes. The solution was then stirred in the cold for 10 minutes. The yellow solution (containing pyridine hydrochloride crystals) was poured into 20 g of ice and extracted with ether. The extracts were combined, washed with 10 percent HCl until acidic, then with water until neutral, dried over $MgSO_4$, filtered, and ether removed *in vacuo* leaving 0.88 g of yellow oil. GC analysis (Col III, 170°C) showed three products: R_t = 0.8 min (daucene), R_t = 1.0 min (acoradiene **9**), R_t = 1.1 min (acoradiene **10**). At 125°C, however, a fourth product was observed: R_t = 3.1 min (daucene, 65%), R_t = 4.2 min (unidentified, 3.5%), R_t = 4.6 min (acoradiene **9**, 11%), R_t = 5.2 min (acoradiene **10**, 20.5%). Chromatography of this mixture on 25 percent silver nitrate-silica gel eluting with distilled olefin free pet ether (30-50) gave three main fractions (in order of elution): 76 percent pure acoradiene **9**, a 10:1 mixture of daucene and acoradiene **10**, and finally pure daucene, which showed the following spectral properties, identical to those reported



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in the literature.[7]

IR: ν_{neat} (cm^{-1}): 3030, 830 (olefinic C-H).

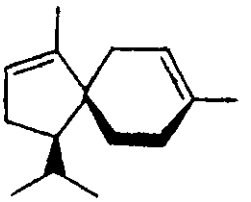
^{1}H-NMR (δ, $CDCl_3$): 0.90 (3H, d, J = 6 Hz); 0.90 (3H, s, tertiary methyl); 1.00 (3H, d, J = 6 Hz); 1.40-2.90 (11H, complex); 5.47 (1H, m, olefinic proton).

^{13}C-NMR (δ, $CDCl_3$): 122.8, 138.8, 139.5, 142.0 (olefinic carbons).

Mass Spectrum: M^+_{found} = 204 (7.4%), calculated ($C_{15}H_{24}$) = 204; base peak m/e = 161.

ORD (c = 2.92, $CHCl_3$): $[\phi]_{700}$ = 62.9, $[\phi]_{600}$ = 66.3, $[\phi]_{589}$ = 69.0 ($[\alpha]^{25}_{589}$ = 34.2), $[\phi]_{500}$ = 94.3, $[\phi]_{400}$ = 150.2, $[\phi]_{350}$ = 178.1, $[\phi]_{300}$ = 337.3.

Acoradiene 9, obtained 70 percent pure (GC Col I, 130°C) by column chromatography on 25 percent silver nitrate-silica gel (1 g mixture to 100 g absorbant) and then isolated 98 percent pure by preparative gas chromatography (Col II, 108°C).



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The NMR, IR, ORD, and mass spectrum of this material were identical to those obtained with an authentic sample.

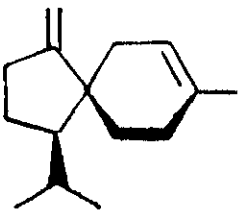
IR: ν_{neat} (cm^{-1}): 3035, 3020, 805, 795 (olefinic C-H).

^{1}H-NMR (δ, $CDCl_3$): 0.80 (3H, d, J = 6.0 Hz); 0.90 (3H, d, J = 6.0 Hz); 1.57 (6H, s, olefinic methyls); 1.40-2.20 (12H, complex); 5.30, 5.37 (1H each, olefinic protons).

Mass Spectrum: M^+_{found} = 204 (13%), calculated ($C_{15}H_{24}$) = 204; base peak m/e = 94.

ORD (c = 1.51, CH_3OH): $[\phi]_{700}$ = -27.0, $[\phi]_{600}$ = -33.4, $[\phi]_{589}$ = -33.8 ($[\alpha]^{25}_{589}$ = -16.3), $[\phi]_{500}$ = -60.8, $[\phi]_{400}$ = -141.8, $[\phi]_{350}$ = -249.9, $[\phi]_{300}$ = -540.4.

Acoradiene 10, obtained 50 percent pure (GC Col I, 130°C) by column chromatography on 25 percent silver nitrate-silica gel (1 g mixture to 100 g absorbant) and then isolated 99 percent pure by preparative gas chromatography (Col II, 140°C), showed the following spectral properties.



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IR: ν_{neat} (cm^{-1}): 1640, 885 (olefinic C-H).

^{1}H-NMR (δ, $CDCl_3$): 0.84 (3H, d, J = 6.0 Hz); 0.94 (3H, d, J = 6.0 Hz); 1.65 (3H, s); 1.15-2.70 (12H, complex); 4.79 (2H, m, olefinic protons); 5.41 (1H, m, olefinic proton).

Mass Spectrum: M^+_{found} = 204 (20%), calculated ($C_{15}H_{24}$) = 204; base peak m/e = 161; exact mass determination 204.187 ± 0.004, calculated exact mass 204.188.

ORD (c = 1.35, CH_3OH): $[\phi]_{700}$ = 34.0, $[\phi]_{600}$ = 52.9, $[\phi]_{589}$ = 55.9 ($[\alpha]^{25}_{589}$ = 27.4), $[\phi]_{500}$ = 86.9, $[\phi]_{400}$ = 162.4, $[\phi]_{350}$ = 256.9, $[\phi]_{300}$ = 460.9.

Attempted Dehydration of Carotol with $POCl_3$

A solution of carotol (1.00 g, 4.5 mmol) in pyridine (4.0 ml) was flushed with nitrogen for 10 minutes, then chilled with an ice bath. To this solution was added by syringe $POCl_3$ (0.82 ml, 1.4 g, 9.0 mmol). The solution was stirred under nitrogen three hours at 0°C. The solution

became dark orange but no new peaks were observed by GC (Col III, 170°C). The solution was allowed to come to room temperature then stirred 89 hours while the reaction was followed by GC. Only a small amount of several low retention time products was observed. The solution was poured into ice (10 g) and extracted with ether. The extracts were combined, washed with 10 percent HCl until acidic, then with water until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo leaving 0.95 g of yellow oil shown to be 90 percent pure carotol by GC (Col III, 170°C). This oil was chromatographed on silica gel eluting with 10 percent benzene in hexane. A small amount of two compounds showing GC retention times identical to daucene (5) and acoradiene 9 were eluted first, followed by the major product. The IR and NMR spectra of this compound were identical to those of the starting material, carotol.

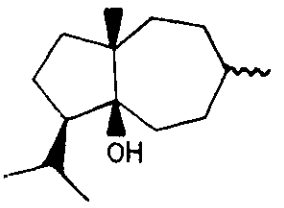
Dehydration of Carotol with Methanesulfonyl Chloride

A stream of nitrogen was passed over a solution of carotol (210 mg, 0.95 mmol) in dry pyridine (4 ml) for 20 minutes. To this solution was added by syringe, methanesulfonyl chloride (0.08 ml, 120 mg, 0.95 mmol). After stirring 28 hours at room temperature, GC analysis (Col III, 170°C) showed only carotol. Enough methanesulfonyl chloride (0.72 ml, 1.06 g, 9.3 mmol) was added to make a ten-fold excess and stirring continued under nitrogen 19 hours. Again no change in the GC trace was observed. The solution was then refluxed 25 hours, causing it to become very dark. Analysis by GC showed four new peaks. Column III, 170°C: R_t = 0.8 min (daucene, 41%), R_t = 1.0 min (acoradiene 9, 20%), R_t = 1.1 min (acoradiene 10, 10%), R_t = 3.0 min (unidentified, 5%), R_t = 3.5 min (carotol 24%);

Column I, 141°C: R_t = 1.5 min (daucene), R_t = 2.0 min (acoradiene 9), R_t = 2.2 min (acoradiene 10); Column IV, 108°C: R_t = 4.0 min (daucene), R_t = 8.8 min (unidentified), R_t = 10.7 min (acoradiene 9), R_t = 12.1 min (acoradiene 10).

4,7-Dimethyl-10-isopropylbicyclo [5.3.0] decanol (14) or Dihydrocarotol[2]

A stirred solution of carotol (3.0 g, 13.5 mmol) in glacial acetic acid (35 ml) containing 243 mg of 83.4 percent PtO_2 was hydrogenated at atmospheric pressure (740 mm) and 22°C.



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After two hours uptake of hydrogen ceased with 415 cc having been consumed. The solution was filtered through Celite 545 and most of the acetic acid removed in vacuo. The remaining liquid was taken up in ether and washed with saturated $KHCO_3$ until basic. The ether solution was then washed with water until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo. The yellow oil thus obtained was distilled under vacuum (68-69°C/0.075 mm) giving 2.75 g (91%) of colorless epimeric dihydrocarotol.

IR: ν_{neat} (cm^{-1}): 3610, 3515 (O-H).

^{1}H-NMR (δ, $CDCl_3$): 0.88-1.03 (9H, overlapping multiplet); 1.00 (3H, s); 1.25 (1H, s, hydroxyl proton); 1.30-2.10 (15H, complex).

^{13}C-NMR (δ, $CDCl_3$): 83.8, 87.8 (hydroxyl carbons-one signal for each epimer).

Mass Spectrum: M^+_{found} = 224 (2%), calculated ($C_{15}H_{28}O$) = 224;

base peak m/e = 163.

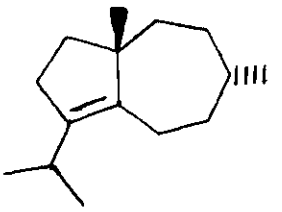
Analysis ($C_{15}H_{28}O$): calculated: C 80.36, H 12.50

found: C 80.34, H 12.50.

Dehydration of Dihydrocarotol with $SOCl_2$

A solution of $SOCl_2$ (2.0 ml, 3.2 g, 27.1 mmol) in dry pyridine (15 ml) was added dropwise over a period of 15 minutes to a solution of dihydrocarotol (1.00 g, 4.46 mmol) in dry pyridine (15 ml) which had been chilled by an ice bath. Stirring was continued 15 minutes after complete addition. The yellow solution containing pyridine hydrochloride crystals was then poured into 10 g of ice/water and extracted with ether. The extracts were combined, washed with 10 percent HCl until acidic, then with water until neutral, dried with $MgSO_4$, filtered, and solvent removed in vacuo leaving 0.92 g (95%) of a pale yellow oil. Analysis of this oil by GC (Col III, 170°C) showed three products: R_t = 0.6 min (28%), R_t = 0.7 min (51%), and R_t = 1.0 min (21%). Chromatography of this oil on 25 percent silver nitrate-silica gel (1 g mixture to 100 g absorbant) eluting with distilled olefin free pet ether (30-60) gave three main fractions (in order of elution): pure minor epimer 16, pure major epimer 15, and a 1:5 mixture of major epimer and olefin 17.

The minor epimer 16 of dehydrodihydrocarotol was isolated as a colorless oil (bp 50-51°C/0.07 mm) and showed the following spectral properties.



16

IR: ν_{neat} (cm^{-1}): 1445 (s), 1360 (m), 1345 (m), 1175 (w), 1100 (w), 1060 (w), 1010 (w), 970 (w).

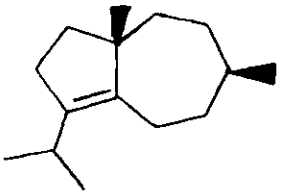
^{1}H-NMR (δ, $CDCl_3$): 0.87 (3H, s, tertiary methyl); 0.88 (3H, d, J = 6 Hz); 1.03 (3H, d, J = 6 Hz); 0.86-0.97 (3H, overlapping multiplet); 1.20-3.00 (14H, complex).

^{13}C-NMR (δ, $CDCl_3$): 139.8, 142.9 (olefinic carbons).

Mass Spectrum: M^+_{found} = 206 (13%), calculated ($C_{15}H_{26}$) = 206; base peak m/3 = 163.

Analysis ($C_{15}H_{26}$): calculated: C 87.37, H 12.63
found: C 87.35, H 12.62.

The major epimer (15) of dehydrodihydrocarotol was also isolated as a colorless oil (bp 50-51°C/0.07 mm) and showed the following spectral properties.



15

IR: ν_{neat} (cm^{-1}): 1540 (s), 1365 (m), 1345 (m), 1080 (w), 1035 (w), 1000 (w), 980 (w).

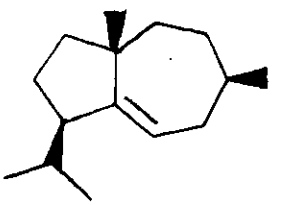
^{1}H-NMR (δ, $CDCl_3$): 0.92 (3H, d, J = 6 Hz); 0.97 (3H, d J = 6 Hz); 0.93 (3H, s, tertiary methyl); 0.92-0.98 (3H, overlapping multiplet).

^{13}C-NMR (δ, $CDCl_3$): 139.7, 140.9 (olefinic carbons).

Mass Spectrum: M^+_{found} = 206 (10%), calculated ($C_{15}H_{26}$) = 206; base peak m/e = 163.

Analysis ($C_{15}H_{26}$): calculated: C 87.37, H 12.63
found: C 87.34, H 12.63.

Olefin 17 was obtained pure by chromatography of the mixture of olefin 17 and major epimer 15 on 25 percent silver nitrate-silica gel (1 g mixture to 100 g absorbant).



17

Pure olefin 17 was obtained as a colorless oil (bp 54-55°C/0.05 mm) and showed the following spectral properties.

IR: ν_{neat} (cm^{-1}): 810 (olefinic C-H).

^{1}H-NMR (δ, $CDCl_3$): 0.88 (3H, s, tertiary methyl); 0.70-0.98 (9H, overlapping multiplets); 1.10-2.70 (13H, complex); 5.40 (1H, m, olefinic proton).

^{13}C-NMR (δ, $CDCl_3$): 118.0, 153.9 (olefinic carbons).

Mass Spectrum: M^+_{found} = 206 (8%), calculated ($C_{15}H_{26}$) = 206; base peak m/e = 163.

Analysis ($C_{15}H_{26}$): calculated: C 87.37, H 12.63
found: C 87.33, H 12.65.

Reaction of Olefins 15, 16, and 17 with HCO_2H

Approximately 10 mg of each olefin was stirred magnetically in 0.5 ml of 90 percent HCO_2H. Each reaction was followed by gas chromatography (Col I, 130°C) for 20 hours. No change was observed in the GC trace of major epimer 15 or minor epimer 16. (These two reactions were repeated at a later date. No reaction was found after stirring in HCO_2H for 30 days.) After one hour the GC trace of the solution containing olefin 17 showed 15 percent conversion to major epimer 15.

In order to confirm product identification, the reaction was repeated using 98 mg (0.475 mmol) of olefin 17 and five ml of 90 percent HCO_2H. After stirring 19 hours at room temperature, five ml of water were added and the cloudy solution extracted with ether. The extracts were combined, washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, filtered and the solvent removed in

vacuo leaving 80 mg of colorless oil. The GC trace of this oil showed 73 percent major epimer 15, 7 percent unidentified, and 20 percent unreacted starting material. Chromatography of this mixture on 25 percent silver nitrate-silica gel eluting with distilled olefin free petroleum ether (30-60) yielded 98 percent pure major epimer 15. Spectral properties (IR and NMR) of this oil were identical to those of authentic material prepared by dehydration of dihydrocarotol.

One Hour Reaction of Dihydrocarotol (14) with HCO_2H

A solution of dihydrocarotol (100 mg, 0.45 mmol) in 90 percent HCO_2H (5 ml) was stirred one hour at room temperature. A GC trace (Col I, 170°C) obtained after 20 minutes showed the presence of three components and no starting material. The solution was stirred an additional 40 minutes, then poured onto several grams of ice and extracted with ether. The ether extracts were combined, washed with saturated $KHCO_3$ until basic, then with H_2O until neutral, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give 82 mg (95%) of a pale yellow oil. This oil was shown to be composed of olefin 16 (25%), olefin 15 (70%), and olefin 17 (5%) by comparison of GC retention times at 132°C with those of authentic material: Col I: R_t = 2.6 min (16), R_t = 3.0 min (15), R_t = 3.9 min (17); Col III: R_t = 3.4 min (16), R_t = 4.0 min (15), R_t = 5.7 min (17); Col IV: R_t = 3.6 min (16), R_t = 4.2 min (15), R_t = 6.4 min (17).

Reaction of Daucene (5) with m-Chloroperbenzoic Acid

A solution of m-chloroperbenzoic acid (208 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred chilled (ice bath) solution of daucene (205 mg, 1 mmol) in CH_2Cl_2 (5 ml). After 45 minutes no peracid

was detected (starch-iodide paper) and the solution contained a large amount of white precipitate. The solution was stirred an additional 15 minutes, allowed to warm to room temperature, washed with saturated $KHCO_3$ until basic, then with H_2O until neutral. The CH_2Cl_2 layer was dried with $MgSO_4$, filtered, and solvent removed in vacuo leaving 185 mg of yellow oil. Four products were observed by GC (Col III, 170°C): R_t = 3.8 min (41%), R_t = 4.2 min (23%), R_t = 13.4 min (8.5%), R_t = 16.0 min (22%). Chromatography of this mixture on silica gel (18 g) separated the first pair of compounds (90 mg, 30% benzene/hexane eluent):

IR: ν_{neat} (cm^{-1}): 1725 (s), 1285 (s), 1270 (s), 1120 (m), 1075 (m), 820 (m).

^{1}H-NMR (δ, $CDCl_3$): 0.85-1.15 (overlapping multiplets), 1.35 (m), 1.80 (m), 4.22 (s), 4.30 (s), 5.43 (m).

Mass Spectrum: M^+_{found} = 210 (10%), calculated ($C_{15}H_{24}O$) = 210; base peak m/e = 124.

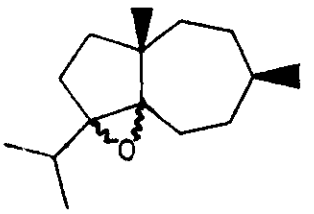
The second pair of compounds (72 mg) was eluted with 20 percent ether-benzene. This mixture (presumably the diepoxides) solidified upon standing at room temperature overnight. No further chromatographic separation was obtained.

IR: ν_{neat} (cm^{-1}): 1450 (s), 1385 (w), 1100 (w), 1080 (w), 1065 (w), 1055 (w), 1020 (w), 1010 (w), 965 (w), 920 (w), 890 (w), 870 (w), 865 (w), 850 (w), 845 (w).

^{1}H-NMR (δ, $CDCl_3$): 1.05 (3H, overlapping multiplets); 1.38 (3H, s); 2.8 (1H, d of d, J = 7.5 Hz, J = 8.0 Hz).

Mass Spectrum: M^+_{found} = 236 (8%), calculated ($C_{15}H_{24}O_2$) = 236; base peak m/e = 43.

Epoxidation of Olefin 15



A solution of 85 percent m-chloroperbenzoic acid (640 mg, 3.72 mmol) in CH_2Cl_2 (20 ml) was added dropwise over a period of 10 minutes to a chilled (ice bath) solution of olefin 15 (500 mg, 2.43 mmol) in CH_2Cl_2 (20 ml). No peracid was detected by starch-iodide paper after stirring 0.5 hour. The solution was stirred an additional 15 minutes and allowed to warm to room temperature. The solution was then washed with saturated $KHCO_3$ until basic, with H_2O until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a colorless oil (497 mg, 93%). The GC trace (Col III, 170°C) of this oil showed two peaks in a 2:1 ratio. Separation of these two components could not be achieved by column chromatography on silica gel, acid washed, neutral, or basic alumina.

IR: ν_{neat} (cm^{-1}): 1450 (s), 1380 (m), 1015 (m), 980 (w), 960 (w), 940 (w), 920 (w), 890 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.85-1.15 (12H, overlapping multiplets).

^{13}C-NMR (δ, $CDCl_3$): 72.4 (C-O), 74.7 (C-O).

Mass Spectrum: M^+_{found} = 222 (13%), calculated ($C_{15}H_{24}O$) = 222; base peak m/e = 43. Exact mass m/e 222: found: 222.196 ± 0.004, calculated: 222.198.

Reaction of Epoxides of Olefin 15 with HCO_2H

A solution of the epoxides of olefin 15 (156 mg, 0.70 mmol) in 90 percent HCO_2H (6 ml) containing dioxane (1.0 ml) and H_2O (0.1 ml) was

stirred at room temperature. The composition of the reaction mixture was found by GC (Col I, 170°C) to remain constant after three minutes. The solution was stirred two hours, H_2O added and the mixture extracted with ether. The ether extracts were combined, washed with saturated $KHCO_3$ until basic, then with H_2O until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a yellow oil (118 mg). GC analysis (Col I, 126°C) of this oil showed three major components: R_t = 3.7 min (45%), R_t = 4.1 min (30%), R_t = 4.4 min (10%). These compounds were separated from the four minor components in the mixture by column chromatography on silica gel (hexane eluent) and showed the following spectral properties (as a mixture):

IR: ν_{neat} (cm^{-1}): 1445 (s), 1375 (m), 1355 (m), 990 (w), 925 (w), 885 (w), 850 (w), 815 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.80-1.10 (complex multiplet), 1.50 (m), 2.1 (m), 5.5 (m), 5.85 (m).

Reaction of Epoxides of Olefin 15 with $SnCl_4$

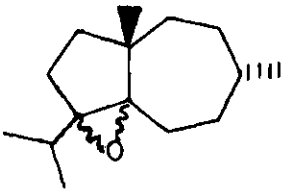
To a chilled (ice bath) solution of the epoxides of olefin 15 (100 mg, 0.45 mmol) in anhydrous benzene (10 ml) was added by syringe $SnCl_4$ (0.2 ml, 0.47 g, 1.8 mmol). The solution was allowed to warm to room temperature and stirred two hours. Ice water (5 g) was added and the mixture extracted with benzene. The benzene extracts were combined, washed with H_2O, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo left a viscous yellow oil (112 mg). GC analysis (Col III, 170°C) of this oil showed 14 products, two of which (R_t = 2.7 min and R_t = 3.0 min) made up about 85 percent of the mixture. No starting material was

present as detected by GC, after 10 minutes reaction time.

IR: ν_{neat} (cm^{-1}): 1450 (s), 1445 (m), 1375 (m), 1100 (w), 1030 (w), 925 (w), 890 (w), 850 (w).

^{1}H-NMR (δ, $CDCl_3$): Complex spectrum containing no signals below 2 ppm.

Epoxidation of Olefin 16



The procedure used in this case was identical to that used for epoxidation of olefin 15, above. Epoxidation of olefin 16 (400 mg, 1.94 mmol) in CH_2Cl_2 (15 ml) with m-chloroperbenzoic acid (510 mg, 2.52 mmol) gave a colorless oil (256 mg, 83%) shown to contain two epoxides in a 1:1 ratio. The reaction mixture was stirred three hours before the peroxide test (starch-iodide paper) was negative.

IR: ν_{neat} (cm^{-1}): 1450 (s), 1380 (m), 1010 (m), 980 (w), 985 (m), 960 (m), 940 (w), 920 (w), 885 (w), 860 (w), 855 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.85-1.20 (12H, overlapping multiplets).

^{13}C-NMR (δ, $CDCl_3$): 75.0, 75.4 (C-O).

Mass Spectrum: M^+_{found} = 222 (20%), calculated ($C_{15}H_{24}O$) = 222; base peak m/e = 43. Experimental exact mass mass: 222.196 ± 0.004, calculated exact mass: 222.198.

Reaction of Epoxides of Olefin 16 with HCO_2H

A solution of epoxides of olefin 16 (244 mg, 1.1 mmol) in 90 percent HCO_2H (8 ml) containing dioxane (1.5 ml) and H_2O (0.2 ml) was stirred

at room temperature. The reaction was followed by GC (Col I, 170°C) and found to be essentially complete after 10 minutes. Stirring was continued for 15 hours then H_2O (8 ml) was added. The solution was extracted with ether, the extracts combined, washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo leaving a yellow oil (220 mg) shown by GC (Col I, 108°C) to contain six major components: R_t = 4.3 min (5%), R_t = 5.7 min (25%), R_t = 6.1 min (35%), R_t = 7.7 min (20%), R_t = 8.5 min (35%), R_t = 10.0 min (10%). This oil was chromatographed on silica gel (20 g) eluting with hexane. The first fraction eluted contained the first five components of the mixture:

IR: ν_{neat} (cm^{-1}): 1455 (s), 1375 (m), 820 (w).

^{1}H-NMR (δ, $CDCl_3$): 5.2-5.9 (bm), 5.9 (m), 6.0 (m).

The second fraction eluted contained component 6 (R_t = 10.0 min) which showed the following spectral properties:

IR: ν_{CCl_4} (cm^{-1}): 1450 (s), 1380 (m), 1375 (m), 1365 (m), 1190 (w), 1015 (w), 990 (w), 975 (w), 885 (m), 870 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.88 (3H, s), 0.90 (3H, d, J = 6 Hz), 0.95 (3H, d, J = 6 Hz), 5.28 (1H).

Reaction of Epoxides of Olefin 16 with $SnCl_4$

To a chilled (ice bath) solution of epoxides of olefin 16 (9.8 mg, 0.05 mmol) in anhydrous benzene (10 ml) was added by syringe $SnCl_4$ (0.02 ml, 0.04 g, 0.15 mmol). The solution was allowed to warm to room temperature and stirred 48 hours. No starting material was observed by GC (Col III, 170°C) after two minutes reaction. The composition of the mix-

ture did not appear to change after 12 minutes reaction time. At least a dozen volatile products were observed by GC; three of those made up about 70 percent of the mixture: R_t = 1.3 min, R_t = 1.6 min, R_t = 2.0 min.

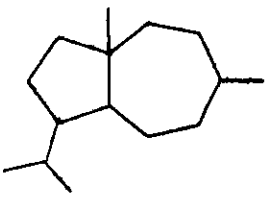
Attempted Hydrogenation of Daucene (5)

A solution of daucene (175 mg, 0.86 mmol) and 83.5 percent PtO_2 (10 mg) in ethyl acetate (5 ml) was stirred under hydrogen at 23°C and 740 mm pressure. After three hours uptake of hydrogen ceased with 25 cc having been consumed (theory requires 43 cc), the solution was then filtered through a Celite 545 pad. The solvent was removed from the filtrate *in vacuo* leaving a pale yellow oil (156 mg, 89%). This oil was shown by GC at 132°C to contain a 1:1 mixture of olefins 15 and 16 obtained from dehydration of dihydrocarotol (14): Col I: R_t = 2.6 min (16), R_t = 3.0 min (17); Col III: R_t = 3.6 min (16), R_t = 4.2 min (17); Col IV: R_t = 3.4 min (16), R_t = 4.0 min (17). This oil was taken up in ethyl acetate (5 ml) and hydrogenation attempted at three atmospheres in the presence of 83.4 percent PtO_2 (10 mg). After shaking 23 hours at room temperature, the reaction was worked up as before. The GC trace obtained under the conditions above showed only starting material in the oil (143 mg) obtained. A final hydrogenation of daucene (220 mg) at three atmospheres was attempted in ethanol (4 ml) containing concentrated HCl (2 drops) and 10 percent Pd/charcoal (15 mg). This solution was shaken 24 hours at room temperature then worked up as before. The colorless oil (215 mg, 96% based on $C_{15}H_{26}$) obtained was found by comparison of GC (Col I, 130°C) retention time with those of authentic samples to be

33 percent major epimer 15, 53 percent minor epimer 16, and 14 percent daucane 18.

Carotane or Daucane (18)[3b]

Carotol (520 mg, 2.34 mmol) in glacial HOAc (5 ml) was stirred at room temperature (22°C) for six days under hydrogen at atmospheric pressure (740 torr) in the presence of 10 percent Pd on charcoal (104 mg). After three hours 75 cc of hydrogen had been absorbed (theory requires 59 cc for one double bond). The rate of absorption then decreased. After six days uptake of hydrogen had ceased with 140 cc having been consumed (theory requires 117 cc). The solution was then filtered through a celite pad and the pad washed with ether (3 x 10 ml). The filtrate was washed with water (3 x 10 ml) then with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, filtered and solvent removed *in vacuo* leaving 465 mg (95%) of colorless oil, bp 44-45°C/0.02 mm. Spectral properties of this oil (98% pure by GC, Col I, 130°C) were identical to those reported.[3b]



18

IR: ν_{neat} (cm^{-1}): 1455 (s), 1380 (m), 1370 (w), 1160 (w), 1080 (w), 1020 (w), 960 (w), 940 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.75-1.00 (9H, overlapping multiplets), 0.93 (3H, s, tertiary methyl), 1.2-1.8 (16H, bs).

Mass Spectrum: M^+_{found} = 208 (23%), calculated ($C_{15}H_{28}$) = 208, base peak m/e = 95.

Analysis ($C_{15}H_{28}$): calculated: C 86.54, H 13.46

found: C 86.49, H 13.47.

Three Hour Reaction of Carotol (3) with HCO_2H

A solution of carotol (97 mg, 0.43 mmol) in 90 percent HCO_2H (4 ml) was stirred three hours at room temperature. Ether was added and the solution washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo. The yellow oil (49 mg) remaining was shown by GC analysis to be composed of six main products. The major components of these six were found to be daucene 5 (40%) and acoradiene 9 (25%) by comparison of GC retention times at 132°C: Col I: R_t = 3.0 min (5), R_t = 3.9 min (9); Col III: R_t = 4.5 min (5), R_t = 6.5 min (9); Col IV: R_t = 4.8 min (5), R_t = 7.5 min (9).

Five Day Reaction of Carotol and HCO_2H

A solution of carotol (1.68 g, 7.4 mmol) in 90 percent HCO_2H (100 ml) was stirred for five days at room temperature. Ether (100 ml) was added and the solution washed with water (3 x 100 ml). The ether layer was washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$ and filtered. Removal of the solvent in vacuo gave 1.45 g of yellow oil. GC analysis (Col I, 170°C) of this oil showed four major components which were separated by chromatography of the mixture on silica gel (140 g). Fraction one (hexane eluate) was shown by GC to contain two components (116 mg). Fraction two (50 percent hexane-benzene eluent) was shown to contain 112 mg of 98 percent pure (GC, Col I, 130°C) 24, bp 44-47°C/0.12 mm (hot box). The following spectral properties were

observed for ether 24:

IR: ν_{neat} (cm^{-1}): 1110, 1040 (ether).

^{1}H-NMR (δ, $CDCl_3$): 0.73 (3H, s); 0.85 (3H, d, J = 6 Hz); 1.13 (3H, d, J = 6 Hz); 1.22 (3H, s); 1.30-2.60 (14H, complex).

^{13}C-NMR (δ, $CDCl_3$): 77.3, 92.8 (ether carbons); 44.0, 77.3, 92.8 (quaternary carbons).

Mass Spectrum: M^{+}_{found} = 222 (43%), calculated ($C_{15}H_{26}O$) = 222; base peak m/e = 179.

ORD (c = 3.39, $CHCl_3$): $[\phi]_{700}$ = -27.9°, $[\phi]_{600}$ = -33.6°, $[\phi]_{589}$ = -39.1° ($[\alpha]_{589}$ = -17.6°), $[\phi]_{500}$ = -50.3°, $[\phi]_{400}$ = -89.5°, $[\phi]_{300}$ = -195.7°.

Analysis ($C_{15}H_{26}O$): calculated: C 81.08, H 11.71, P 7.21

found: C 81.04, H 11.73, P 7.23.

Fraction three (50 percent hexane-benzene eluent) contained 392 mg of 95 percent pure (GC Col I, 130°C) 26, bp 83-87°C/0.1 mm (hot box). The following spectral properties were observed for 26:

IR: ν_{neat} (cm^{-1}): 1730 (C=O), 1180, 1150 (C-O).

^{1}H-NMR (δ,$CDCl_3$): 0.83 (3H, s); 0.97 (3H, s); 0.98 (3H, d, J = 7 Hz); 1.07 (3H, d, J = 7 Hz); 8.13 (1H, s).

^{13}C-NMR (δ, $CDCl_3$): 101.1 (C-O), 160.2 (HCO_2^{-}), 45.9, 50.0, 618, 101.1 (quaternary carbons).

Mass Spectrum: M^{+} not observed, calculated = 250, M^{+}-HCO_2H = 204 (34%), base peak m/e = 161.

ORD (c = 4.52, $CHCl_3$): $[\phi]_{700}$ = 48.9°, $[\phi]_{600}$ = 66.4°, $[\phi]_{589}$ = 71.9° ($[\alpha]_{589}$ = 28.8°), $[\phi]_{500}$ = 99.5°, $[\phi]_{400}$ = 176.9°, $[\phi]_{300}$ = 365°.

Analysis ($C_{16}H_{26}O_2$): calculated: C 76.80, H 10.40, O 12.80

found: C 76.83, H 10.41, O 12.76.

Fraction four (50 percent hexane-benzene eluent) contained 313 mg of 98 percent pure (GC Col I, 130°C) 25, mp 46-47°C. The following spectral properites were observed:

IR: ν_{KBr} (cm^{-1}): 3450 (O-H), 1070, 1020 (C-O).

^{1}H-NMR (δ, $CDCl_3$): 0.85 (3H, s); 0.93 (3H, s); 1.02 (3H, d, J = 7 Hz); 1.15 (3H, d, J = 7 Hz); 1.42 (1H, m, O-H).

^{13}C-NMR (δ, $CDCl_3$): 91.7 (hydroxyl carbon); 47.4, 48.5, 60.2, 91.7 (quaternary carbons).

Mass Spectrum: M^+_{found} = 222 (6%), calculated ($C_{15}H_{26}O$) = 222, base peak m/e = 179.

ORD (c = 5.67, $CHCl_3$): $[\emptyset]_{700}$ = 43.1°, $[\emptyset]_{600}$ = 52.9°, $[\emptyset]_{589}$ = 54.8° ($[\alpha]_{589}$ = 24.7°), $[\emptyset]_{500}$ = 78.3°, $[\emptyset]_{400}$ = 137°, $[\emptyset]_{300}$ = 301.1°.

Analysis ($C_{15}H_{26}O$): calculated: C 81.08, H 11.71, O 7.21

found: C 81.28, H 11.75, O 6.97.

Fraction one was rechromatographed on 25 percent silver nitrate-silica gel (10 g). Olefin 22 (69 mg; bp 42-45°C/0.05 mm, hot box) was eluted 98 percent pure (GC Col I, 110°C) with distilled olefin free pet ether (30-50) and showed the following spectral properties:

IR: ν_{neat} (cm^{-1}): 810 (trisubstituted olefin).

^{1}H-NMR (δ, $CDCl_3$): 0.72 (3H, d, J = 6 Hz); 0.90 (3H, d, J = 6 Hz); 1.00 (3H, s); 1.62 (3H, m); 5.07 (1H, m).

^{13}C-NMR (δ, $CDCl_3$): 116.2, 142.4 (olefinic carbons, s and d respectively, in off resonance decoupled spectrum), 52.5 (quaternary carbon).

Mass Spectrum: M^+_{found} = 204 (35%), calculated ($C_{15}H_{24}$) = 204; base peak

m/e = 123.

ORD (c = 3.01, $CHCl_3$): $[\phi]_{700}$ = 54.3°, $[\phi]_{600}$ = 74.5°, $[\phi]_{589}$ = 81.2° ($[\alpha]_{589}$ = 39.8°), $[\phi]_{500}$ = 122.0°, $[\phi]_{400}$ = 210.1°, $[\phi]_{300}$ = 576.1°.

A second fraction (pet ether eluate) contained several milligrams of a mixture of olefins 22 and 23. A third fraction (benzene eluate) contained 7 mg of 95 percent pure (GC Col I, 110°C) olefin 23 which showed the following spectral properties:

IR: ν_{CCl_4} (cm^{-1}): 1445 (s), 1370 (m), 1145 (w), 1110 (w), 1095 (w), 1020 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.83 (3H, s); 0.95 (3H, s); 1.58 (6H, m); 2.30 (1H, m); 2.78 (1H, m).

Mass Spectrum: M^+_{found} = 204 (100%), calculated ($C_{15}H_{24}$) = 204; experimental exact mass = 204.190 ± 0.004, calculated = 204.187.

Reaction of Olefin 22 with HCO_2H

A solution of olefin 22 (4 mg) in 90 percent HCO_2H (0.5 ml) was agitated at room temperature and the reaction followed by GC (Col I, 170° C) for a period of 30 days. A single peak (corresponding to starting material) was observed in the GC trace until 21 hours reaction, at which time a small shoulder was noticed on the side of this peak. The shoulder, corresponding to olefin 23, and starting olefin 22 remained in a 2:1 ratio for 70-145 hours reaction time. After 289 hours, the composition of the mixture was (Col I, 119°C): olefin 22 (58%), olefin 23 (41%), and alcohol 25 (1%).

Reaction of Ether 24 with HCO_2H

A solution of ether 24 (5 mg) in 90 percent HCO_2H (0.5 ml) was agitated at room temperature for 30 days. The reaction was followed by GC (Col I, 119°C). A small amount (2 or 3 percent based on amount of ether 24) of daucene (5) was observed after 21 hours and remained until 144 hours. At 288 hours the composition of the solution was found to be one percent olefin 22, one percent olefin 23, 69 percent ether, 21 percent alcohol 25, and seven percent formate 26.

Reduction of Formate 26 with Lithium Aluminum Hydride

A solution of formate 26 (117 mg, 0.46 mmol) in anhydrous ether (3 ml) was cooled by an ice bath and $LiAlH_4$ (160 mg, 4.20 mmol) added. After stirring 10 minutes the solution was allowed to warm to room temperature. Stirring was continued an additional 50 minutes. Excess $LiAlH_4$ was destroyed by cautious addition of small pieces of ice. The solution was stirred until no gray coloration was observed. The ether layer was separated, washed with water, dried over $MgSO_4$, and filtered. Removal of the solvent *in vacuo* gave 99 mg (95%) of off-white solid, mp 46-47°C. The NMR, IR, and mass spectrum of this solid were identical to those of alcohol 25. A mixed melting point of this alcohol and alcohol 25 showed no depression.

NMR Shift Study of Alcohol 25 Using $Eu(fod)_3$

Alcohol 25 (25.2 mg) was weighed into a small flask and CCl_4 (0.6 ml) added by pipet. The solution was transferred by pipet to an NMR tube, a drop of TMS added, and the NMR spectrum recorded. Approximately 10 mg

of $Eu(fod)_3$ shift reagent was added directly to the NMR tube. The tube was shaken several times to completely dissolve the shift reagent and the spectrum recorded. This procedure was repeated 10 times using the amounts of shift reagent listed in Table 1.

NMR Shift Study of Alcohol 25 Using $Eu(dpm)_3$

A solution of alcohol 25 (20 mg) in CCl_4 (0.7 ml) was prepared and an NMR spectrum recorded. Several drops of a solution of $Eu(dpm)_3$ (20 mg) in CCl_4 (1.3 ml) was added and the NMR spectrum recorded. This procedure was repeated four more times. The signal at δ 0.85 ppm corresponding to a tertiary methyl group was observed to shift downfield as shown in Figure 5 (p. 107).

67 Day Reaction of Carotol (3) with HCO_2H

A solution of carotol (16 mg) in 90 percent HCO_2H (1.0 ml) was agitated at room temperature and the reaction followed by GC (Col I, 170°C). After 10 minutes reaction, the GC trace of a sample obtained directly from the reaction mixture showed a peak with the retention time of daucene corresponding to 90 percent of the volatile components. Peaks corresponding to the known products of this reaction (page 59) were observed at 21 hours. The composition of the solution remained essentially constant after seven days, and at 67 days was found to be olefins 22 and 23 (6%), daucene (5, 1%), ether 24 (3%), alcohol 25 (62%), formate 26 (16%), and four unidentified products (2%). Another experiment (10 mg carotol in 1.0 ml HCO_2H) was followed by GC at 119°C (Col I). The composition of the solution as determined from the GC trace is given in Table 2 (p. 114). The solution became amber colored after several

Table 1. ^{1}H-NMR Shift Study of Alcohol 25/Eu(fod)$_3$ Solutions*

Eu(fod)$_3$		Chemical Shift (δ, ppm)										
wt in mg	moles†	R_p	OH	H	H‡	H	H	H	CH_3	CH_3‡	CH_3‡	CH_3
12.5	0.28	0.25	6.95	---	---	---	---	---	1.53	1.53	1.33	1.20
20.5	0.46	0.40	11.97	---	---	---	---	---	2.20	1.92	1.62	1.52
32.2	0.72	0.64	19.26	6.33	5.60	4.97	4.20	---	3.10	2.43	2.02	1.90
42.1	0.94	0.83	25.00	7.99	6.75	5.97	5.05	4.33	3.82	2.90	2.37	2.23
52.0	1.16	1.03	---	9.58	7.90	7.05	5.90	5.03	4.58	3.43	2.70	2.55
62.5	1.40	1.23	---	11.17	8.88	8.08	6.63	5.70	5.30	3.78	3.03	2.88
77.9	1.74	1.54	---	13.00	10.10	9.10	7.42	6.47	6.05	4.27	3.33	3.18
96.7	2.16	1.91	---	15.13	11.53	10.47	8.40	7.32	6.92	4.83	3.78	3.60
114.4	2.56	2.26	---	16.00	12.50	11.37	9.03	7.90	7.50	5.23	4.07	3.88
130.5	2.92	2.57	---	---	13.02	11.97	9.48	8.32	7.87	5.43	4.23	4.02
150.2	3.36	2.96	---	---	13.58	12.43	9.78	8.45	8.22	5.62	4.35	4.17

*25.2 mg, 1.135 x 10^{-4} moles alcohol 25 in 0.6 ml CCl_4. †Moles x 10^{-4}. ‡Isopropyl group.

hours, but remained homogeneous. This experiment was repeated on the same scale in order to check the abnormal percentages of daucene and formate found at 48 hours. At 45 hours in this reaction, the percentages were found to be in agreement with the general course of the previous reaction: 15 percent daucene and 33 percent formate.

Reaction of Alcohol 25 with $SOCl_2$ in Pyridine

A solution of $SOCl_2$ (0.2 ml, 0.32 g, 2.7 mmol) in pyridine (2 ml) was added dropwise over a 10 minute period to a chilled (ice bath) solution of alcohol 25 (100 mg, 0.45 mmol) in pyridine (2 ml). A pyridine hydrochloride precipitate appeared immediately. The GC trace (Col I, 130°C) of a sample taken directly from this solution showed less than 10 percent reaction. An additional 0.2 ml of $SOCl_2$ in 1.0 ml of pyridine was added dropwise over a five minute period. The solution was stirred an additional 50 minutes after completion of this addition, then poured onto ice (5 g) and extracted with ether. The ether extracts were combined, washed with H_2O until neutral, dried over $MgSO_4$, filtered, and solvent removed *in vacuo*. The yellow oil (78 mg) obtained was shown to contain four products by GC (Col I, 130°C): R_t = 2.4 min (13%), R_t = 3.4 min (43%), R_t = 7.0 min (15%), R_t = 11.0 min (29%). None of these products had retention times corresponding to the olefins obtained in the reaction producing the starting alcohol 25. Mixed injection (under the conditions above) of this mixture and daucene showed the second component to have the same retention time as daucene (R_t = 2.3 min). A mixed injection on Col III (170°C) also indicated the second component of the mixture was daucene: R_t = 1.0 min, R_t = 1.2 min (daucene), R_t = 2.8 min, and R_t = 5.0

min. A mixed injection on Col IV (150°C) however showed the presence of five components, one of which did have the same retention time as daucene: R_t = 2.4 min (13%), R_t = 3.1 min (20%, daucene), R_t = 3.4 min (23%), R_t = 6.9 min (15%), R_t = 10.6 min (29%).

Reaction of Alcohol 25 with $SOCl_2$ in Anhydrous Pyridine

A solution of $SOCl_2$ (0.2 ml, 0.32 g, 2.7 mmol) in freshly distilled anhydrous pyridine[22] (2 ml) was added dropwise to a previously chilled (ice bath) solution of alcohol 25 (98 mg, 0.45 mmol) in anhydrous pyridine (2 ml). No precipitate had appeared after stirring 40 minutes. The GC trace (Col I, 130°C) of a sample obtained directly from this solution showed no starting material present. After stirring a total of one hour, the solution was poured onto ice (5 g) and extracted with ether. The ether extracts were combined, washed with H_2O until neutral, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The yellow oil (68 mg) obtained was shown by mixed injection on three different GC columns to contain five products with retention times identical to those of the products from the previous reaction: Col IV (150°C): R_t = 2.4 min (39%), R_t = 3.1 min (5%, daucene), R_t = 3.4 min (13%), R_t = 6.9 min (3%), R_t = 10.6 min (40%).

Reaction of Alcohol 25 with HCO_2H

A solution of alcohol 25 (10 mg) in 90 percent HCO_2H (0.5 ml) was agitated at room temperature. The reaction was followed by GC (Col I, 119°C). The composition of the solution obtained from GC traces is given in Table 3 (p.114). The solution remained colorless and homogeneous throughout the reaction.

Reaction of Formate 26 with HCO_2H

A solution of formate 26 (10 mg) in 90 percent HCO_2H (0.5 ml) was agitated at room temperature. The reaction was followed by GC (Col I, 119°C). The composition of the solution obtained from GC traces is given in Table 4 (p. 115). The solution remained colorless and homogeneous throughout the reaction.

Twelve Day Reaction of Daucene (5) with $HCO_2H/HClO_4$

A solution of daucene (208 mg, 1.02 mmol) in 90 percent HCO_2H (10 ml) containing 1.0 ml of 20 percent $HClO_4$ was stirred at room temperature. After 12 days the composition of the reaction mixture had remained constant for five days as determined by GC (Col I, 170°C). Ether (25 ml) was added and the solution washed with H_2O (3 x 5 ml). The ether layer was then washed with saturated $KHCO_3$ until basic, with H_2O until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent from the filtrate gave a yellow oil (185 mg) which contained four major volatile components (GC Col I, 170°C): R_t = 1.0 min (40%), R_t = 1.2 min (27%), R_t = 2.2 min (30%), R_t = 3.4 min (6%). Chromatography of this mixture on silica gel (20 g) separated four components subsequently found to be identical to those formed in the reaction of carotol (3) with HCO_2H (p. 59). The first fraction (hexane eluent) contained the first component (R_t = 1.0 min) shown by gas chromatography (Col I, 109°C) to be a mixture of two compounds: R_t = 4.6 min (62%), R_t = 4.9 min (38%). Comparison of IR, NMR, and GC retention times showed these to be the same as olefins 22 and 23, respectively. A second fraction (70% benzene-hexane eluent) contained the second component (28 mg, R_t = 1.2 min) found by comparison of IR, NMR,

and GC retention time with those of an authentic sample to be ether 24. A third fraction (70% benzene-hexane eluent) contained the third compound (23 mg, R_t = 2.2 min) in the mixture. By comparison of IR, NMR, and GC retention time this compound was found to be alcohol 25. A final fraction (70% benzene-hexane eluent) was found to contain formate 26 (10 mg, R_t = 4.9 min) the remaining component of the mixture. This compound was identified by comparison of its IR, NMR, and GC retention time with those of an authentic sample.

This reaction was also carried out using 90 percent HCO_2H (0.8 ml) containing 25 µl of 70 percent $HClO_4$ and daucene (27 mg). After 2.5 hours stirring at room temperature, the GC trace (Col I, 170°C) of a sample obtained directly from the reaction mixture showed more than 60 percent of the volatile components to be alcohol 25 and formate 26 in approximately a 1:2 ratio. After four hours, these components comprised less than 30 percent of the reaction mixture as determined by GC as above. The reaction was worked up as before after stirring 25 hours. The yellow oil obtained was found by GC comparison with authentic materials to contain the following volatile components: daucene (5), olefins 22 and 23 (44%), ether 24 (20%), alcohol 25 (24%), formate 26 (7%), and unidentified (5%).

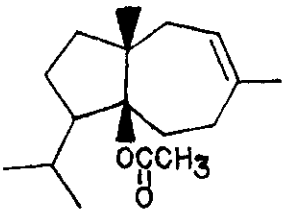
Reaction of Daucene (5) with HCO_2H

A solution of daucene (10 mg) in 90 percent HCO_2H (0.5 ml) was agitated at room temperature and the reaction followed by GC (Col I, 119°C). The products were identified by comparison of GC retention times with those of authentic materials. The composition of the mixture given in Table 5 (p. 117) is illustrated graphically in Figure 9 (p. 118). In a separate

experiment (14 mg of daucene/1.0 ml 90% HCO_2H), the reaction was followed by GC (Col I 170°C) for 67 days. The reaction mixture maintained approximately the same composition as in the previous experiment. The composition at 22 days was found (as above) to be: 22 (2%), 23 (4%), 24 (14%), 25 (55%), 26 (22%), and 5 percent of five unidentified products. At 67 days the composition was 22 (3%), 23 (3%), 24 (14%), 25 (56%), 26 (20%) and 2 percent unidentified product.

Carotol Acetate (33)[7]

Acetyl chloride (5.5 ml, 6.05 g, 77 mmol) was cautiously added via syringe to a solution of carotol (5.5 g, 25 mmol) in freshly distilled N,N-dimethylaniline (20 ml). The solution was stirred at 50°C for 36 hours. A bright blue color which deepened with time appeared after 15 minutes of heating. The solution was cooled to room temperature, poured onto ice (20 g) and the blue solution extracted with ether until the ether extracts were colorless. The extracts were combined and washed with 10 percent HCl until acidic, then with water until neutral, dried over $MgSO_4$, filtered and solvent removed *in vacuo* leaving 5.99 g of yellow oil. Distillation of this oil from K_2CO_3 in an apparatus rinsed with 1 N NaOH then washed with water, yielded 5.49 g (82%) of colorless carotol acetate 80-81°C/0.06 mm. The spectral properties of this oil were identical to those reported in the literature.[7]



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IR: ν_{neat} (cm^{-1}): 1730 (C-O), 1250, 1015 (C-O).

^{1}H-NMR (δ, $CDCl_3$): 0.93 (3H, d, J = 6 Hz), 0.97 (3H, s), 1.00 (3H, d, J = 6 Hz), 1.65 (3H, s), 1.92 (3H, s), 5.25 (1H, m).

^{13}C-NMR (δ, $CDCl_3$): 97.4 (C-O), 121.2, 136.0 (C=C), 169.5 (C=O).

Mass Spectrum: M^+ not observed. $M^+-C_2H_4O_2$ = 204 (13.5%), base peak m/e = 161.

Rearrangement of Carotol Acetate (33) on Silica Gel

Carotol acetate (5.19 g, 19.7 mmol) was chromatographed on a silica gel (300 g) column prepared in distilled hexane. Several fractions (hexane eluate) were obtained and found to contain identical mixtures composed of five major products (GC Col I, 130°C). The column was then washed with benzene. No volatile products were detected by GC. The hexane fractions were combined and solvent removed *in vacuo* to give 4.83 g (91% yield based on daucene) of colorless oil; five products were observed by GC (Col I, 130°C): R_t = 2.7 min (54%), R_t = 3.4 min (7%), R_t = 3.6 min (19%), R_t = 3.9 min (15%), and R_t = 5.5 min (5%). A sample of the major component (R_t = 2.7 min) of the mixture was isolated by preparative gas chromatography (Col II, 101°C). The NMR spectrum of this material was identical to that of authentic daucene (5). A sample (isolated by preparative GC as before) containing 64 percent of component three (R_t = 3.6 min) was shown to be acoradiene 9 by comparison of its NMR spectrum and GC retention time to that of an authentic sample. A sample containing 84 percent of component four (R_t = 3.9 min) was also isolated and identified by its NMR spectrum and GC retention time as acoradiene 10. One gram of the original mixture was chromatographed on 25 percent $AgNO_3$/silica gel (100 g). The first fraction eluted (distilled olefin-free pet ether) contained 113 mg of a 3:2 mixture of components two and five. Preparative gas chromatography (as above) afforded both components in greater than 98

percent purity. Component two (R_t = 3.4 min) exhibited the following spectral properties:

IR: ν_{neat} (cm^{-1}): 815 (trisubstituted olefin), 710 (disubstituted olefin).

^{1}H-NMR (δ, $CDCl_3$): 0.83 (3H, d, J = 6 Hz); 0.92 (3H, d, J = 6 Hz); 0.85 (3H, s); 1.63 (3H, m); 5.23 (1H, d, J = 10 Hz); 5.32 (1H, m); 5.67 (1H, d, J = 10 Hz).

Mass Spectrum: M^+_{found} = 204 (14%), calculated ($C_{15}H_{24}$) = 204; base peak m/e = 119; experimental exact mass: 204.187 ± 0.004, calculated exact mass: 204.188.

Compound five (R_t = 5.5 min) exhibited the following spectral properties:

IR: ν_{CCl_4} (cm^{-1}): 1445 (s), 1370 (m), 1130 (w), 1125 (w), 1100 (w), 1060 (w), 1015 (w), 980 (w).

^{1}H-NMR (δ, $CDCl_3$): 0.70 (3H, s); 1.50-1.80 (9H, m); 5.40 (1H, m).

Mass Spectrum: M^+_{found} = 202 (11%), calculated ($C_{15}H_{24}$) = 204; base peak m/e = 159.

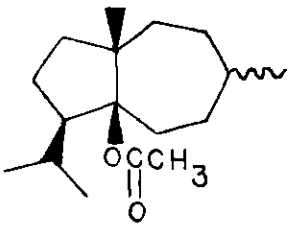
Reaction of Carotol Acetate (33) with HCO_2H

Carotol acetate (6.2 mg, 0.024 mmol) was stirred in 90 percent HCO_2H (0.4 ml) at room temperature. The GC trace (Col I, 170°C) of a sample (after one minute reaction time) showed two peaks, neither of which had retention times corresponding to carotol acetate. After 30 minutes, the composition of the mixture had not changed, as detected by GC. Ether (1 ml) was added to the solution, which was washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, and filtered. Mixed injections at 130°C of this mixture and authentic materials

showed the two peaks to correspond to daucene (83%) and acoradiene 9 (17%): Col I: R_t = 3.0 min (daucene), R_t = 3.9 min (acoradiene 9); Col III: R_t = 4.5 min (daucene, R_t = 6.5 min (acoradiene 9); Col IV: R_t = 4.8 min (daucene), R_t = 7.5 min (acoradiene 9). This reaction was repeated at a later date with 16 mg of carotol acetate in 1.0 ml of 90 percent HCO_2H. The reaction was followed by GC (Col I, 170°C). After stirring two hours at room temperature, the GC trace of a sample obtained directly from the reaction mixture showed peaks with retention times the same as those of the products from the reaction of carotol with HCO_2H (p. 65). The composition of the reaction mixture became essentially constant after 10 days: 6 percent daucene, olefin 22, and olefin 23; 15 percent ether 24; 53 percent alcohol 25; 22 percent formate 26; and 4 percent of five unidentified components.

Dihydrocarotol Acetate (36)

Carotol acetate (2.00 g, 7.6 mmol) in ethyl acetate (20 ml) was stirred in the presence of 50 mg of 83.4% PtO_2 under an atmosphere of hydrogen at room temperature (23°C) and atmospheric pressure (740 mm). After two hours, 198 cc of hydrogen had been absorbed (theory requires 188 cc). The solution was filtered and the ethyl acetate, 85 percent pure (GC Col I, 170°C). Distillation of this oil from K_2CO_3 in an apparatus rinsed in 1 N NaOH, then washed with water, yielded dihydrocarotol acetate, 95 percent pure as detected by GC.



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IR: ν_{neat} (cm^{-1}): 1730 (C=O), 1250, 1015 (C-O).

^{1}H-NMR (δ, $CDCl_3$): 0.88 (3H, d, J = 6 Hz), 0.92 (3H, s), 0.93 (3H, d, J = 6 Hz), 1.03 (3H, s), 1.95 (3H, s), 1.2-1.8 (15H, complex).

^{13}C-NMR (δ, $CDCl_3$): 98.2 (C-O), 169.2 (C=O).

Mass Spectrum: M^+ not observed, $M^+-C_2H_4O_2$ = 206 (10.2%), base peak m/e = 163. Exact mass m/e 206: found = 206.204 ± 0.004, calculated = 206.204.

Attempted Preparation of Dihydrocarotol Acetate (36)

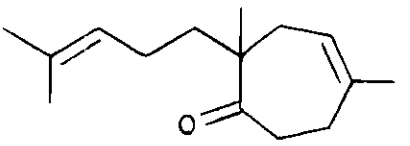
Acetyl chloride (0.53 ml, 0.57 g, 7.3 mmol) was cautiously added via syringe to a solution of dihydrocarotol (0.53 g, 2.37 mmol) in freshly distilled N,N-dimethylaniline (5 ml). A condensor with drying tube was added and the solution stirred at 50°C for 38 hours. A pale blue color appeared in the solution after 15 minutes and darkened to deep blue after several hours. The solution was allowed to cool to room temperature, poured into ice (20 g) and the mixture washed with ether until the extracts were colorless (the blue color remained in the water layer). The ether extracts were combined, washed with 10 percent HCl until acidic, then with water until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave 0.48 g of colorless oil. GC analysis (Col I, 170°C) of this oil showed six volatile products. The desired acetate comprised approximately 30 percent of this mixture as determined by GC comparison with a sample prepared by hydrogenation of carotol acetate. A better yield was obtained by catalytic hydrogenation of carotol acetate.

Reaction of Dihydrocarotol Acetate 36 with HCO_2H

Dihydrocarotol acetate (6.3 mg, 0.024 mmol) was stirred in 90 percent HCO_2H (0.4 ml) at room temperature. The GC trace (Col I, 170°C) of a sample (after one minute reaction time) showed three peaks, none of which had retention times corresponding to dihydrocarotol acetate. After 30 minutes the composition of the mixture had not changed as detected by GC. Ether (1 ml) was added to the solution, which was washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$ and filtered. Mixed injections (130°C) of this mixture and authentic materials showed the three peaks to be the minor epimer of dehydrodihydrocarotol (16, 16%), the major epimer (15, 81%) and olefin 17 (3%): Col I: R_t = 2.6 min (16), R_t = 3.0 min (15), R_t = 3.9 min (17); Col III: R_t = 3.6 min (16), R_t = 4.2 min (15), R_t = 6.4 min (17); Col IV: R_t = 3.4 min (16), R_t = 4.0 min (15), R_t = 5.7 min (17).

2,5-Dimethyl-2-(4-methyl-3-pentenyl)-4-cycloheptenone (39)[23]

A solution of cis and trans nerolidol (4.44 g, 20 mmol, Aldrich H 5960-5) and N-bromosuccinimide[24] (3.74 g, 22 mmol) in 44 ml of dry CCl_4 was stirred five days at room temperature. Fifty milliliters of petroleum ether (30-60) was added and the succinimide precipitate removed by filtration. After addition of freshly distilled collidine (9.7 g) the solution was reduced in vacuo to a constant volume at aspirator vacuum. The remaining liquid was heated under nitrogen one hour at 110°C and three hours



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at reflux then made acidic by addition of excess cold 10 percent HCl. This solution was extracted with ether and the combined extracts washed with water until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo leaving 4.04 g of brown oil. Chromatography of this material on 25 g of silica gel eluting with hexane yielded 2.04 g (46%) of 95 percent pure (Col I, 160°C) cycloheptenone. Infrared and NMR spectra were similar to those previously reported.[23]

IR: ν_{neat} (cm^{-1}): 1700 (carbonyl).

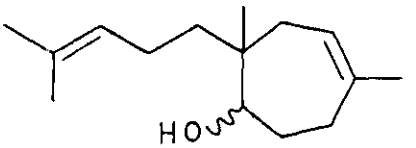
^{1}H-NMR (δ, $CDCl_3$): 1.05 (3H, s, tertiary methyl); 5.05 (1H, bs, olefinic proton); 5.45 (1H, bm, olefinic proton).

^{13}C-NMR (δ, $CDCl_3$): 121.6, 124.3, 131.4, 136.7 (olefinic carbons); 215.9 (carbonyl carbon).

Mass Spectrum: M^+_{found} = 220 (1%), calculated ($C_{15}H_{24}O$) = 220; base peak m/e = 138.

2,5-Dimethyl-2-(4-methyl-3-pentenyl)-4-cycloheptenol (42)

A solution of cycloheptenone (39) (1.02 g, 4.64 mmol) and $LiAlH_4$ (1.75 g, 4.40 mmol) in anhydrous ether (40 ml, freshly distilled from $LiAlH_4$) was stirred three hours at room temperature. The solution was then cooled with an ice bath and excess $LiAlH_4$ destroyed by cautious addition of small pieces of ice. Water (15 ml) was added and the organic layer separated. The aqueous layer was extracted with ether. The extracts were combined with the organic layer and washed with water, dried over $MgSO_4$ and filtered. The



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solvent was removed *in vacuo* leaving 1.03 g of yellow oil. Chromatography of this oil on 55 g of silica gel eluting with 50 percent benzene in hexane gave 0.70 g (70%) of pure alcohol (Col I, 160°C) bp 60-61°C/0.05 mm.

IR: ν_{neat} (cm^{-1}): 3400 (O-H); 1015 (C-O).

^{1}H-NMR (δ, $CDCl_3$): 0.82, 0.98 (3H, s in 1:2 ratio, tertiary methyl); 1.65 (9H, s, olefinic methyls); 3.48 (1H, m, proton on hydroxyl carbon); 5.25 (2H, m, olefinic protons).

^{13}C-NMR (δ, $CDCl_3$): 81.2 (hydroxyl carbon); 122.4, 125.4, 130.9, 140.1 (olefinic carbons).

Mass Spectrum: M^{+}_{found} = 222 (16%), calculated ($C_{15}H_{26}O$) = 222; base peak m/e = 41.

Analysis ($C_{15}H_{26}O$): calculated: C 81.02, H 11.78

found: C 80.84, H 11.80.

Attempted Reaction of Cycloheptenol 42 with HCO_2H/Acetone

A solution of cycloheptenol 42 (50 mg, 0.23 mmol) and several drops of 90 percent HCO_2H in acetone (5 ml) was refluxed 19 hours. No change in the reaction mixture was observed by GC (Col I, 170°C). The solution was allowed to cool to room temperature and H_2O (5 ml) added. The solution was made basic (pH 10) by addition of 0.1 N NaOH and extracted with ether (3 x 15 ml). The ether extracts were combined, washed with H_2O until neutral, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The yellow oil (45 mg) thus obtained was shown to be starting material by comparison of its IR to that of an authentic sample.

Reaction of Cycloheptenol 42 with Refluxing HCO_2H

A solution of cycloheptenol 42 (60 mg, 0.23 mmol) was refluxed in 90 percent HCO_2H (5 ml) for 1.5 hours. The solution was allowed to cool to room temperature, H_2O (5 ml) added and then extracted with ether (3 x 30 ml). The ether extracts were combined, washed with 0.1 N NaOH until basic, then with H_2O until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo to give a yellow oil (20 mg). Analysis of this oil by GC (Col I, 170°C) showed three products in addition to starting material: R_t = 2.0 min (38%), R_t = 2.3 min (26% cycloheptenol), R_t = 3.1 min (26%), R_t = 3.4 min (10%).

Reaction of Cycloheptenol 42 with HCO_2H at 23°C

A solution of cycloheptenol 42 (98.6 mg, 0.45 mmol) in 90 percent HCO_2H (4 ml) was stirred at room temperature for three hours. A pale blue color, which became more intense with time, was first noticed after 0.5 hours. The solution was then poured into H_2O (4 ml), destroying the blue color. The cloudy solution was extracted with ether (3 x 15 ml), the extracts combined, washed with saturated $KHCO_3$ until basic, then with water until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a yellow oil (84.6 mg) shown by GC (Col I, 170°C) to contain 15 distinct components: R_t = 1.5 min (1%), R_t = 2.1 min (7%), R_t = 2.3 min (5% starting material), R_t = 3.6 min (3%), R_t = 4.0 min (6%), R_t = 4.4 min (4%), R_t = 5.1 min (37%), R_t = 5.8 min (3%), R_t = 6.2 min (23%), R_t = 7.5 min (2%), R_t = 8.0 min (3%), R_t = 11.0 min (3%), R_t = 12.0 min (3%), R_t = 16.5 min (3%).

IR: ν_{neat} (cm^{-1}): 3500, 3400, 1725, 1175, 1190.

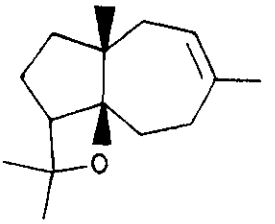
Attempted Preparation of Cycloheptenol Tosylate (43)[25]

A solution of cycloheptenol 42 (0.20 g, 0.8 mmol) in dry pyridine (5 ml) was cooled to 0°C by an ice bath. p-Toluene-sulfonyl chloride (0.30 g, 1.6 mmol) was added and dissolved by shaking. The solution was then stoppered and placed in a refrigerator for six days. The pale yellow solution was extracted with ether, the extracts combined and washed with cold 1:1 water-concentrated HCl until acidic, then with water until neutral, dried over $NaSO_4/Na_2CO_3$, filtered and solvent removed with a water aspirator at room temperature. The infrared spectrum of the yellow oil (0.22 g) thus obtained was identical to that of the starting material.

This procedure was repeated allowing 19 days reaction time. Infrared and NMR spectra of the product were again identical to that of starting material.

3,3,7,10-Tetramethyl-2-oxo-tricyclo [5.5.0.0]^{1,4}-9-dodecene or Carotol Ether (40)[23]

A solution of cycloheptenone (39) (7.5 g, 34 mmol) in dry freshly distilled CH_3NO_2 (75 ml) was purged 15 minutes with a stream of nitrogen then chilled with an ice/water bath. To this stirred solution $SnCl_4$ (0.70 ml) was added dropwise over a five hour period. The solution was extracted with ether; the extracts combined, dried over $MgSO_4$, filtered, and ether removed in vacuo to yield 5.6 g of yellow oil. Chromatography of this oil on silica gel eluting with 40 percent benzene in hexane gave 4.6 g (62%) of 95 percent pure



40

(Col I, 160°C) carotol ether. Infrared and NMR spectra were similar to those previously reported.[23]

IR: ν_{neat} (cm^{-1}): 905, 950 (ether).

^{1}H-NMR (δ, $CDCl_3$): 1.04 (3H, s, tertiary methyl); 1.22, 1.29 (3H each, s, isopropyl methyls); 1.65 (3H, s, olefinic methyl); 5.37 (1H, m, olefinic proton).

^{13}C-NMR (δ, $CDCl_3$): 78.0, 86.7 (ether carbons); 119.9, 134.0 (olefinic carbons).

Mass Spectrum: M^+_{found} = 220 (6%), calculated ($C_{15}H_{24}O$) = 220; base peak m/e = 94.

Attempted Preparation of β-Acoratriene (41)[23]

A solution of $AlCl_3$ (1.37 g, 10.3 mmol) in four milliliters of anhydrous ether (freshly distilled from $LiAlH_4$) was added to a chilled (ice bath) solution of $LiAlH_4$ (0.19 g, 5.15 mmol) in four milliliters of anhydrous ether. The resulting dark solution was then heated to reflux and a solution of carotol ether 40 (1.12 g, 5.08 mmol) in five milliliters of anhydrous ether was added in one milliliter portions over a period of ten minutes. After two hours at reflux, the solution was cooled to room temperature and the remaining $LiAlH_4$ destroyed by slow addition of wet ether (5 ml) and saturated NH_4Cl (3 ml). The solution was then extracted with ether and the extracts combined, washed with water, dried over $MgSO_4$, filtered and solvent removed *in vacuo* leaving 1.04 g of yellow oil. The GC trace (Col I, 170°C) showed a complex mixture containing at least seven components and no major product. Chromatography of the mixture on silica gel using benzene and ethyl acetate did not affect separation as reported

in the literature.[23] Additional chromatographies on silica gel and alumina also failed to separate the mixture.

Reaction of Carotol Ether (40) with HCO_2H

A solution of carotol ether (103 mg, 0.47 mmol) in 90 percent HCO_2H (4 ml) was stirred at room temperature. After stirring three hours, four components were present as detected by GC (Col I, 170°C): R_t = 1.6 min (6%), R_t = 2.3 min (63%, carotol ether), R_t = 3.8 min (14%), R_t = 5.3 min (18%). The solution was then heated to 50°C and stirred for three hours. The reaction mixture was cooled to room temperature, H_2O (5 ml) added, and the solution extracted with ether. The ether extracts were combined, washed with saturated $KHCO_3$ until basic, then with H_2O until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent in vacuo gave a yellow oil (84 mg), which was shown by GC (Col I, 165°C) to contain at least seven volatile components: R_t = 1.8 min (47%), R_t = 2.7 min (21%, carotol ether), R_t = 3.2 min (6%), R_t = 4.2 min (10%), R_t = 4.6 min (5%), R_t = 5.0 min (5%), R_t = 6.2 min (6%). The oil was rapidly chromatographed on silica gel (8 g). The first fraction (hexane eluent) contained the first component (R_t = 1.8 min) which gave the following IR spectrum:

IR: ν_{CCl_4} (cm^{-1}): 1465 (s), 1460 (s), 1450 (s), 1435 (s), 1375 (m), 1360 (m), 1150 (w), 930 (w), 910 (w).

The second fraction (1:1 benzene/hexane eluent) contained component six (R_t = 5.0, 5 mg, 85% pure) which gave the following IR absorptions:

IR: ν_{CCl_4} (cm^{-1}): 1725 (s), 1175 (s).

Two fractions containing 90 percent pure compounds were obtained eluting with $CHCl_3$. The first contained component seven (R_t = 6.2 min, 13 mg)

and showed the following IR absorptions:

IR: ν_{CCl_4} (cm^{-1}): 1720 (s), 1705 (sh), 1180 (s).

The second contained component four (R_t = 4.2 min, 5 mg) which showed the following IR absorptions:

IR: ν_{CCl_4} (cm^{-1}): 1960 (w), 1815 (w), 1465 (sh), 1465 (s), 1370 (m), 1225 (m), 1210 (m), 1030 (m), 670 (s).

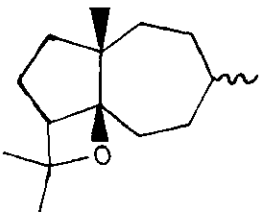
A final fraction (ethyl acetate eluent) gave component six (R_t = 5.0 min, 5 mg) which gave the following IR spectrum:

IR: ν_{CCl_4} (cm^{-1}): 3500 (w), 3400 (w), 1450 (s), 1375 (s), 1180 (m), 1160 (m), 1100 (m), 1065 (m), 960 (m), 910 (w), 895 (w), 890 (w).

This reaction was repeated with 11 mg of carotol ether in 1.0 ml of 90 percent HCO_2H. The solution was stirred at room temperature for 30 days. After three days stirring, the GC trace (Col I, 170°C) was identical to that obtained from the 50°C three hour reaction above.

3,3,7,10-Tetramethyl-2-oxo-tricyclo [5.5.0.0]^{1,4}-9-dodecane or Dihydrocarotol Ether 44[23]

A stirred solution of carotol ether (483 mg, 2.2 mmol in glacial acetic acid (6 ml) containing 39.4 mg of 83.4 percent PtO_2 was hydrogenated at atmospheric pressure (740 mm) and 23°C. After two hours uptake of hydrogen ceased with 68 cc having been consumed. The solution was filtered through Celite 545 and most of the acetic acid removed in vacuo. The remaining liquid was taken up in ether and washed with saturated $KHCO_3$ until



44

basic. The ether solution was then washed with water until neutral, dried over $MgSO_4$, filtered and solvent removed in vacuo yielding 267 mg (55%) of yellow oil. GC analysis (Col III, 170°C) showed an 86:14 ratio of the two possible epimers of dihydrocarotol ether. This oil was purified by chromatography over silica gel (1 g mixture to 100 g absorbant) eluting impurities with 50 percent hexane in benzene. The pure epimeric ether was then eluted with benzene.

IR: ν_{neat} (cm^{-1}): 900, 945 (C-O).

^{1}H-NMR (δ, $CDCl_3$): 0.90-1.15 (3H, overlapping multiplet); 1.00 (3H, s, overlapping multiplet); 1.20 (3H, s); 1.25 (3H, s); 1.40-1.90 (13H, complex); 2.10 (1H, m).

^{13}C-NMR (δ, $CDCl_3$): 77.5, 86.4 (ether carbons).

Mass Spectrum: M^+_{found} = 222 (11%), calculated ($C_{15}H_{26}O$) = 222, base peak m/e = 43.

Reaction of Dihydrocarotol Ether (44) with $SnCl_4$

A solution of $SnCl_4$ (83 mg, 0.03 ml, 0.32 mmol) in anhydrous benzene (2 ml) was added dropwise over a period of 10 minutes to a chilled (ice water) solution of dihydrocarotol ether (71 mg, 0.32 mmol) in anhydrous benzene (5 ml). This mixture was stirred 1.0 hours and saturated $KHCO_3$ added until basic. After stirring an additional 15 minutes, the now colorless solution containing a white precipitate was extracted with benzene. The benzene extracts were combined, washed with H_2O until neutral, dried over $MgSO_4$, and filtered. Removal of the solvent from the filtrate gave a yellow oil (51 mg) shown by GC (Col III, 170°C) to contain five major volatile components:

R_t = 1.3 min (8%), R_t = 1.7 min (26%), R_t = 2.1 min (35%), R_t = 3.7 min (15%, dihydrocarotol ether), R_t = 7.8 min (16%). Chromatography of this oil on silica gel (5 g) separated the first three components of this mixture (hexane eluent). Benzene eluted first dihydrocarotol ether (identified by GC retention time and comparison of IR and NMR spectra with those of an authentic sample) and second the fifth component (R_t = 7.8 min) 80 percent pure by GC. The IR spectra of both these mixtures showed absorption at 1700 cm^{-1}. No other characteristic absorptions were observed due to the mixture of compounds involved in both cases. An NMR spectrum of the fifth compound was unobtainable due to the small amount of material available. The NMR spectrum of the mixture of the first three compounds showed a complex signal at δ 0.75-2.50 ppm. A broad multiplet at δ 5.25 ppm indicated olefinic protons were present.

Reaction of Dihydrocarotol Ether (44) with HCO_2H

A solution of dihydrocarotol ether (11 mg, 0.05 mmol) in 90 percent HCO_2H (1 ml) was stirred at room temperature for 30 days. The reaction was followed by GC (Col I, 170°C) and found to contain greater than 90 percent starting material after stirring one month. The remainder of the mixture was found to contain several low retention time components.

CHAPTER IV

DISCUSSION OF RESULTS

As mentioned in the introduction section, the purpose of this research was to begin a study of the chemistry of the carotane sesquiterpenes paying special attention to the interrelationship of the carotanes and any other sesquiterpene skeletal type discovered during the course of the investigation. A logical starting point for such a study is the reinvestigation of any known reactions involving the carotane skeleton. The dehydration of carotol with thionyl chloride[7] is such a case, allowing not only an opportunity to obtain another member of the carotane family, but also the chance to look specifically for other skeletal types which may be formed in the reaction.

The carotol available to us was obtained from two sources. A quantity of 90 percent pure carotol (bp 86-94°C/0.1 mm) had been purified by previous workers by fractional distillation of carrot seed oil obtained from Magnus, Mabee, and Reynard, Inc., New York, N. Y. This material was further purified to 98 percent by chromatography on silica gel. A second sample of carotol was obtained 99 percent pure (bp 72-74°C/0.35 mm) by two fractional distillations[26] (on a Nester-Faust 36 inch stainless steel spinning band column) of the essential oil obtained from P. Robertet and Co., Grasse, France.

Dehydration of carotol was carried out with $SOCl_2$-pyridine at ice bath temperature according to the published procedure.[7] The oil obtained

from this reaction was shown by GC analysis to contain not only the reported daucene (5) in 65 percent yield, but also two additional products: 9 in 11 percent yield and 10 in 20.5 percent yield. A third product (3.5 percent) was observed in the GC trace, but was not isolated. Separation of this mixture was achieved by chromatography on silver nitrate-silica gel. The properties of the daucene obtained were identical in all respects to those reported in the literature for the naturally occurring compound.[7] The ORD curve of this compound was also obtained and found to be a plain positive curve as expected from the reported value of the specific rotation at the sodium D line.

The second compound (9) isolated from this reaction was found to be a member of the acorane sesquiterpene family. The NMR spectrum of 9 (Figure 2) shows two multiplets (one hydrogen each) in the olefinic region indicating the presence of an additional trisubstituted double bond not present in daucene. The methyl region of the spectrum shows a pseudo-triplet corresponding to the methyl groups on the isopropyl substituent. The remaining two methyl groups are observed near δ 1.7 ppm, indicating each is attached to a doubly bonded carbon atom. These facts ruled out dehydration into the seven-membered ring, the only other dehydration pathway of carotol possible without rearrangement. The presence of trisubstituted double bonds was confirmed by absorption at 795 and 805 cm^{-1} in the IR spectrum. The absence of oxygen in the compound was suggested by lack of absorption in IR spectrum and confirmed by a molecular ion of m/e 204 ($C_{15}H_{24}$) in the mass spectrum.

A literature search revealed a report of the isolation of the enantiomer of 9 from the essential oil of *Vetiveria zizanoides* (Staph).[27]

The spectral properties of an authentic sample of this natural product were virtually identical to those of acoradiene 9.[28] Both natural and synthetic 9 have essentially identical plain negative ORD curves. Since the absolute stereochemistry of carotol is well documented,[7] the absolute stereochemistry of the naturally occurring compound must be that shown in 9.

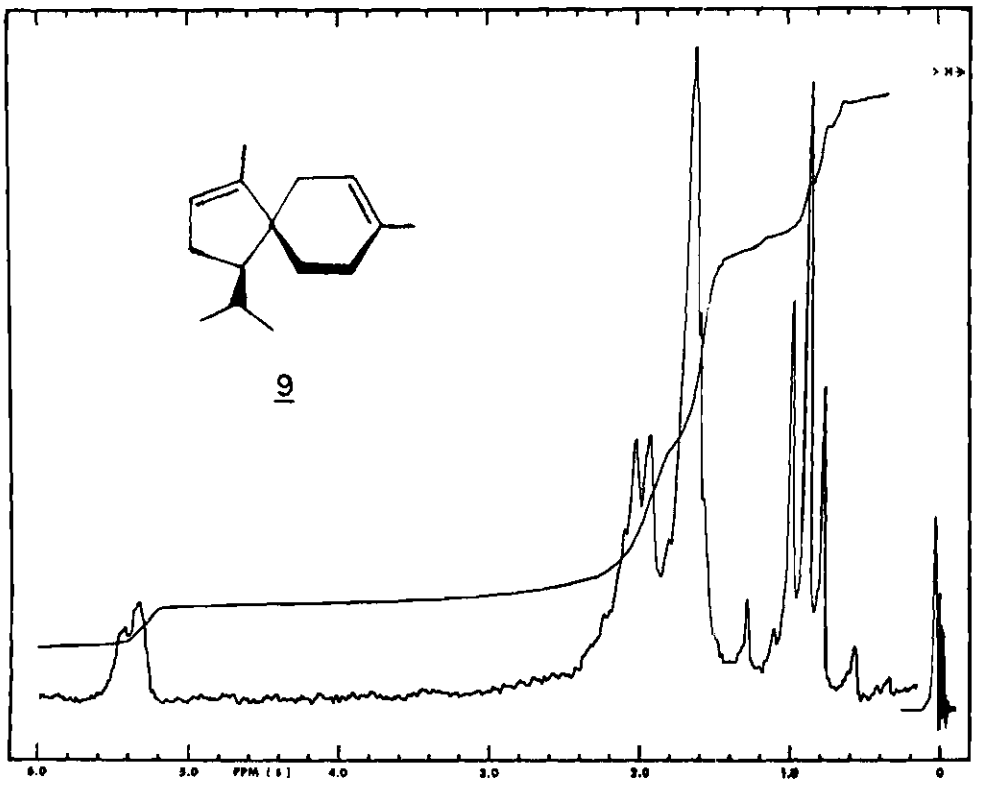


Figure 2. ^{1}H-NMR Spectrum of Acoradiene 9

The third compound (10) isolated showed spectral properties very similar to those of 9. The NMR spectrum of 10 (Figure 3) again shows a pseudotriplet from the isopropyl methyl groups. The olefinic region of

the spectrum, however, shows only one hydrogen on a trisubstituted double bond. A signal corresponding to a vinylidene grouping was observed at δ 4.79 ppm, with only one methyl group attached to a double bond. The mass spectrum again indicated a molecular formula of $C_{15}H_{24}$, but the base peak was due to simple elimination of the isopropyl group and not to rearrangement as was the case with acoradiene 9. Confirmation of the vinylidene grouping was confirmed by absorption at 885 cm^{-1} in the IR spectrum. A plain positive ORD curve was obtained. From the known absolute configuration of carotol (3) and the spectral evidence given above, this dehydration product was assigned the structure and absolute configuration indicated in 10.

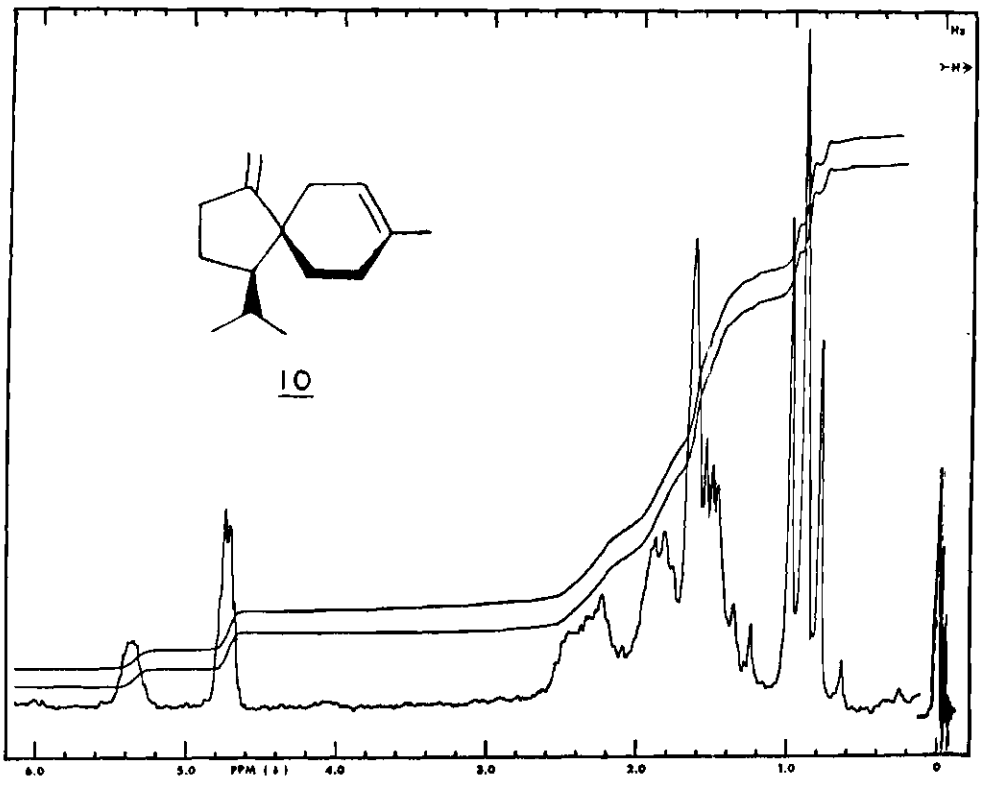
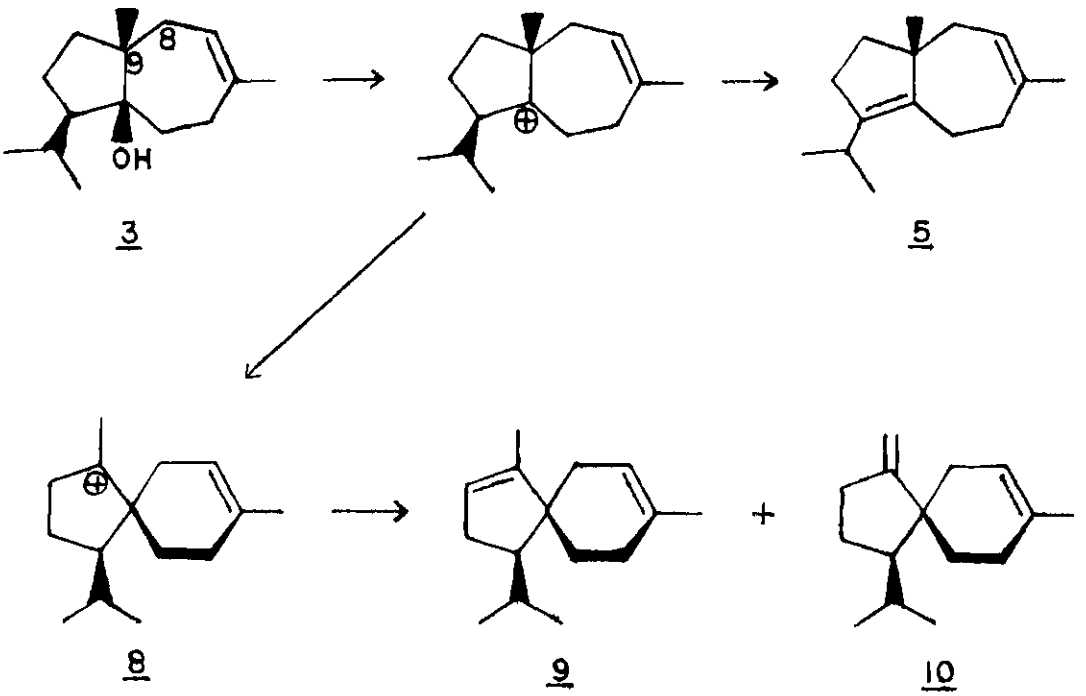


Figure 3. ^{1}H-NMR Spectrum of Acoradiene 10

It seems likely that both acoradienes 9 and 10 arise by simple deprotonation of acorenyl cation 8. The ratio of 10 to 9 formed (two-to-one) approaches the statistical ratio (three-to-two) of hydrogens available for deprotonation in 8, accounting for the large yield of the less stable disubstituted double bond.

Inspection of a model of the carbonium ion generated by loss of water from carotol shows that the seven-membered ring can easily assume a conformation in which the C_8-C_9 bond is antiparallel to the leaving group. When the molecule adopts the conformation allowing complete coplainarity of the four atoms involved in the rearrangement, the seven-membered ring must assume a boat configuration. The double bond is then positioned directly under the incipient carbonium ion and may stabilize the positive charge long enough for rearrangement to occur.



Biogenetically, both acoradiene 9 and acoradiene 10 (not a known natural product as this time) may arise from the previously postulated β-acorenyl cation[27] as shown in Figure 4. The absolute configuration of acoradiene 9 is consistent with the co-occurrence of this compound with (+)-zizaene, a sesquiterpene postulated to arise biogenetically from the β-acorenyl cation.[27] A simple 1,4-hydride shift would give cation 8, which can yield 9 and 10 on deprotonation. A 1,4-hydride shift as indicated in 11, a related system, has recently been suggested.[29]

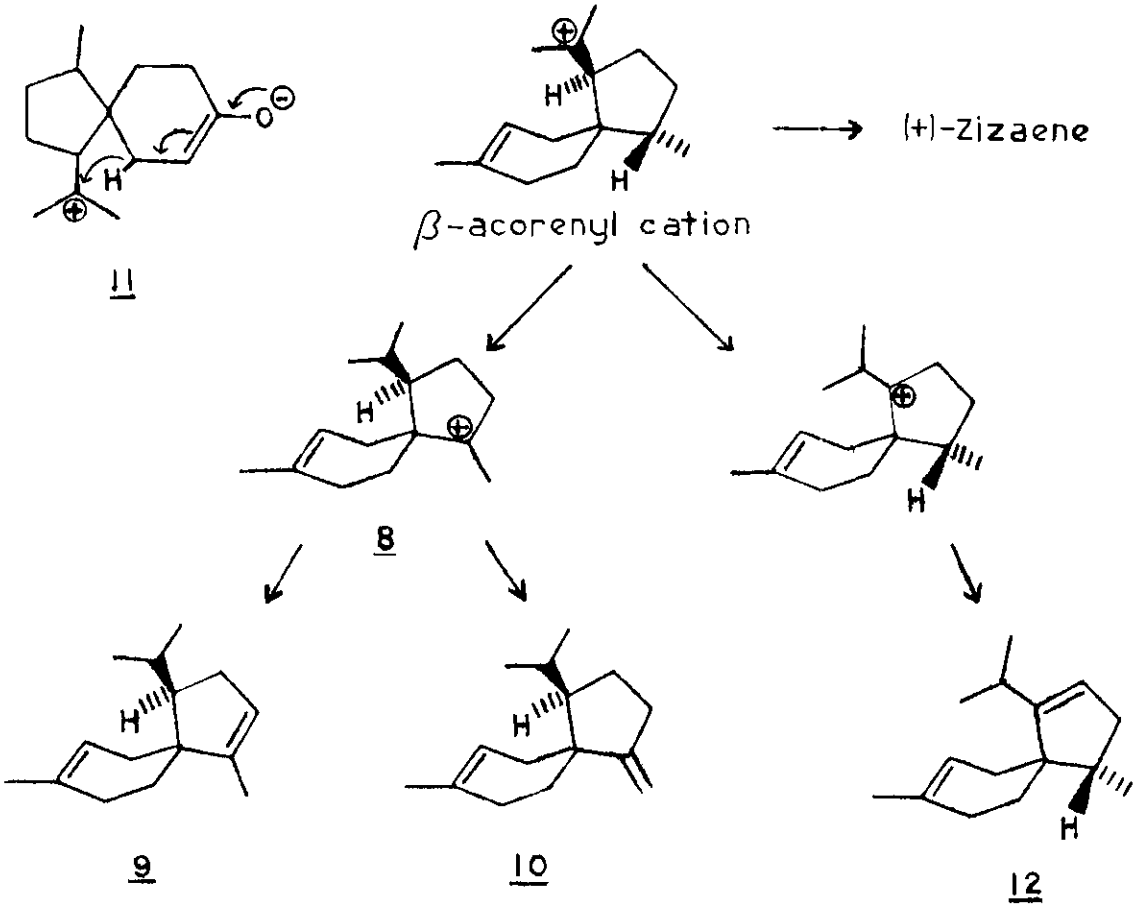
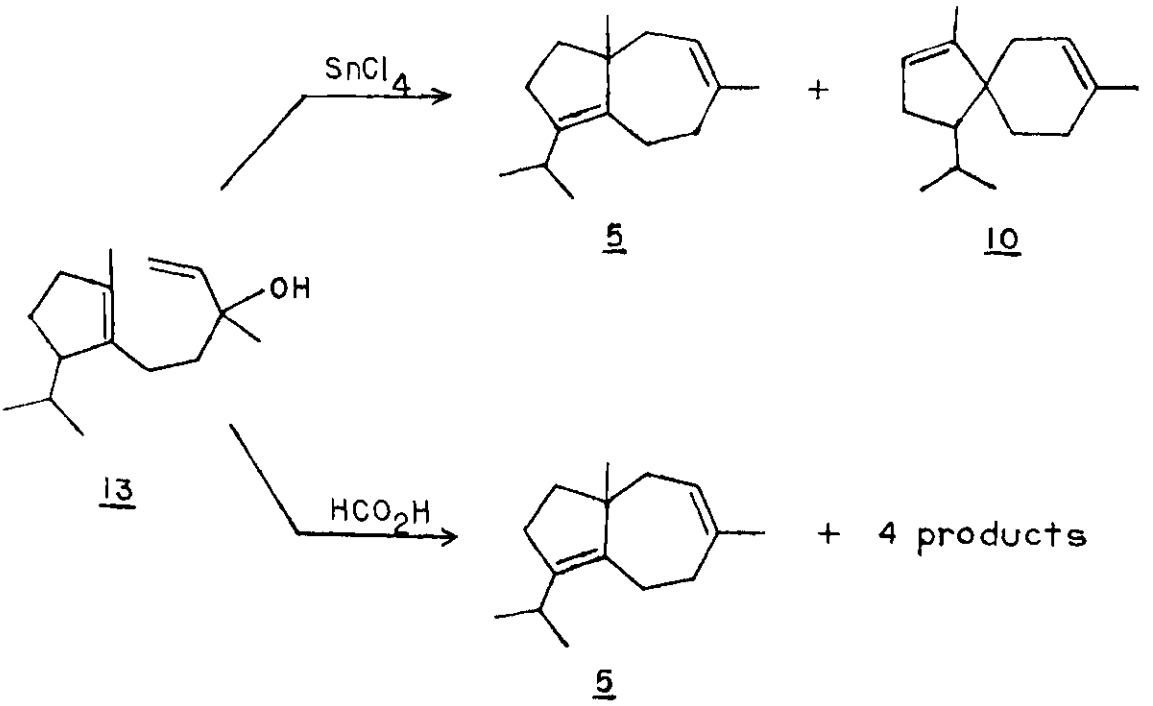


Figure 4. Proposed Biogenesis of Acoradienes 9 and 10

The configuration of a second acoradiene isolated from vetiver oil was not fully determined.[27] If it arises from the same β-acorenyl precursor, it would have the absolute configuration 12.

Daucene (5) and acoradiene 9 have been previously related as the products (in 70 and 20 percent yield, respectively) of the reaction of synthetic alcohol 13 with tin (IV) chloride in benzene-ether (five-to-one ratio) at 0°C.[11] In this instance, 13 was prepared from racemic dehydrolinalool. This alcohol has, however, been prepared optically active from (+)-limonene.[12] Acid catalyzed cyclization of optically active 13 with formic acid for 10 minutes at room temperature gave a mixture of five compounds. The main component (42 percent) was (-)-daucene, the enantiomer of the naturally occurring compound. While one of the remaining products was identified as an uncyclized formate, the remaining components of the mixture were not identified. Surely one or more of these must have the acorane skeleton!



Having completed this investigation of the dehydration of carotol by $SOCl_2$-pyridine, it was decided an investigation of this dehydration under other conditions would be of interest. Thionyl chloride-pyridine is known to be a stronger reagent than $POCl_3$-pyridine for the dehydration of alcohols.[26] Dehydration of carotol with the latter reagent, however, gave essentially no reaction. The solution was stirred at ice bath temperature three hours, then almost four days at room temperature. The oil obtained on work up was shown by GC and spectral data to be 90 percent starting material. Chromatography of this oil gave, in addition to pure carotol, a mixture of two compounds with GC retention times corresponding to daucene (5) and acoradiene 9. Some bubbling was noticed as water was added to the reaction mixture during work up, indicating the presence of unreacted $POCl_3$. Apparently carotol is too hindered and/or $POCl_3$-pyridine too mild a reagent for the reaction to occur.

The reaction of carotol with mesyl chloride was similar to reaction with $POCl_3$-pyridine. No reaction was obtained after more than one day at room temperature. A ten-fold excess of mesyl chloride was added, but no reaction obtained. The solution was then refluxed (115°C) for a day and then gave the same products obtained earlier with $SOCl_2$-pyridine: daucene (41 percent), acoradiene 9 (20 percent), acoradiene 10 (10 percent), unreacted starting material (24 percent), plus one unidentified component (5 percent).

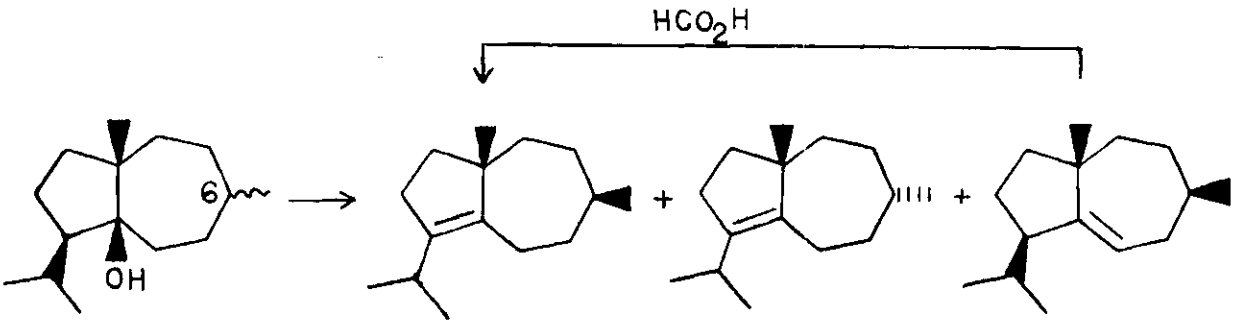
In order to learn more of the effect of the double bond in the dehydration of carotol (3), dihydrocarotol (14) was prepared by catalytic hydrogenation of carotol.[2] The spectral properties of the product were identical with those reported in the literature.[2] The first indication

that reduction of the double bond had not occurred stereospecifically was found in the ^{13}C-NMR spectrum. In addition to the expected 15 signals, another apparently complete set of signals was observed. The height of these peaks was approximately half the height of the "main" signals. The result of this second set of signals was to make each carbon atom appear to have a pair of signals (one large and one small) associated with it. The obvious explanation of this duplication of signals is the presence of two epimeric (at C_6) forms of dihydrocarotol.

The areas under ^{13}C-NMR peaks are usually not a reliable guide to the numbers of ^{13}C atoms present in a molecule due to long relaxation times for ^{13}C nuclei and varying degrees of Nuclear Overhauser Enhancement. In this case, all of the "large" peaks are very nearly the same height, and as well, the "small" peaks are all of equal height. This fact suggests, keeping the above cautions in mind, that the two epimers were formed in approximately the same ratio as the peak heights, i.e., two-to-one.

Dehydration of dihydrocarotol by $SOCl_2$-pyridine was carried out as with carotol. The three products obtained were separated by chromatography on silver nitrate-silica gel and assigned structures 15 (51 percent), 16 (28 percent), and 17 (20 percent) based on the following spectroscopic and chemical evidence. Each of these compounds showed similar mass spectra. The molecular ion in each case had m/e 206 indicating a $C_{15}H_{26}$ formula. The base peak of m/e 163, in each case, resulted from loss of the isopropyl group from the molecular ion. The ^{1}H-NMR spectra of 15 and 16 were very similar in that each showed a pair of doublets (J = 6 Hz) for the methyl groups on the isopropyl substituent, as well as a singlet corresponding

to a methyl group attached to an aliphatic carbon atom. The doublet for the cycloheptyl methyl group was partially hidden by the other signals in this region. No olefinic protons were observed. The IR spectrum of these compounds also offered little help in structure elucidation. No oxygen was indicated, confirming the mass spectral evidence, nor was any olefinic carbon-hydrogen absorption observed. The key to the identification of these compounds was to be found in the ^{13}C-NMR spectra. Each of these spectra showed two signals for carbons in the olefinic region, requiring the existence of one double bond in each compound. The similar chemical shifts of each pair of signals (see Experimental) implied that not only must the two double bonds involved be in similar environments, but that the two compounds containing these double bonds also be very similar. The IR and ^{1}H-NMR spectra required that these double bonds be tetrasubstituted. Since the mass spectra indicate the presence of isopropyl groups (i.e., no isopropylidene grouping) the most logical structures for these compounds are those given in 15 and 16, the major and minor epimers, respectively, of dehydrodihydrocarotol (dihydrodaucene). Further evidence in support of these structures was obtained by the hydrogenation of daucene described below.



14 15 16 17

The third compound (17) isolated from the dehydration of dihydrocarotol was shown to be a trisubstituted olefin by the presence of a signal (one hydrogen) in the olefinic region of the ^{1}H-NMR spectrum. A corresponding absorption (810 cm^{-1}) was observed in the IR spectrum. The mass spectrum again showed a molecular ion of m/e 206 ($C_{15}H_{26}$) and a base peak (m/e 163) due to loss of the isopropyl group from the molecular ion. The ^{13}C-NMR spectrum also indicated the difference in the carbon atoms of the double bond by the large difference in chemical shift of the two signals involved (118 and 154 ppm). Assuming no rearrangement, the most logical structure for this olefin is that indicated in 17. Reaction of 17 with formic acid for 19 hours showed 73 percent conversion into major epimer 15, proving the stereochemistry of the methyl group at C_6 to be the same as in the major epimer 15. Both 15 and 16 showed no reaction under these conditions.

Reaction of dihydrocarotol with formic acid gave the same dehydration products: 15 (70 percent), 16 (25 percent), and 17 (5 percent). The amount of 17 produced is less in this case due to the aforementioned equilibration of 17 and 15.

With these structures in mind, it is now possible to return to the cautious statement made earlier: that the relative peak heights in the ^{13}C-NMR spectrum of dihydrocarotol indicated the epimers were in a two-to-one ratio. The minor epimer 16 made up almost one-third of the dehydration mixture, while products enantiomeric at C_6 made up two-thirds. This finding indicates a two-to-one ratio of C_6 epimers in dihydrocarotol--the same as indicated by the ^{13}C-NMR spectrum of dihydrocarotol.

Inspection of a model of carotol shows that the seven-membered ring

can assume a variety of presumably low energy conformations. It is not clear which one of the least strained conformations is preferred. It seems most likely, however, that absorption onto a catalytic surface would be on the bottom side of the molecule, away from the bulk of the quasi-axial methyl, hydroxyl, and isopropyl groups. The seven-membered ring would be in a chair conformation allowing hydrogen transfer from the catalytic surface to produce a quasi-axial methyl group at C_6 (the major epimer 15). Hydrogenation of the double bond with the cycloheptyl ring in a twist boat conformation would produce the minor epimer 16 with the methyl group away from the other substituents on the ring. Inspection of models shows this twist boat cycloheptane to be more stable than the cyclohexane twist boat, due to the additional atom in the former.

Partial hydrogenation of daucene (see p. 98) gave a one-to-one mixture of 15 and 16 under mild conditions. Hydrogenation of daucene under more vigorous conditions gave 33 percent major epimer 15, 53 percent minor epimer 16, and 14 percent daucane (carotane). Assuming little epimerization during hydrogenation, this finding implies major epimer 15 is more easily hydrogenated than minor epimer 16. This would be the case if 15 were in the flatter chair form, making absorption onto the surface of the catalyst more facile than with the more bulky twist boat.

The most interesting facet of the dehydration of dihydrocarotol (14) is the absence of rearranged products. This reaction gives straight forward dehydration products, all of which are equivalent to the formation of daucene in the dehydration of carotol (3). Carotol gives 35 percent rearranged products. The presence or absence of the double bond in the seven-membered ring must certainly explain part of this difference in reation pathways (see p. 89).

Epoxidation of olefins 15 and 16 was achieved with m-chloroperbenzoic acid in methylene chloride. A mixture of the two possible epoxides was obtained in both cases. The epoxides of olefin 15 were found by GC to be in a two-to-one ratio, but the epoxides of olefin 16 were in a one-to-one ratio. The only difference in these olefins is the stereochemistry of the methyl group in the seven-membered ring. The low energy conformations of this ring appear to be determined by the stereochemistry of this methyl group, and in turn determine the direction of epoxidation of the double bond in the five-membered ring.

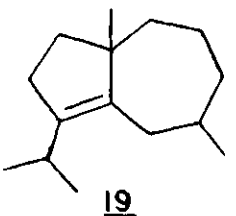
The spectral properties of these mixtures indicated epoxides were present, but since two compounds were present in each mixture, specific structural assignments could not be made in several instances. The ^{1}H-NMR, for example, must contain in each case signals for an isopropyl group in two different environments, as well as two methyl groups in a similar situation. Moreover, all of these signals must occur in a relatively small region of the spectrum. Separation of these mixtures could not be accomplished by column chromatography.

Reaction of the epoxides from olefin 15 with formic acid at room temperature produced a mixture of seven products. Reaction of these epoxides with tin (IV) chloride in benzene was even more complex; at least a dozen products were formed. Similar results were obtained with the epoxides of olefin 16 under the same reaction conditions.

The difficulties encountered above in assignment of structures to compounds containing a double bond as the only functional group gave rise to an interest in the parent compound of these sesquiterpenes, carotane (18). Depending on its source, this compound has been called both carotane

and daucane. The terms will be used interchangeably here. The IR spectrum of carotane would show absorptions due only to the carotane skeleton. These patterns should then prove useful in determining if an unknown compound is of the carotane type. Any unknown olefins obtained could then be hydrogenated and the IR spectrum of the product compared with that of carotane to determine if the unknown had the same skeleton. This procedure should also be applicable to all unknowns providing any functional groups present could be removed without skeletal rearrangement.

Several attempts at preparation of carotane by hydrogenation of daucene were unsuccessful. Daucene gave, upon hydrogenation at room temperature and pressure in the presence of PtO_2 in ethyl acetate, two products identified by GC mixed injection as 15 and 16. These are the major and minor epimers, respectively, of dihydrodaucene obtained earlier by dehydration of dihydrocarotol with $SOCl_2$-pyridine. This result firmly establishes the structures of these compounds. These epimers were unreactive under the hydrogenation conditions above, even at three atmospheres pressure overnight. A final hydrogenation of daucene was carried out overnight at three atmospheres using 10 percent paladium on charcoal in ethanol containing several drops of concentrated hydrochloric acid. The oil obtained was found by GC mixed injection to be 14 percent daucane (carotane), 33 percent major epimer 15, and 53 percent minor epimer 16. Dauben, Hubbell, and Vietmeyer have reported a similar resistance to hydrogenation under similar conditions of a related compound (19).[27]



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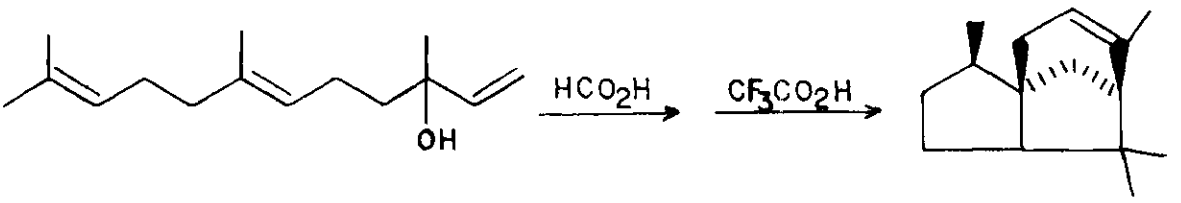
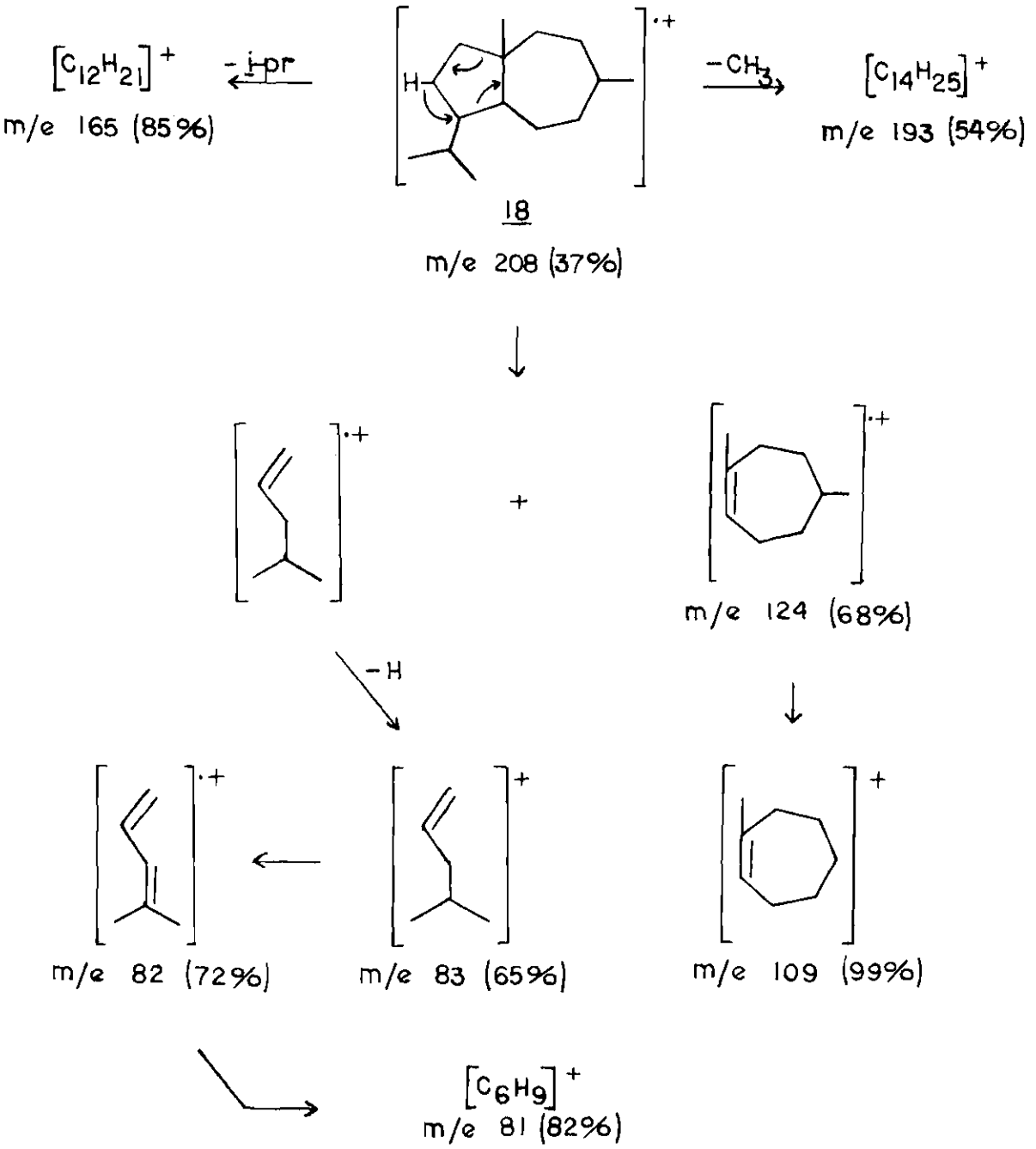


20 21

Carotane was finally prepared by reduction and hydrogenolysis of carotol.[3b] A 95 percent yield was obtained by stirring a solution of carotol in glacial acetic acid containing 10 percent paladium on charcoal under hydrogen at atmospheric pressure. The spectral properties of the product were identical with those reported in the literature.[3b] The strong absorptions in the fingerprint region of the IR spectrum of carotane are listed in the Experimental Section. Many of the prominent peaks in the mass spectrum of carotane can be rationalized as shown below. Peaks at m/e 193 (54 percent) and 165 (85 percent) correspond to loss of a methyl and isopropyl group, respectively, from the molecular ion.

With this background knowledge of the fundamental rearrangements of carotol, it was now possible to begin an investigation into the unknown chemistry of the carotanes. The biogenesis of sesquiterpenes is postulated to occur via carbonium ion type rearrangements as stated in the introduction. It is, therefore, logical to study the reaction of natural products in acidic media if one wishes to obtain information of possible biogenetic significance. Andersen has reported that nerolidol (20) can be converted in 20 percent yield to α-cedrene (22) in a one pot synthesis by first treating a pentane solution of nerolidol with formic acid and then trifluoroacetic acid.[28]

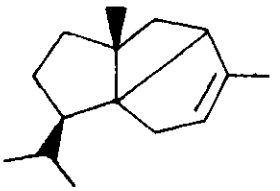


A solution of carotol in 90 percent formic acid was stirred three hours at room temperature. The oil obtained from this reaction contained six components. The major components were identified by GC mixed injection: daucene (40 percent) and acoradiene 9 (25 percent). The remaining

four components comprised only 35 percent of the reaction mixture. Before working with the small quantities involved in this reaction, it was decided to repeat the experiment allowing a longer reaction time. The reaction was stirred five days and followed by GC. The reaction proceeded as before. After one day several new peaks were observed in the GC trace. After stirring five days, the GC trace was essentially the same as that obtained after four days so the reaction was worked up. The four major components in the oil obtained were separated by column chromatography on silica gel.

The first fraction obtained from this chromatography was shown by GC, at a lower temperature than above, to contain two components. (The composition as determined from GC traces, of the crude product mixture was: olefins 22 and 23 (11 percent), ether 24 (12 percent), alcohol 25 (42 percent), formate 26 (33 percent), and four unidentified products (2 percent). Since the IR and NMR spectra of this mixture indicated both compounds were olefins, the mixture was rechromatographed on silver nitrate-silica gel. The first fraction eluted from this chromatography contained pure olefin 22, a colorless oil. The mass spectrum of this oil showed a molecular ion of m/e 204 indicating a $C_{15}H_{24}$ formula, and a base peak at m/e 123. The IR spectrum confirmed the presence of a trisubstituted double bond by an absorption at 810 cm^{-1}. The ^{13}C-NMR spectrum also indicated the difference in the carbon atoms forming the double bond (116 and 142 ppm). Only one quaternary carbon atom was observed in the off resonance spectrum. The double bond carbon atom at 142 ppm was also a singlet in the off resonance spectrum, indicating it to be tetrasubstituted. The ^{1}H-NMR spectrum of olefin 22 showed a single olefin proton as well as the usual pair of

doublets (J = 6 Hz) for the isopropyl methyl groups. A singlet arising from a methyl group attached to a saturated carbon atom and a signal for a methyl group attached to a double bond carbon were also observed. Olefin 22 gave a plain positive ORD curve. From these data, the unidentified structure of 22 must be optically active, have a $C_{15}H_{24}$ formula, and contain one quaternary carbon, an isopropyl group, and a methyl substituted double bond. One such structure formed from carotol with little rearrangement is shown below.



22 (?)

A second fraction from this chromatography contained a mixture of olefins 22 and 23. A third fraction contained enough pure olefin 23 to obtain some spectral data. The mass spectrum of 23 gave a molecular ion and base peak of m/e 204, requiring a $C_{15}H_{24}$ formula. The IR and ^{1}H-NMR spectra showed no olefinic protons. In addition, two interesting multiplets (one proton each) were observed at δ 2.30 and δ 2.78 ppm. The structure of this interesting olefin could not be assigned on this small amount of spectral evidence.

Olefin 22, when stirred with formic acid for one day, gave a small amount of olefin 23, as detected by GC. After stirring 12 days, the ratio

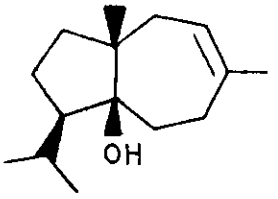
of olefin 22 to olefin 23 was two to one. A very small amount of alcohol 25 was also observed in the GC trace.

The third compound isolated from the reaction of carotol (3) with formic acid was assigned structure 24. The mass spectrum of this colorless oil gave a molecular ion of m/e 222, indicating a formula of $C_{15}H_{26}O$. The base peak (m/e 179) corresponds to elimination of the isopropyl group from the molecular ion. The IR spectrum showed no alcohol or carbonyl absorption, indicating an ether linkage was involved. This was confirmed by appropriate signals in the ^{13}C-NMR spectrum. Both these signals as well as one additional signal appeared as singlets in the off resonance spectrum. The ^{1}H-NMR spectrum showed the expected pair of doublets (J = 6 Hz) for the isopropyl methyl groups as well as two singlets for the remaining two methyl groups. The compound was also shown to be optically active by its plain negative ORD curve. The simplest structure consistent with this spectral evidence is that indicated in 24.

Further evidence in support of structure 24 was obtained by treatment of 24 with formic acid. After stirring 12 days in formic acid, the solution contained 69 percent 24, 21 percent alcohol 25, 7 percent formate 26, and 1 percent each of olefins 22 and 23.

The two remaining products of this reaction comprised 75 percent of the mixture. Since alcohol 25 and formate 26 are of the same skeletal type, they will be treated together. Reduction of formate 26 by lithium aluminum hydride gave alcohol 25 in 95 percent yield. The chemical and physical properties of this alcohol were identical to those of authentic alcohol 25 isolated from the reaction mixture. The spectral properties of formate 26 (see experimental section) are consistent with the assignment

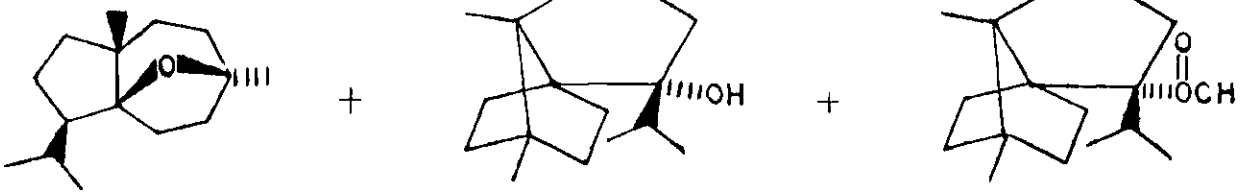
of structure 26. Reaction of 26 with formic acid is discussed below (see p. 115).



3

HCO_2H | 5 days ↓

22 + 23



24 25 26

Alcohol 25 was isolated as a low melting solid and purified by sublimation at room temperature under 0.2 mm vacuum. The molecular ion m/e 222, in the mass spectrum, required a $C_{15}H_{26}O$ formula. The base peak of m/e 179 corresponds to the loss of the isopropyl group from the molecular ion. An intense peak (78 percent of the base peak) due to loss of water and isopropyl group from the molecular ion was observed at m/e 161. The

^{1}H-NMR spectrum showed the hydroxyl proton at δ 1.42 ppm. This signal disappeared upon addition of deuterium oxide to the sample. Overlapping singlets and doublets (12 hydrogen integration) represented the four methyl groups in the molecule, but could not be further assigned from this simple spectrum. The IR spectrum showed the appropriate absorptions for an alcohol. The compound is optically active as shown by its plain positive ORD curve.

Thus, the compound is an optically active alcohol containing an isopropyl group and two methyl groups, each attached to saturated carbon atoms. If a double bond is present, it must be tetrasubstituted. The molecule may be spherical in shape since it is a solid and sublimes at moderate temperatures.

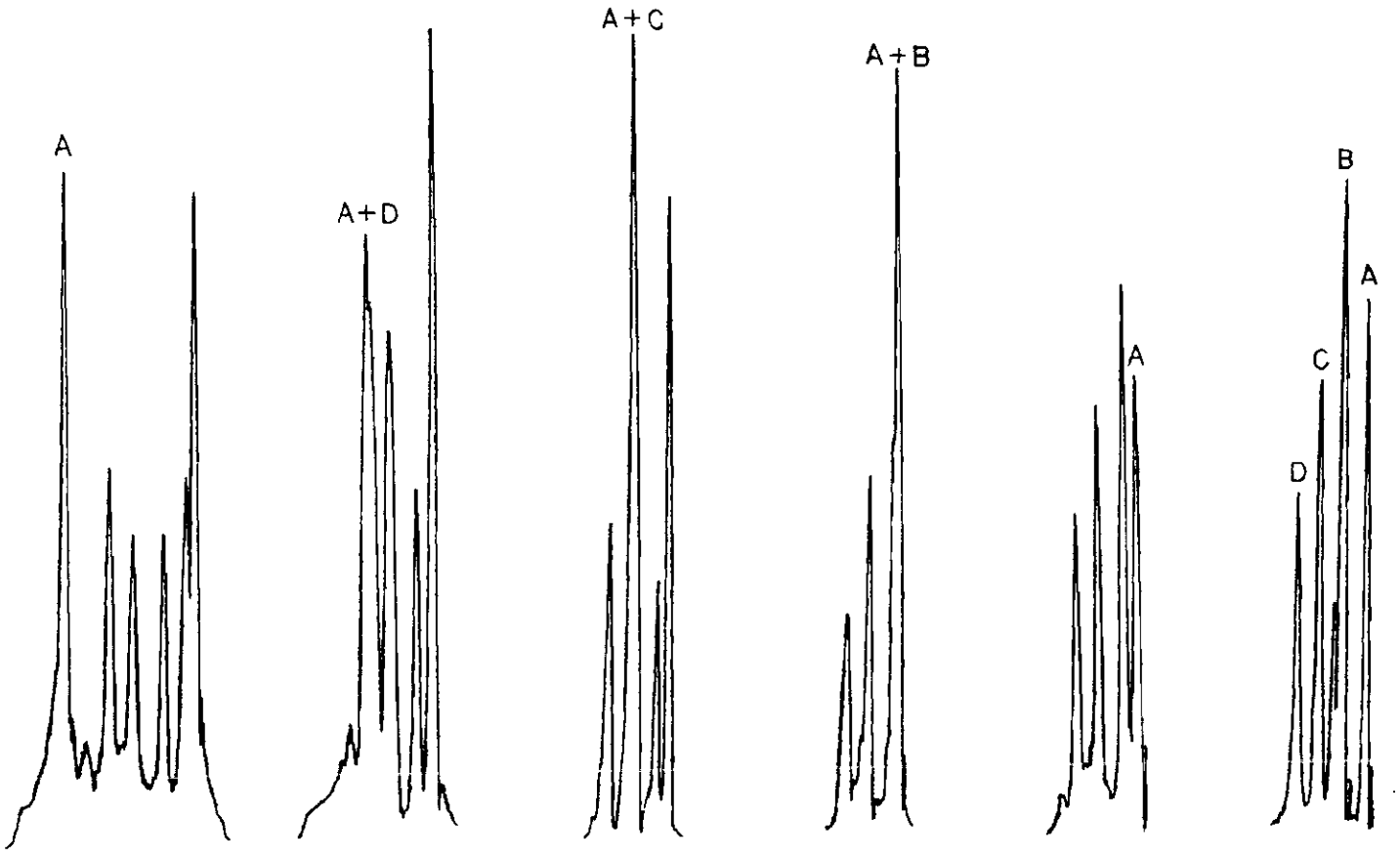
The key to the structure of 25 lies in the ^{13}C-NMR spectrum. There are no signals in the olefinic region of the spectrum. The proton decoupled spectrum contains a signal (91.7 ppm) for the hydroxyl bearing carbon atom in the expected region of the spectrum. Three additional signals (47.4, 48.5, and 60.2 ppm) are well separated from the rest of the signals. The usual "rule of thumb" predicts quaternary carbon atoms to give rise to signals at 40 ± 10 ppm. The off resonance proton decoupled spectrum bears out this suggestion. All three of these signals are singlets in the off resonance spectrum. More importantly, the signal due to the hydroxyl carbon atom is also a singlet. Thus, there are four tetrasubstituted carbon atoms in the structure of this alcohol.

Evidence in support of the presence of an isopropyl group and two methyl groups on quaternary carbon atoms in alcohol 25 was obtained in a series of ^{1}H-NMR chemical shift studies. A solution of alcohol 25 in

carbon tetrachloride was prepared and the spectrum obtained. Several drops of a solution of shift reagent [$Eu(dpm)_3$] in carbon tetrachloride were added and the spectrum obtained. This process was repeated until the signals from each of the methyl groups in the molecule were clearly visible. The methyl regions of the spectra obtained in this series of experiments are shown in Figure 5. One methyl group (signal A in Figure 5), which is not part of the isopropyl group, was observed to shift downfield rapidly indicating its proximity to the alcohol--europeum complex.

In a second series of experiments, a larger amount of solid $Eu(fod)_3$ shift reagent was added to the sample solution between each spectrum obtained. The results are illustrated graphically in Figure 6, a plot of the chemical shift of each signal vs. R_p (the mole ratio of shift reagent to sample). Ten sets of signals shifted out of the initial complex spectrum. The hydroxyl proton (square points), being nearest to the alcohol--Europeum complex, is shifted the most, followed by five individual protons (round points), and finally, the four methyl groups (triangular points). Of the individual protons shifted, only the isopropyl proton may be assigned a specific multiplet in the spectrum--δ 8.96 in Figure 7. Irridation of this multiplet caused the doublets corresponding to the isopropyl methyl groups to coalesce to singlets. The relatively large slope of the line in Figure 6 corresponding to this isopropyl proton suggests its proximity to the hydroxyl group in 25.

Due to restricted rotation about the bond joining the isopropyl group to the molecule, the methyl groups on this substituent are shifted to different extents. The remaining methyl groups are also shifted differently. The reason for this difference in slope is best seen in



NOTE: Amount of 3.8×10^{-5} M $Eu(dpm)_3$ in CCl_4 added to 9.0×10^{-5} M alcohol in CCl_4/TMS.

Figure 5. Methyl Regions of ^{1}H-NMR Spectra of Alcohol 25/$Eu(dpm)_3$ Solutions

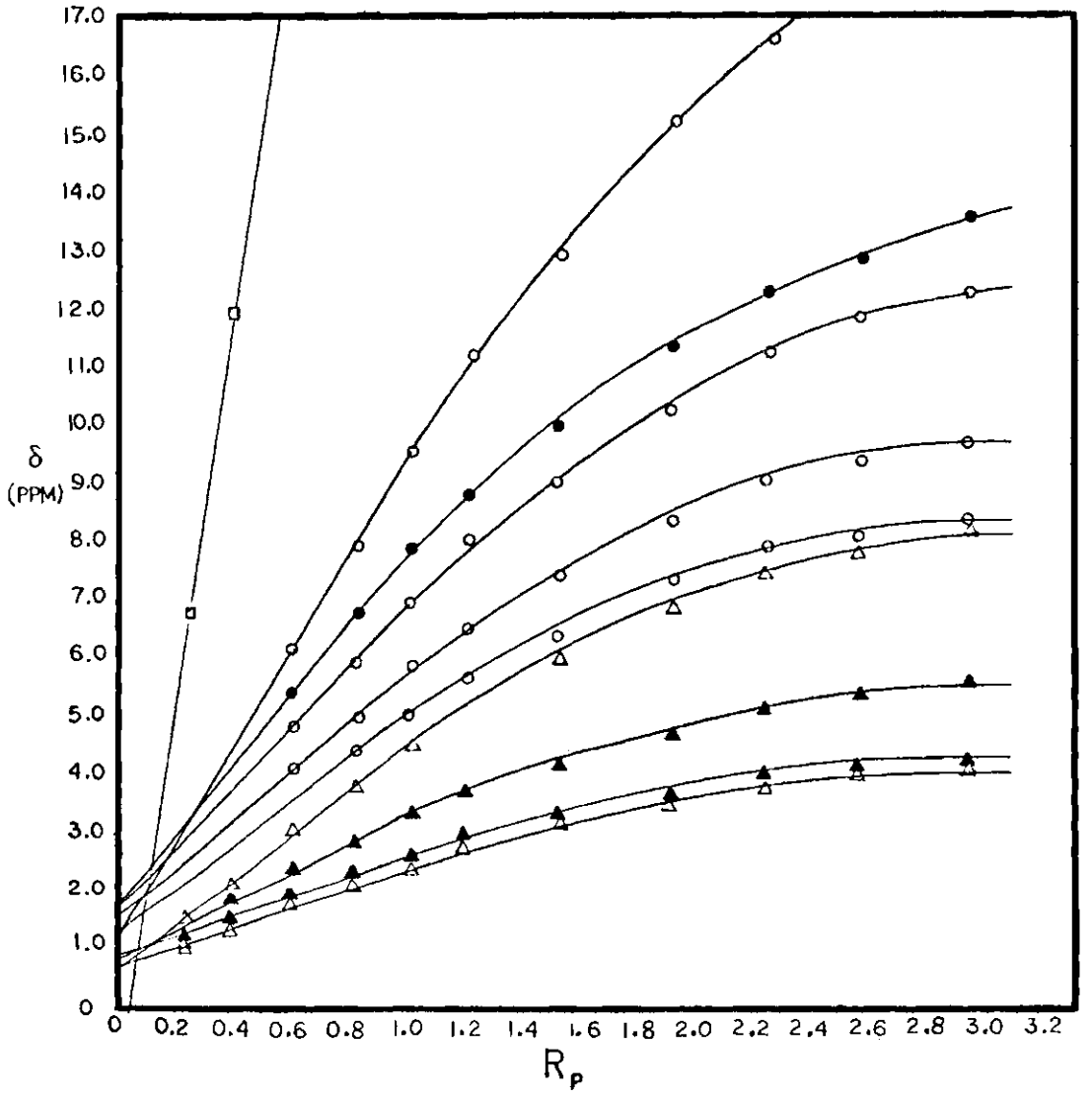


Figure 6. Chemical Shift vs. R_p for Alcohol 25/Eu(fod)$_3$ Solutions

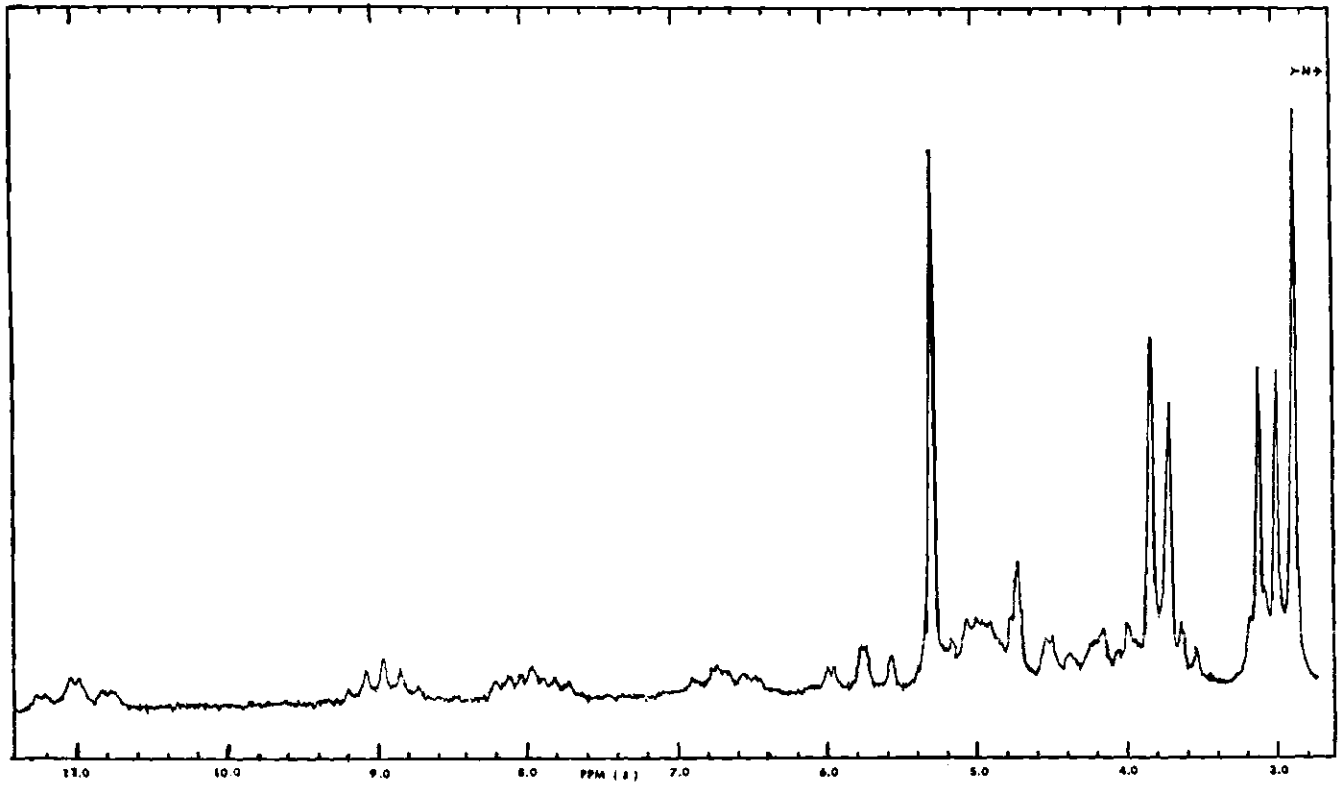


Figure 7. ^{1}H-NMR Spectrum of Eu(fod)$_3$/Alcohol 25 Solution (2.96 to 1.00)

structure 25a. One methyl group is on the same side of the cyclopentyl ring, whereas the other methyl group is at the opposite end of the molecule away from the complex and therefore shifted to a smaller degree. Figure 7 illustrates the spectrum at R_p 2.96.

The proposed structure then, must be consistent with the following data: tertiary alcohol, isopropyl group, two methyl groups-presumably on tertiary carbon atoms, three quaternary carbon atoms, and spherical-type structure with a tricyclic $C_{15}H_{24}O$ formula. Structure 25 meets all of these criteria. The postulated mechanism for the formation of 25 from carotol (3) is shown in Figure 8.

As noted above, the structure of alcohol 25 must contain three quaternary carbon atoms as well as a tertiary alcohol. Initial studies on the reaction of carotol in the presence of $SOCl_2$-pyridine and formic acid suggested that the dehydration products arose from a common carbonium ion precursor. Daucene (5) was formed by simple loss of a proton from this carbonium ion. The two acoradienes (9 and 10) were formed by rearrangement of the carbonium ion followed by deprotonation. A tertiary alcohol could be obtained by capture of either of these carbonium ions by water followed by deprotonation. Each of these products, however, would still contain only a single quaternary carbon atom. Further rearrangement must therefore occur. This rearrangement must lead to two additional quaternary centers as well as the tertiary alcohol. It appears reasonable to assume that these centers will be formed from carbon atoms which are already tertiary in nature, thus requiring the smallest degree of rearrangement to obtain the desired end.

The only "functional group" in the molecule is a double bond which

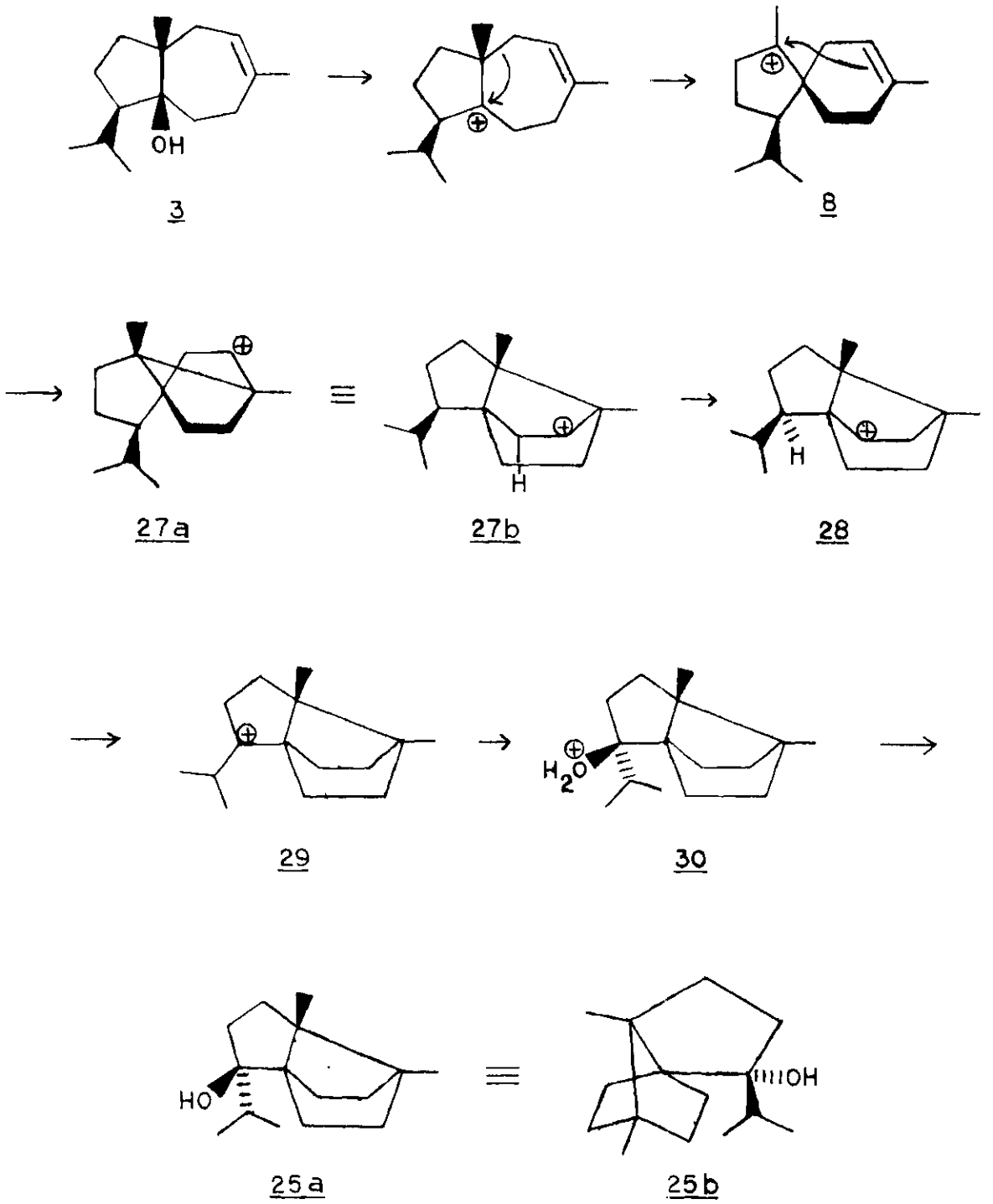
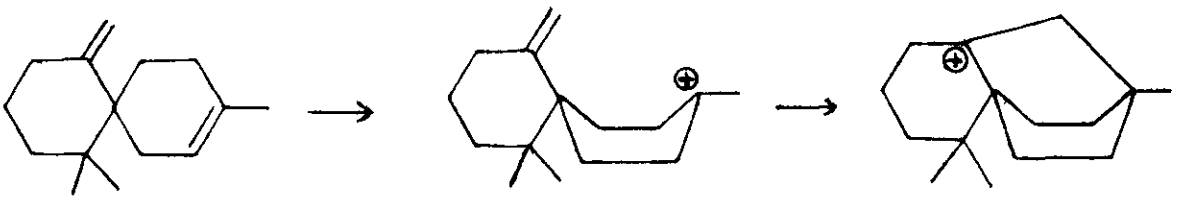


Figure 8. Proposed Mechanism for Formation of Alcohol 25 from Carotol (3)

is known from spectral data to be absent in the final structure. Reaction of this double bond with the carbonium ion in 8 produces structure 27a, containing both of the remaining quaternary carbon atoms required. Considering only the atoms involved in the cyclohexyl and cyclopentyl rings of 8, the molecule contains a plane of symmetry including all of the carbon atoms in the cyclopentyl ring. Attack upon this carbonium could be from either side. Addition to this system of a double bond and isopropyl group on opposite sides of this plane, as in 8, necessitates reaction on the side of the carbonium ion away from the isopropyl group.

All that remains is creation of a tertiary alcohol. Neither of the two remaining tertiary carbon atoms in 27a are close to the carbonium ion. Inspection of models shows 27a to have the stereochemistry depicted in 27b. It is now possible to visualize a 1,2-hydride shift, moving the carbonium ion in 28 one atom closer to the tertiary atoms. A 1,3-hydride shift will form a tertiary carbonium ion which in turn will give the desired tertiary alcohol. The isopropyl group and site of reaction in 28 are again on opposite sides of the molecule. The hydrogen atom on the carbon bearing the isopropyl group is not only on the same side of the molecule as the carbonium ion, but due to the rigid structure of the spiro skeleton, is very close to it. At first glance it is not possible to determine the direction of attack in 29. However, if the 1,3-hydride shift (28 → 29) and attack on the carbonium ion formed (29 → 30) were a concerted process, the absolute stereochemical outcome would be that shown in 25.

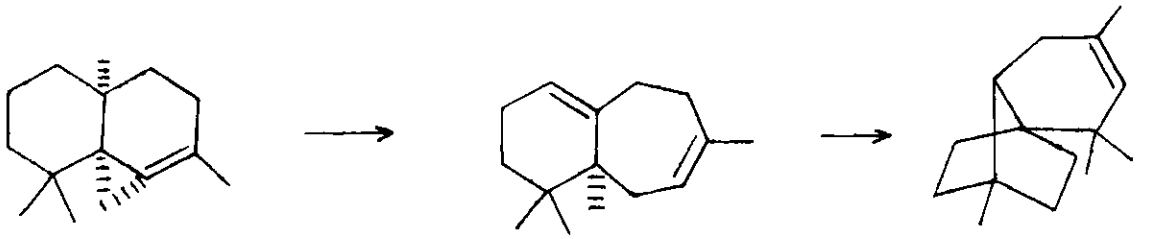
Dauben and Aoyagi have postulated a mechanism similar to 8 → 27 for the conversion of β-chamigrene into 31.[33] This rearrangement occurs when β-chamigrene is allowed to react at room temperature with 0.02 M perchloric



β-chamigrene 31

acid--acetic acid. These conditions are similar to those used in the formation of alcohol 25: 90 percent formic acid at room temperature.

Olefin 32, possessing a structure similar to that of alcohol 25, had been found to be the major hydrocarbon formed when thujopsene (7) is treated with 0.02 M perchlorid acid in refluxing acetic acid.[34] Dauben



7 32

notes that the energy for the conversion of this bicyclic olefin into the tricyclic olefin must be obtained from the net transformation of one carbon-carbon double bond into two carbon-carbon single bonds. This observation is appropriate in the present case, as daucene (5), when treated with formic acid under the same conditions as carotol (3), gives an identical mixture of compounds (see p. 116).

In an attempt to determine the rate and order of formation of these products, carotol was allowed to stir in formic acid for 67 days. The

composition of the solution, as determined by GC, is given in Table 2. The GC samples were obtained directly from the reaction mixture, which appeared to remain homogeneous throughout the reaction. But, the percentages should be viewed only as approximations. The table does show the immediate formation of daucene, which forms alcohol 25 and formate 26 over a period of time.

Table 2. Reaction of Carotol (3) with Formic Acid

TIME		PERCENT COMPOSITION						
(hr)	(day)	(22)	(23)	(5)	(24)	(9)	(25)	(26)
0.5	0	2		84		14		
1.0		6		66	3	11		
2.3		8		68	9	6	6	
3.5		11	1	54	8	5	4	7
24	1	6	3	28	15	6	18	28
48	2	6	3	36	17	1	23	12
71	3	8	3	4	14		37	35
95	4	3	2	2	13		45	33
120	5	4	2	1	15		48	31
216	9	2	1	1	17		58	21

Dehydration of alcohol 25 by $SOCl_2$-pyridine produced five compounds as detected by GC. None of these compounds had retention times corresponding to any of the products obtained in the reaction of carotol with formic acid (to give 25, etc.). This dehydration mixture was found by GC to contain 20 percent daucene. When the reaction was carried out in carefully prepared anhydrous pyridine, only three percent daucene was obtained.

Reaction of alcohol 25 in formic acid under the conditions of its formation also produced a large amount of daucene immediately. Table 3 shows the composition of this reaction mixture determined from GC retention times as above. After 10 days, the composition of this mixture was similar to that produced by reaction of carotol with formic acid for nine days.

Table 3. Reaction of Alcohol 25 with Formic Acid

TIME		PERCENT COMPOSITION					
(hr)	(day)	(22)	(23)	(5)	(24)	(25)	(26)
0	0					100	
1				16		83	1
24	1	2	2	35		61	a
46	2	1	1	2	1	77	17
70	3	8	10	18	3	56	4
96	4	1	1	16	4	64	13
270	11	2	1	< 1	7	68	23

[a]GC turned off before retention time of this compound

A similar experiment was carried out with formate 26. The results, given in Table 4, show a similar trend: initial formation of daucene, which equilibrates over a period of 11 days to essentially the same composition as obtained with alcohol 25.

Table 4. Reaction of Formate 26 with Formic Acid

TIME (hr)	TIME (day)	PERCENT COMPOSITION (22)	(23)	(5)	(24)	(25)	(26)
0	0						100
0.5		2	1	19		2	76
26	1	2	1	23	5	27	44
48	2	5	5	10	10	35	35
71	3	3	2	38	8	39	11
122	5	2	2	15	9	55	17
270	11	1	1	< 1	10	65	23

The reoccurrence of daucene (5) in each of these reactions prompted new interest in this olefin. Daucene was stirred in 90 percent formic acid for 12 days. The composition of the reaction mixture, determined as above, became essentially constant after seven days. The products were isolated in the same manner as the products from the reaction of carotol and formic acid. Spectral data of the five products showed them to be the same as those obtained from carotol. This reaction was repeated and followed by GC for 67 days. The composition of the mixture is given in Table 5. The results for the major components of the mixture are illustrated graphically in Figure 9. The concentration of daucene decreases steadily over 48 hours. Since the concentration of formate ion in the solution is much greater than the concentration of water, formate 26 is formed faster than alcohol 25. Slow hydrolysis of formate 26 occurs in the acid solution so that the equilibrium mixture shows a two-to-one ratio

Table 5. Reaction of Daucene (5) with Formic Acid

TIME	PERCENT COMPOSITION						
(hr)	(22)	(23)	(5)	(24)	(?)	(25)	(26)
2	13		87				
22	9	6	45	13	1	13	12
45	7	6	6	10	3	26	44
69	5	2	4	13	3	37	42
91	6	2	3	12	6	36	30
187	3	2	< 1	15	3	54	20
259	3	2	$\ll 1$	12	1	57	23

of alcohol 25 to formate 26.

From this and the preceding reactions, the following conclusions can be drawn. Ether 24 is formed and slowly rearranges to alcohol and formate. Without knowing the structures of olefins 22 and 23, it is difficult to assess their role in this reaction. Olefin 22 contains one quaternary carbon atom and a trisubstituted double bond, and cannot, therefore, be formed by direct deprotonation of any of the intermediates proposed in the formation of alcohol 25. Neither olefin 22 nor 23 is a dehydration product of alcohol 25, so perhaps they are ring opened products. Carotol initially leads to daucene which appears to lead reversibly to the various products. When ether 24, alcohol 25, or formate 26 are subjected to the reaction conditions under which they were formed, all five products are found. Olefin 23 could not be tested, but olefin 22 produced

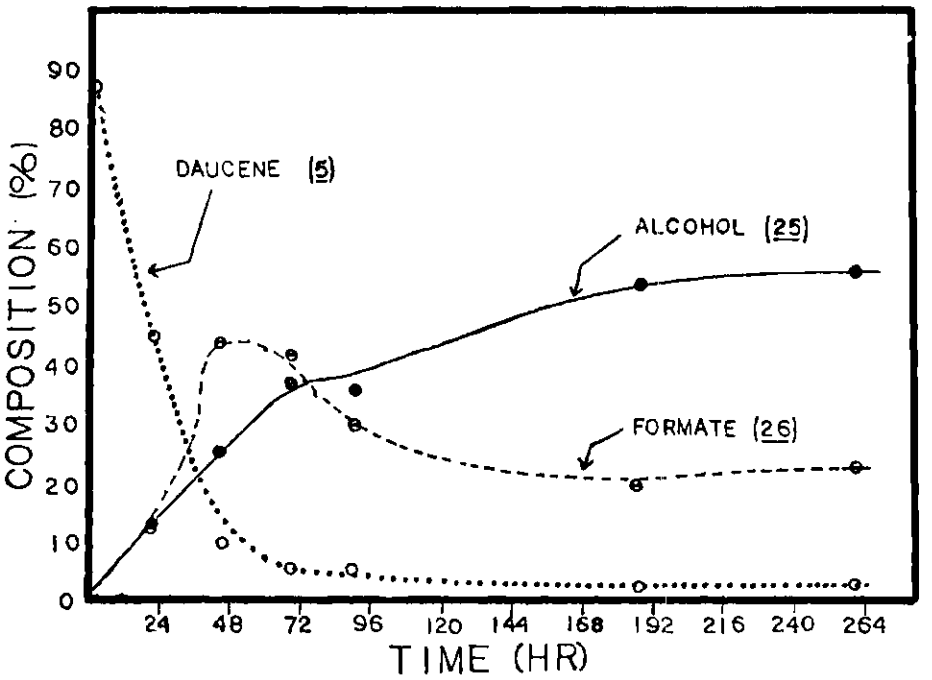


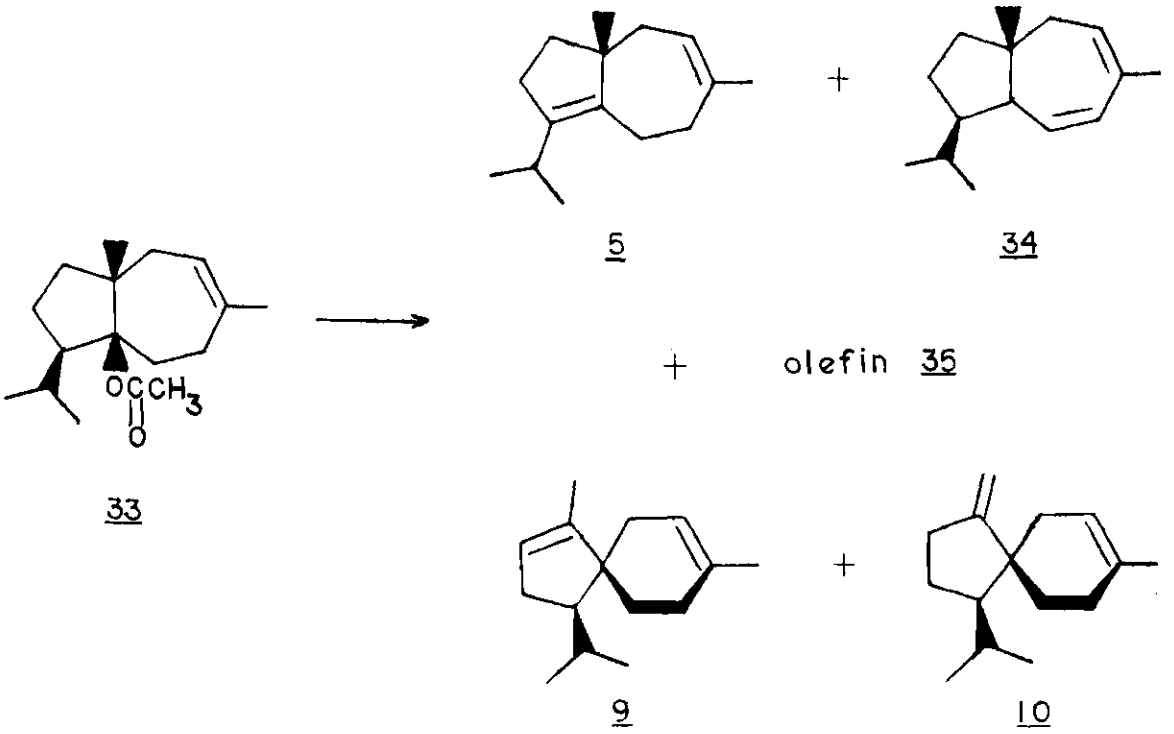
Figure 9. Reaction of Daucene (5) with Formic Acid

olefin 23 as well as some alcohol 25. Alcohol 25 is known to form ether 24 and formate 26 under these conditions. Further study of this interesting rearrangement of carotol and daucene is needed to fully determine the mechanisms and equilibria involved.

Carotol acetate (33), a known derivative of carotol, is easily prepared by the action of acetyl chloride on the latter.[7] In light of the previous discussion, a study of the reaction of carotol acetate with formic acid was of interest. The reactivity of this compound should be enhanced due to the better leaving group properties of acetate.

Carotol acetate was prepared in 87 percent purity according to the published procedure.[7] Purification by chromatography on silica gel was attempted. No carotol acetate was eluted; a mixture of olefins was

obtained. Daucene (5) comprised 54 percent of the mixture. Only two of the four remaining compounds had been previously reported[35]: olefin 34 (7 percent), acoradiene 9 (19 percent), acoradiene 10 (15 percent), and olefin 35 (5 percent). From the weight and purity of the carotol acetate applied to the column, and the weight of the olefinic material eluted, a 91 percent yield of olefin was obtained.



5 34

33

9 10

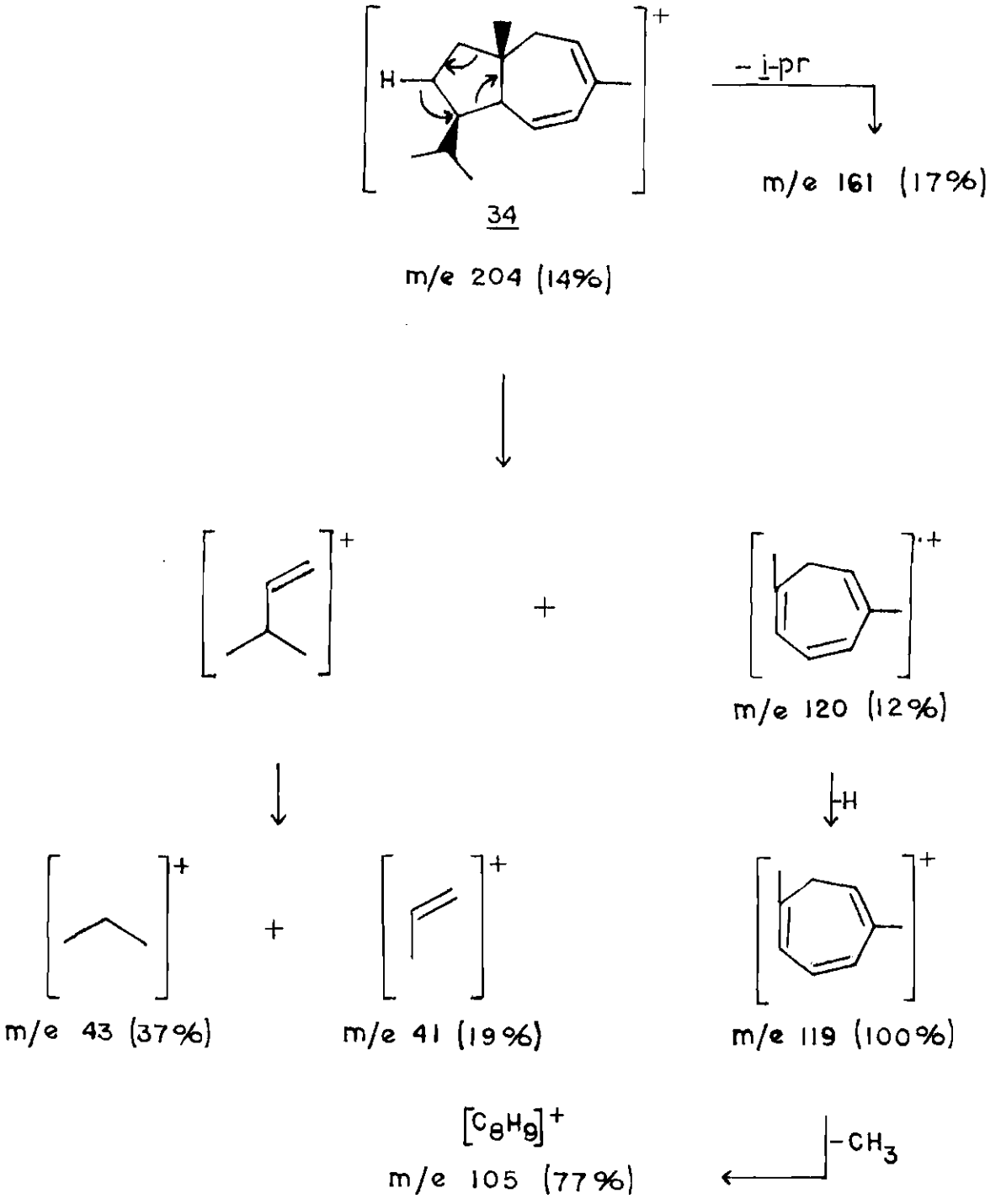
This olefinic mixture was chromatographed on silver nitrate-silica gel. The first fraction eluted contained pure daucene (5), which exhibited spectral properties identical to those of authentic material. Each of four additional fractions eluted from this column contained one of the four remaining components of sufficient purity so as to be isolated at least 98 percent pure by preparatory gas chromatography.

The presence in this mixture of acoradienes 9 and 10, indicated by

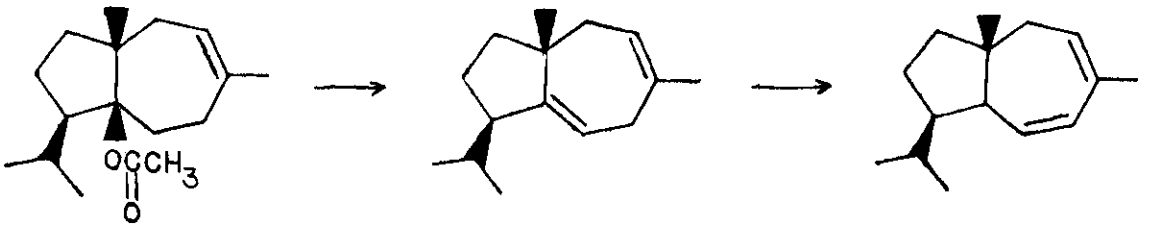
GC, was confirmed by comparison of spectral properties of these compounds with those of authentic materials.

The IR spectrum of olefin 34 showed absorption for a cis-disubstituted double bond (710 cm^{-1}) and a trisubstituted double bond (815 cm^{-1}). The methyl group region of the ^{1}H-NMR spectrum showed a pseudo-triplet corresponding to the overlapping pair of doublets from an isopropyl group, as well as a singlet due to a methyl group attached to a quaternary carbon atom. A singlet due to a methyl group attached to a double bond was also present. The olefinic region of the spectrum showed a doublet at δ 5.67 ppm (J = 10 Hz) which integrated for one proton. An unsymmetrical doublet which integrated for two protons was observed at δ 5.23 ppm (J = 10 Hz). The downfield signal in this doublet integrated for 1.5 protons, and the upfield signal for 0.5 protons. These results supported the infrared evidence for the presence of both di- and tri-substituted double bonds. Although the extinction coefficient was extremely low, the ultraviolet spectrum suggested conjugated double bonds.

The mass spectrum showed a molecular ion of m/e 204, indicating a $C_{15}H_{24}$ formula. Possible pathways to all of the major peaks in the mass spectrum of olefin 34 are given below. This proposed sequence requires the double bonds to be conjugated in the seven-membered ring. This structure appears logical in view of the spectral evidence obtained and the conditions under which this compound was formed. Deprotonation into the seven-membered ring of the carbonium ion formed by loss of acetate, or a direct cis elimination, followed by isomerization to the more stable conjugated olefin would give the proposed structure (34).



The ^{1}H-NMR spectrum of olefin 35 showed a one proton multiplet in the olefinic region, and only one three proton singlet in the methyl group



33 34

region. Integration of the spectrum revealed the remaining three methyl groups to all be attached to double bonds. One of these must be attached to the same double bond as the olefinic proton. The remaining two must be part of an isopropylidene group. Due to the small amount of material on hand, the IR spectrum was obtained in solution and any olefinic carbon-hydrogen bending present was occluded by solvent absorptions.

The mass spectrum of olefin 35 showed a molecular ion of m/e 202, and therefore a formula of $C_{15}H_{22}$. The base peak at m/e 159 corresponded to loss of an isopropyl group from the molecular ion. These results do not agree with the presence of an isopropylidene or a formula of $C_{15}H_{24}$. The spectrum was therefore obtained again on a sample purified from the same original mixture by preparatory gas chromatography at a later date. This mass spectrum was almost identical to that obtained earlier. It seems highly unlikely that reduction would have occurred, even under the heterogeneous reaction conditions employed in this case. A trisubstituted double bond is present, and loss of acetic acid could produce a second double bond, but a mechanistic explanation for the third double bond (or ring) is difficult to imagine.

Carotol acetate was finally purified by vacuum distillation from potassium carbonate in an all glass apparatus which had been washed with

10 percent potassium hydroxide, then rinsed in distilled water and dried. (Distillation without these precautions resulted in a distillate consisting of almost 50 percent rearranged products.)

Reaction of carotol acetate (33) with 90 percent formic acid at room temperature for 30 minutes gave 83 percent daucene (5) and 17 percent acoradiene 9. A small peak (1 percent) corresponding to acoradiene 10 was observed in the GC trace. Had the reaction been continued, this compound most probably would have comprised a larger part of the mixture. When this reaction was allowed to proceed for 10 days, the products and composition of the mixture were essentially the same as those from carotol (3) under the same conditions.

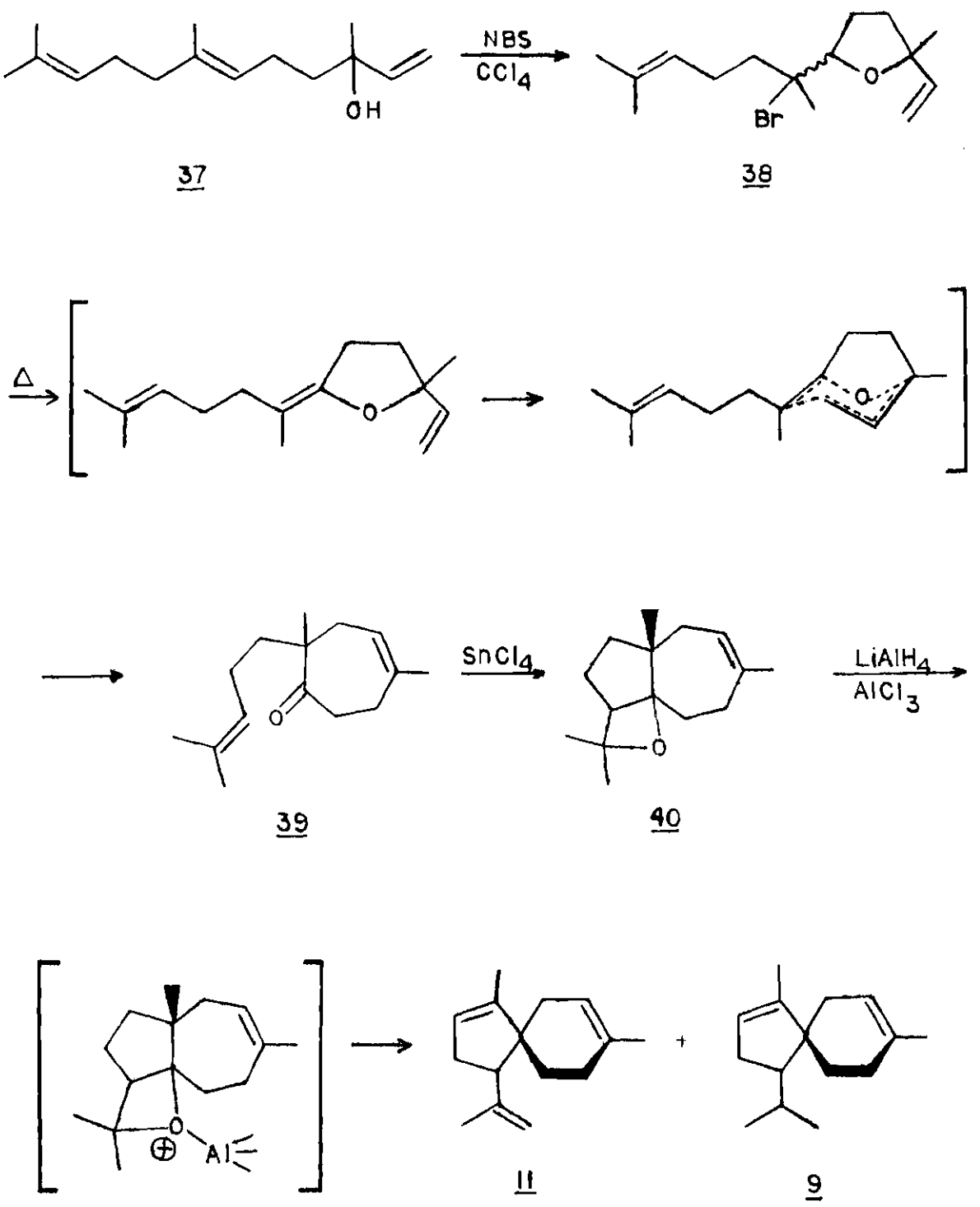
Carotol acetate (33), then, is more reactive than carotol (3) under some of the conditions used. To determine the effect of the double bond in the seven-membered ring on reactivity in carotol acetate, dihydrocarotol acetate (36) was prepared by hydrogenation of carotol acetate. This oil obtained was successfully purified by distillation from potassium carbonate. Preparation of this compound by reaction of acetyl chloride with dihydrocarotol (14) resulted in a mixture of six GC detectable products, only 36 percent of which was the desired acetate.

The spectral properties of dihydrocarotol acetate (36) were very similar to those of carotol acetate (33). The ^{13}C-NMR showed barely detectable peaks corresponding to the epimer of the major product, indicating that reduction occurred predominantly from one face of the molecule. Catalytic hydrogenation of dihydrocarotol (14), discussed above, showed a two-to-one ratio of epimers.

Reaction of dihydrocarotol acetate (36) with formic acid gave the same compounds as reaction of dihydrocarotol (14) under identical conditions: olefin 15 (81 percent), olefin 16 (16 percent), and olefin 17 (3 percent). The products were identified by mixed GC injection with authentic samples on three different GC columns. The percentages of the major epimer products (15 and 17) and the minor epimer product (16) are in a five-to-one ratio, agreeing with the conclusions reached from ^{13}C-NMR peak height evidence. These results offered more evidence for participation of the double bond in the seven-membered ring in complex rearrangements. Without this double bond, only simple dehydration products are obtained, even with a good leaving group at the site of initial reaction.

Carotol ether (40), an unusual ether related to carotol, has been prepared by Demole et al. in their synthesis of cedrene.[23] The synthesis of carotol ether (40) and its rearrangement to the acorane skeleton is given in Figure 10. Reaction of nerolidol (37) with N-bromosuccinimide (NBS) in carbon tetrachloride is thought to involve formation of a bromonium ion at the central double bond of nerolidol. Reaction of this bromonium ion with the hydroxyl group produces the bromo tetrahydrofuranyl intermediate (38). This bromo intermediate is then refluxed, without isolation, in collidine causing dehydrobromination and a [3,3] sigmatropic rearrangement which forms cycloheptenone 39. This cycloheptenone is converted into carotol ether (40) by a [2 + 2] cycloaddition catalyzed by tin (IV) chloride.

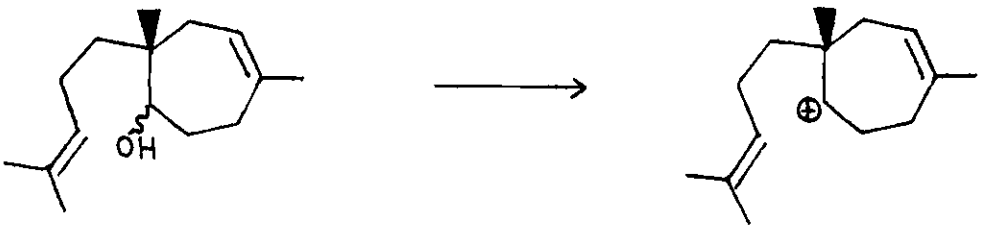
It is interesting that this laboratory synthesis of carotol ether involves an intermediate very similar to that postulated in the biogenesis of carotane sesquiterpenes (Figure 1). The spectral properties of cycloheptenone 39 were identical to those reported in the literature.[23]



37 38 39 40 11 9

Figure 10. Synthesis of Carotol Ether (40)[10]

Reduction of this ketone should produce cycloheptenol 42, which upon solvolysis may give the postulated biogenetic intermediate. Cycloheptenol 42 was prepared from cycloheptenone 39 by reduction with lithium aluminum hydride. The spectral properties observed for this alcohol were consistent with the assigned structure. It is interesting that the ^{1}H-NMR spectrum showed two singlets, in a two-to-one ratio, for the methyl group attached to the quaternary carbon atom. The ^{13}C-NMR spectrum also showed the non-stereospecific nature of this reduction by the presence of two signals for each carbon atom in the molecule.



42

Cycloheptenol 42 was refluxed overnight in acetone containing several drops of 90 percent formic acid. No change was observed in the GC trace of the mixture. The oil obtained on work-up was shown to be starting material by comparison of spectral data with those of an authentic sample. Reaction of this alcohol in refluxing formic acid produced a mixture of three major compounds in addition to starting material. Reaction for three hours in formic acid at room temperature also produced a complex mixture (15 compounds as detected by GC). Since none of these reaction conditions yielded mixtures containing a single major product (greater than 50 percent of the mixture), preparation of the tosylate of alcohol 41

was deemed necessary. The cycloheptenol tosylate (43) should react under very mild conditions and give an intermediate containing a great deal of free carbonium ion character. In this manner it was hoped to obtain a single (at least major) product, presumably cyclized to the carotane skeleton. Preparation of tosylate 43 was attempted according to the procedure of Fieser.[30] Only starting material was recovered from this reaction. The procedure was repeated allowing three weeks reaction time in a refrigerator. Again, only starting material was recovered. Further investigation into the reactions of this possible precursor to the proposed intermediate in the biosynthesis of carotol was left for future workers.

Carotol ether (40) was prepared from cycloheptenone 39 as outlined above. The spectral properties of the product were identical to those given in the literature.[23] Reaction of carotol ether with lithium aluminum hydride--aluminum chloride, the next step in the published synthesis of cedrene, was repeated in order to obtain a sample of acoratriene 41. The product mixture obtained contained at least seven GC detectable components, which could not be separated by the published procedure.[23]

Carotol ether appeared to be a likely candidate for conversion into carotol (3). Demole has reported preliminary attempts at achieving this goal using lithium aluminum hydride in various solvents without success. A strong Lewis acid ($SnCl_4$) was used in the preparation of carotol ether. It was therefore of interest to determine the result of the reaction of pure carotol ether with another acid. Carotol ether was stirred three hours in 90 percent formic acid. A GC trace of a sample obtained from the reaction mixture showed three products in addition to carotol ether, which comprised 63 percent of the mixture. The solution was then heated to 50°C

and stirred at that temperature for three hours. The reaction was worked up and found by GC to contain seven components, including carotol ether (21 percent). These products were partially purified by chromatography, but due to the small yield of purified products eluted, only IR spectra were obtained. Those spectra showed the presence of an alcohol, formate, and several olefins in the original mixture. Further investigation of this potentially useful reaction is needed.

Dihydrocarotol ether (44) was prepared from carotol ether (40) by catalytic hydrogenation at atmospheric pressure. The spectral properties of this compound were similar to those of carotol ether. Reaction of dihydrocarotol ether with tin (IV) chloride produced a complex mixture of five GC detectable compounds, including 15 percent unreacted starting material. Chromatography of this mixture on silica gel removed the starting material, but no further purification was achieved. The IR spectrum of the mixture eluted contained a carbonyl absorption at 1700 cm^{-1}. The ^{1}H-NMR spectrum indicated the presence of olefinic hydrogens by a multiplet at δ 5.25 ppm.

After treatment of dihydrocarotol ether with 90 percent formic acid for 30 days, less than 10 percent reaction was observed by GC. Since dihydrocarotol ether did not form any major products upon treatment with either of these acids, investigation of this compound was terminated.

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

A reinvestigation of the dehydration of carotol (3) by thionyl chloride has shown the presence of two new products in addition to the previously reported daucene (5). These products have been isolated and identified as acoradienes 9 and 10. A biogenetic pathway to these products has been proposed. The importance of the seven-membered ring double bond in the rearrangement has been demonstrated by the absence of acorane products in the dehydration of dihydrocarotol (14).

The acoranes have not been considered biogenetically related to the carotane sesquiterpenes. In light of the facile conversion of carotol to acoradienes presented in this work, a study of the conversion of acorane to carotane skeletal types should be undertaken to shed more light on the biogenesis of both types of sesquiterpenes.

Upon prolonged treatment with formic acid, carotol (3) and daucene (5) gave the same mixture of five products. The structures of the major products, alcohol 25 and formate 26, were determined from spectral evidence, especially ^{13}C-NMR. An X-ray crystallographic study of a heavy atom derivative of alcohol 25 should confirm the structure and stereochemistry of these products. Perhaps ^{13}C-NMR shift studies (especially off resonance studies) would give further spectral proof of these structures. Confirmation of the structure of ether 24 should be obtained. This compound should be readily prepared from daucol. A structure was proposed for one (olefin

22) of the two minor products in the mixture. The structure of the other minor product could not be determined from the minimal spectral evidence available, and awaits reinvestigation.

Further investigation into the mechanism of the formation of these products would also be of interest. Preliminary studies of the composition of the mixture with time have shown the large amount of daucene initially present rearranges rapidly to alcohol 25 and formate 26. Originally, more formate is produced, but hydrolyzes to alcohol with time, so that the equilibrium mixture contains approximately 60 percent alcohol 25 and 20 percent formate 26. A plot of the composition of the mixture with time shows an unexpected plateau in the curve representing alcohol 25. Further study should be done to determine if this plateau really exists.

A study of the reaction of carotol (3) and daucene (5) with other acids would be pertinent. Changes in the acidic medium of the reaction would likely change the nature and reactivity of the carbonium ions formed. The composition of the product mixture may change or an entirely different set of products created. The proposed mechanism for the formation of alcohol 25 involves an acorenyl cation. Acoradienes are known products of reaction of carotol with formic acid. The acorane sesquiterpenes are therefore prime candidates for study as possible biogenetic precursors to tricyclic sesquiterpenes.

Carotol acetate (33) gave the same products as carotol (3) when treated with formic acid. Whereas carotol acetate rearranges on silica gel, carotol does not. The major products of this rearrangement were identified as daucene (5), acoradiene 9, and acoradiene 10. Two minor products need further structural clarification. Finally, the reactions

of the epoxides of olefins 15 and 16 must be studied in greater detail.

Biogenetically, cycloheptenol 42 is of great importance as a potential precursor of a postulated intermediate in the biogenesis of carotol (3). By using various conditions and by variations in the nature of the leaving group derived from this alcohol, a broad spectrum of intermediates, with varying amounts of positive charge on the seven-membered ring will give an opportunity to simulate "in vitro" the postulated biogenesis of carotol.

This work, then, begins an investigation into the chemistry of the carotane sesquiterpenes. Much work remains to be done. Now that a few of the structures of the many products formed by the carotanes are known, and some of the chemistry of the carotanes investigated, it is possible to begin a more systematic study into this interesting area of natural products chemistry.

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21. The ^{13}C-NMR spectra were run by Mr. James Horton; Acknowledgment is made to the National Science Foundation for partial support of the PFT-100 spectrometer.

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VITA

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In August, 1968 he married Rebekah Abbott of Bristol, Tennessee. They have a son, Christopher, and a daughter, Caroline.

Graduate studies in the School of Chemistry at the Georgia Institute of Technology were begun in September, 1969.

Mr. Clower is a member of the American Chemical Society and the Society of the Sigma Xi.

ERRATA

Page 2, line 11: azidine, read aziridine.

Page 5, line 1: endo-aziridine, read endo-aziridine 5c.

Page 35, line 11: D,L-alaninate, read dl-alaninate.

Page 79, line 14: $[5.5.0.0.]^{1,4}$, read $[5.5.0.0^{1,4}]$.

Page 82, line 15: same as page 14.

Page 89, line 9: coplainarity, read coplanarity.

Page 92, line 5: reference 26, read reference 30.

Page 98, line 23: reference 27, read reference 32.

Page 99, line 3: paladium, read palladium.

Page 99, line 20: reference 28, read reference 32.

Page 113, line 6: perchlorid, read perchloric.