I. SYNTHESIS OF dl-cis-TETRAHYDROEREMOPHILONE

II. STUDIES ON SYSTEMS FREE FROM ANGULAR STRAIN

Thesis by

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ABSTRACT

I. The total synthesis of racemic cis-tetrahydroeremophilone (17) has been achieved. The key feature of the synthesis was a solvolytic cyclization that proceeded through a symmetrical cation 41 and gave rise to two major products, one of which had the stereochemistry required for the synthesis of tetrahydroeremophilone.

II. Attempts on the synthesis of the alcohol 1 have been investigated in three related reaction sequences (Schemes 1, 4, 5, and 6). Although none of the reaction sequences gave the desired alcohol 1 that was intended for use in a solvolysis study, an unexpected product, the keto acetate 48, resulted in one sequence and afforded adamantanone (44) upon chromatography on alumina.

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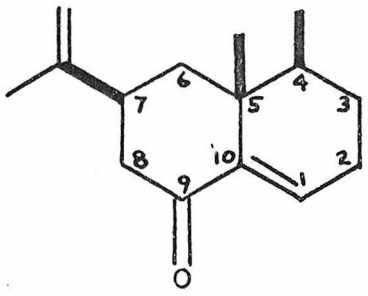
PART I

THE SYNTHESIS OF dl-cis-TETRAHYDROEREMOPHILONE

INTRODUCTION

Eremophilone (1), a non-isoprenoid sesquiterpene, has attracted the interest of chemists who are engaged in the elucidation of the structure of natural products, and also those who are working in organic synthesis. The molecular constitution of l-eremophilone (1) has been determined by Simonsen (1,2) and Djerassi (3,4) and



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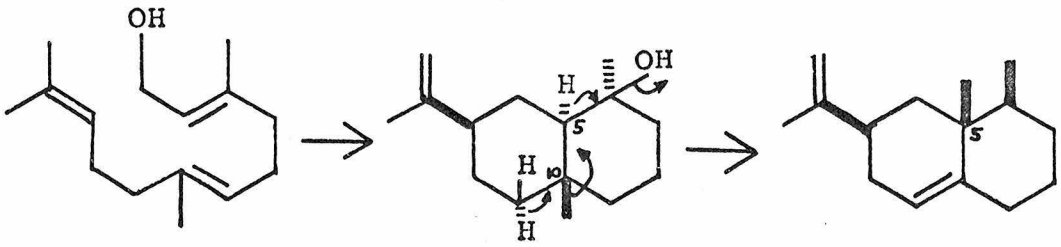
their co-workers. An important feature of structure 1 is the appearance of a β-methyl group at C_5. At some stage in the biogenesis of the eremophilane sesquiterpenes from farnesol (2) (5a), possibly by way of an intermediate such as neo-intermedeal (3) (5b), the methyl group originally at C_{10} in 3 has migrated to C_5, as illustrated in a possible eremophilone precursor 4. Therefore, the rearranged structures do not follow the isoprene rule (6), which states that the structures of terpenes are composed of five-carbon isoprene units,

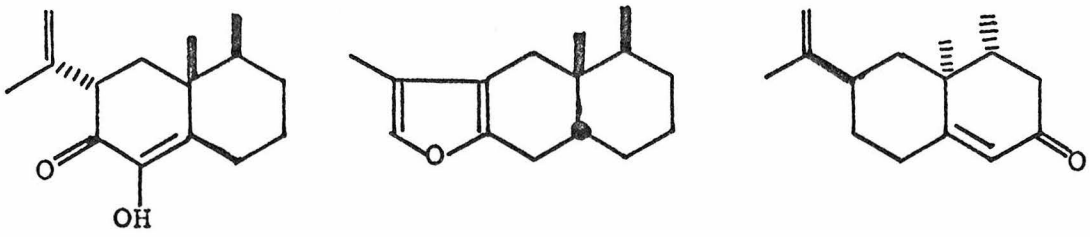
which are linked head-to-tail or tail-to-tail.



2 3 4

⟶ Eremophilane sesquiterpenes

The importance of eremophilone (1) as a natural product has become enhanced recently, since it heads a rapidly expanding list of eremophilone sesquiterpenes. The skeletal characteristics of this class of sesquiterpenes is demonstrated by the following illustrative examples: eremophilone (1); hydroxyeremophilone (5) (3); furanoeremophilane (6) (7,8); nootkatone (7) (9); aristolene (8) (10); and α-ferulene (9) (11). The latter two compounds, being optical isomers, are included to illustrate the occurrence of some eremophilane sesquiterpenes in optically antipodal forms.



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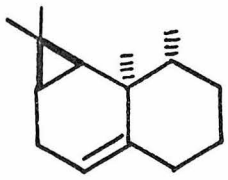

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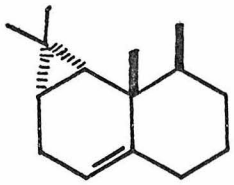

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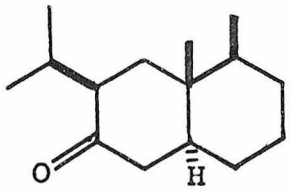
As the discovery of new types of eremophilane sesquiterpenes has increased, attempts at the total synthesis of these natural products have also been expanded. The first compounds related to eremophilone to have been synthesized (4) were ketone 10, which has the eremophilone stereochemistry, and ketone 11, which is a degradation product of eremophilone and has the hydroxyeremophilone stereochemistry. Although neither



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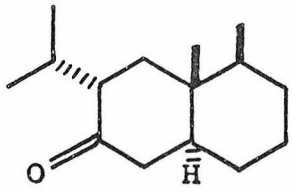

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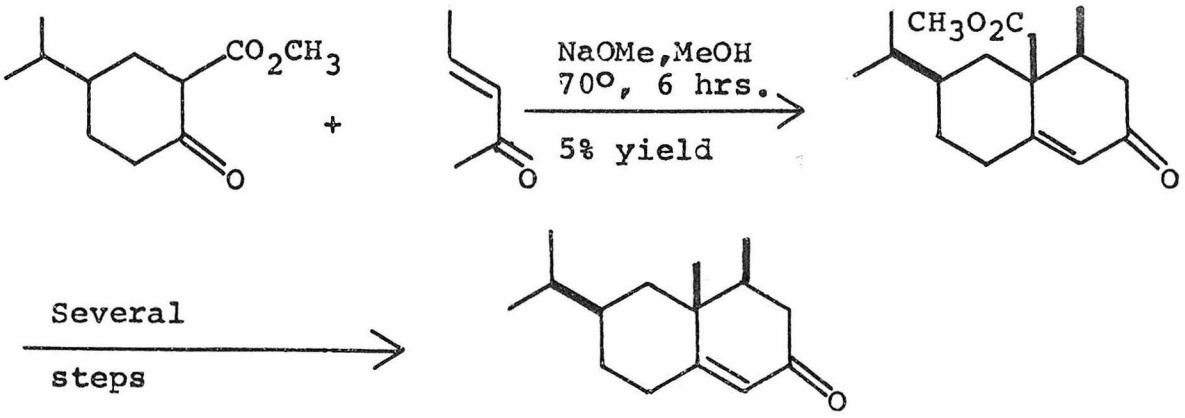
of these two ketones has been found in nature, they have played an important role in the assignment of the absolute configuration of eremophilone and related sesquiterpenes.

Another degradation product of eremophilone (1), enone 12, has been prepared in racemic form by Piszkiewicz (12). The main feature of this synthesis is a Michael reaction, which introduces all the asymmetric centers simultaneously, albeit in low yields.



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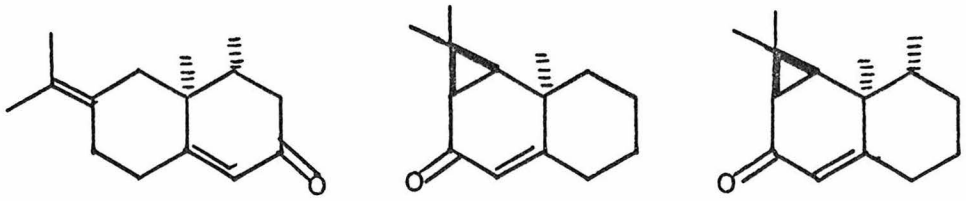
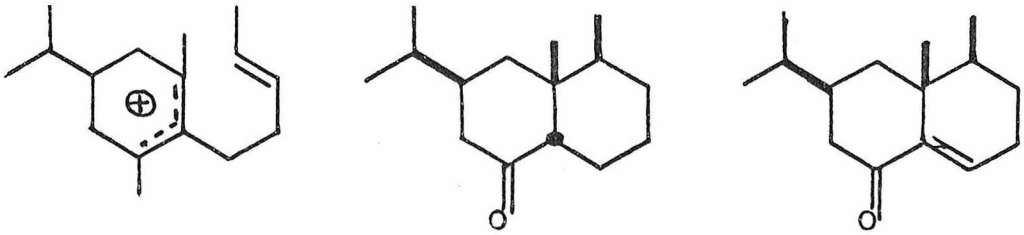
The total synthesis of racemic isonootkatone (13), which contains only two asymmetric centers, has been reported by Marshall and co-workers (13). This compound represents the first synthesis of a naturally occurring eremophilane sesquiterpene to be reported. The synthesis of racemic 4-demethylaristolone (14) has been successfully completed (14), and also progress has been reported on

the total synthesis of aristolone (15).



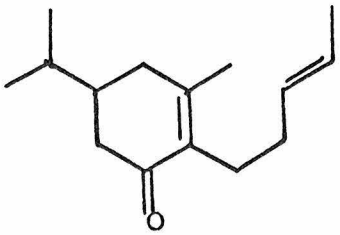
13 14 15

The present work was initiated in an effort to prepare by solvolysis a symmetrical cation 16, which would cyclize to give three cis-alkyl groups on an octalin carbon skeleton and would thereby lead to the synthesis of tetrahydroeremophilone 17 or dihydro-eremophilone 18. The results of this study are discussed below in three sections. The first phase describes the



16 17 18

preparation of the monocyclic dienone 19, which was previously prepared by Chan (15) in this laboratory. Chan's work is summarized here in order to present a complete account of these synthetic studies. The second



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phase concerns the solvolytic cyclization, and the third phase describes the successful conversion of one product of the cyclization into racemic cis-tetrahydroeremophilone (17).

DISCUSSION AND RESULTS

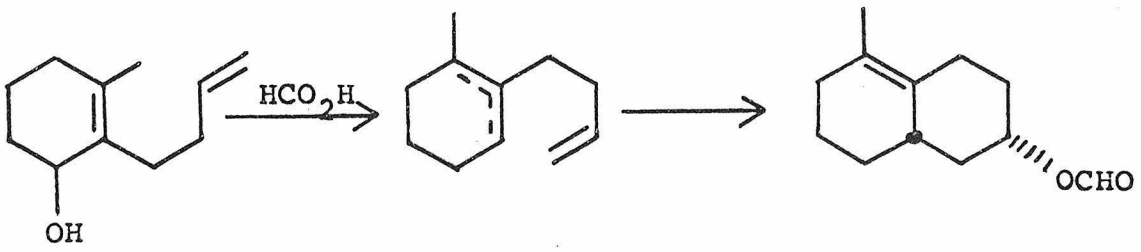
The Monocyclic Dienone 19. The first key monocyclic intermediate was the dienone 19, which was prepared by Chan (15) by the alkylation of enone ester 20 with trans-1-bromopentene-3 (21). The enone methyl ester 20 was prepared in quantity by Chan (15) who used a modification of the procedure of Horning and coworkers (16) for the preparation of the corresponding ethyl ester. The condensation of two moles of methyl acetoacetate with one mole of isobutyraldehyde in the presence of piperidine catalyst yielded a monocyclic bis-ester 22, which was partially hydrolyzed and decarboxylated in the presence of sulfuric and acetic acids to give a mixture of enone esters in 69% yield. Vapor phase chromatography (v.p.c.) indicated the following composition of the ester mixture: 5% of 3-methyl-5-isopropyl-2-cyclohexen-1-one (23), 17% of 4-carbomethoxy-3-methyl-5-isopropyl-3-cyclohexen-1-one (24), and 78% of cis- and trans-4-carbomethoxy-3-methyl-5-isopropyl-2-cyclohexen-1-one (20). Since all three enone esters (cis-20, trans-20, and 24) would lead to the same enolate anion 25 upon treatment with a strong base, further purification at this stage was not necessary.

In order to prepare the bromide 21 that was required for the alkylation of enolate 25, the procedure of Julia and co-workers (17a) was used by Chan (15). However, in another preparation by this author cyclopropylmethyl ketone (26) was reduced with lithium aluminum hydride according to the procedure of Overberger and Borchert (17b) to the corresponding cyclopropylmethylcarbinol (27) (96% purity). The product analysis was done by v.p.c. on a Carbowax 20M column. When a sample of carbinol 27 (96% 27, 4% 26) was stirred with 48% hydrobromic acid for 10 min. at 25°, a mixture containing 5% ketone 26, 9% olefin, 50% bromide 21, and 36% of a second bromide 28 was obtained by v.p.c. analysis. However, bromide 28 was converted completely to bromide 21, when the mixture was filtered through a short column of alumina (I). Since Chan (15) observed cyclopropyl hydrogens in the n.m.r. spectrum in his preparation, bromide 28 is probably cyclopropylmethylcarbinyl bromide, a product that was observed in the reaction of phosphorous tribromide with carbinol 27 (18).

The alkylation of enone esters 20 and 24 with bromide 21 was conducted by Chan (15) with the use of sodium hydride in benzene-dimethylformamide. A 5:1 ratio of C-alkylated ester 29 to O-alkylated ester 30 was produced (54% yield). The mixture of esters 29 and 30 was

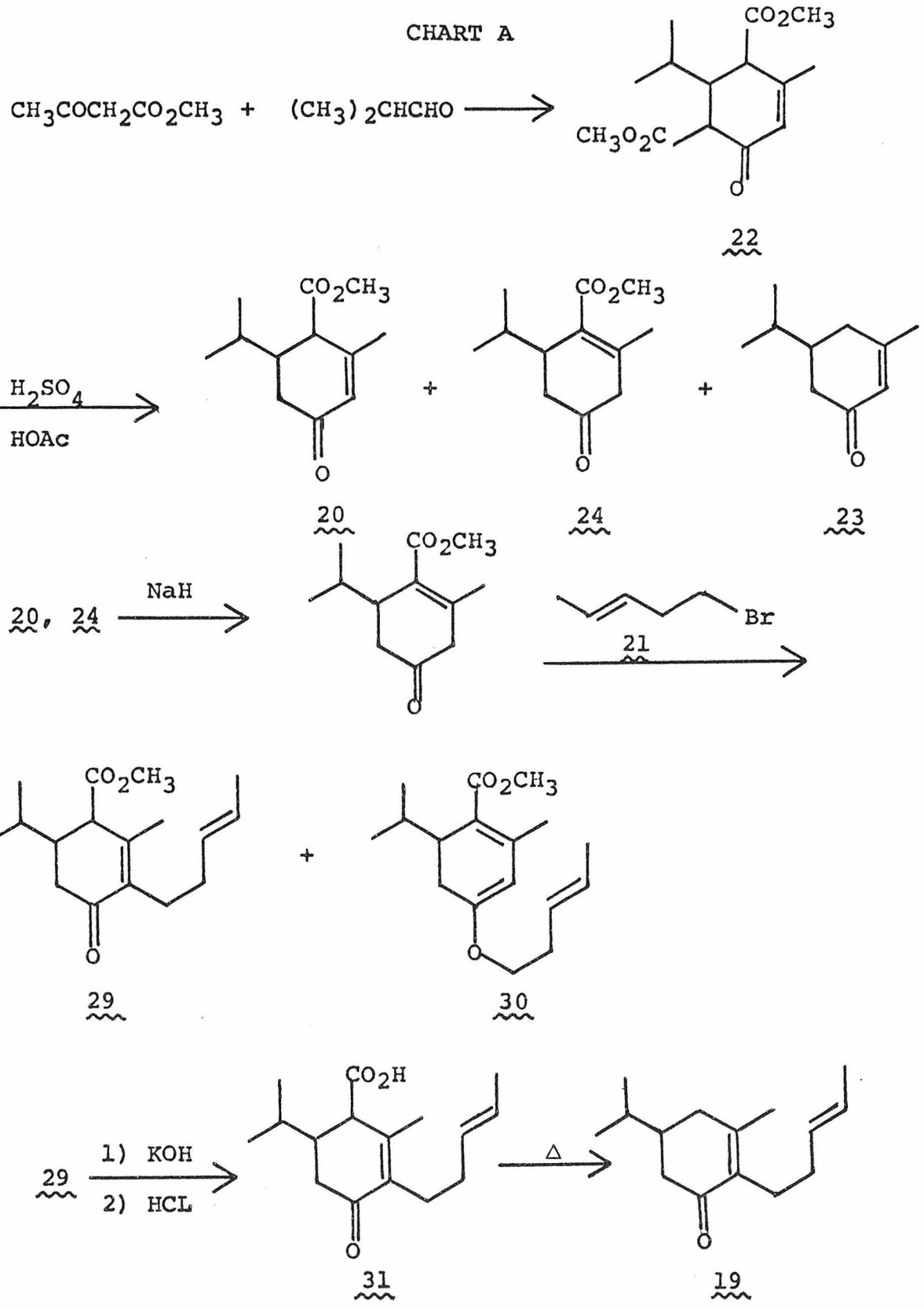
saponified mildly with potassium hydroxide in aqueous methanol. The neutral material isolated from the reaction consisted largely of the O-alkylated ester 30, and the alkaline residue gave crude acid 31 upon acidification with hydrochloric acid in 72% yield. The crude acid 31 was decarboxylated thermally at 100-140° under water aspirator pressure to give a 77% yield (30% overall from esters 20 and 24) of the desired dienone 19, b.p. 90-92° (0.5 mm.).

The Solvolytic Cyclization. Solvolytic cyclizations of polyolefins are established methods for the preparation of substituted octalins that are important intermediates in the synthesis of natural products. Johnson and co-workers (19, 20) have studied the cyclization of the dienol 32, which cyclizes in the direction of the secondary carbon rather than the tertiary carbon of the allylic cation 33 to give formate 34. Furthermore, by using the methyl homolog, Marshall and co-workers (21, 22) have shown that

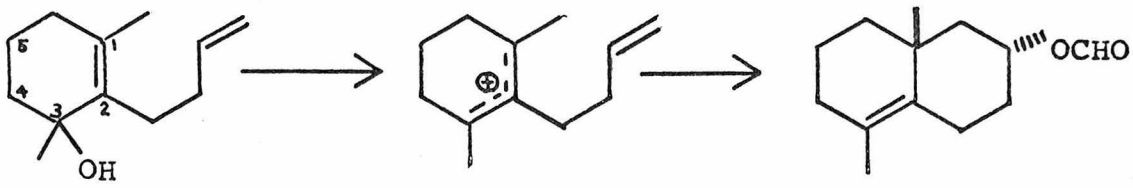


32 33 34

CHART A


CH3COCH2CO2CH3 + (CH3)2CHCHO
CO2CH3
CH3O2C
O
22
H2SO4
HOAc
CO2CH3
O
+
CO2CH3
O
+
O
20
24
23
20, 24
NaH
CO2CH3
O
Br
21
CO2CH3
O
+
CO2CH3
O
29
30
29
1) KOH
2) HCL
CO2H
O
Δ
O
31
19

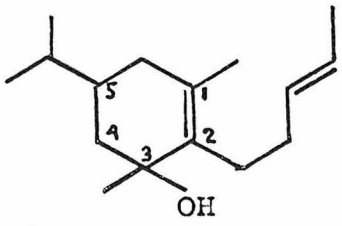
the dienol 35 readily cyclizes by way of the symmetrical cation 36 to the octalyl ester 37, which has the angular methyl group that is found in many sesquiterpenes and higher terpenes.



35 36 37

One of the goals of our work in the synthesis of eremophilone-like structures is the formation of the three asymmetric centers of the bicyclic system in one solvolytic reaction. If an isopropyl group is added to the ring at C_5, and the butenyl side chain is extended to a trans-3-pentenyl moeity, the symmetry of cation 36 is retained. Because the dienol 38 or triene 39 has a trans-double bond in the side chain, the solvolysis product 40 from these precursors should contain two cis-methyl groups. For our purposes, a cis-isopropyl group is required at C_7. There is a possibility that the isopropyl group may influence the stereochemistry of the methyl groups, since the carbonium ion can suffer nucleophilic attack by the double bond on either the surface syn to the isopropyl

group or on the anti-surface. An anti-attack will produce the desired all-cis-arrangement of the alkyl groups, while a syn-attack will give an isopropyl group trans to the angular methyl group.



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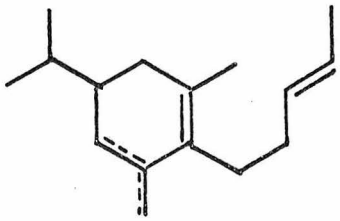

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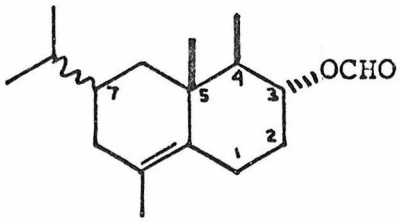

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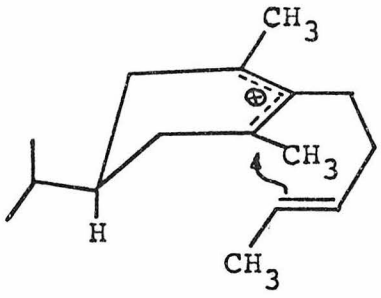

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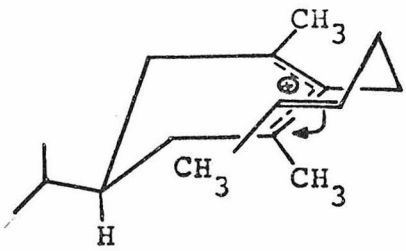
Anti-attack



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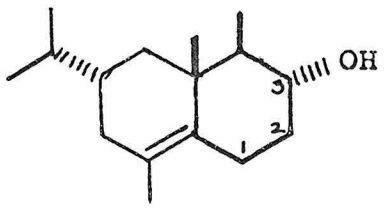
Syn-attack

The C-15 ketone 19 was alkylated with methyllithium to give the C-16 carbinol 38 that would generate a symmetrical allylic cation 41 upon treatment with formic acid. In the initial experiments when carbinol 38 was stirred in anhydrous formic acid, a rapid dehydration to olefins occurred first, as evidenced by the separation of an oily layer. Cyclization then occurred to give a

mixture of formates. In later experiments the alkylation of the C-15 ketone 19 was followed immediately by phosphorous oxychloride-pyridine dehydration to afford two trienes 39, on the basis of infrared (ir. and v.p.c. analysis.

The triene mixture 39 was stirred with anhydrous formic acid at 25° for 20 min. to produce a mixture of formates, which was crudely separated from olefins and diformates by chromatography on Florisil. The crude formates 40 obtained in 67% yield, were reduced with lithium aluminum hydride to yield two alcohols 42 and 43 in a ratio of 3:2. Careful chromatography on alumina (IV) yielded a crystalline alcohol 42, m.p. 91-93°, and an impure oily alcohol, which was purified by conversion to the 3,5-dinitrobenzoate 44. After having been recrystallized from hexane, the ester 44, m.p. 117-119°, was reduced with lithium aluminum hydride to afford a second crystalline alcohol 43, m.p. 47-54°. The stereochemical assignment of these alcohols is based upon the conversion of alcohol 43 to cis-tetrahydroeremophilone (17), which is known to possess the all-cis-configuration. The alpha orientation of the hydroxyl groups is supported by the findings of other workers (20, 21, 22) on related cyclizations and by the nuclear magnetic resonance (n.m.r.) splitting pattern of the C_3 hydrogen of the benzoate derivative of 42 and

and the 3,5-dinitrobenzoate 44. With both esters the C_3 hydrogens appear as triplets (J_2 = 10 Hz.) that are split into sextets by a smaller coupling constant (J_1 = 4-5 Hz.). This splitting pattern is consistent for an axial hydrogen adjacent to two other axial hydrogens and one equitorial hydrogen on a six-membered ring.



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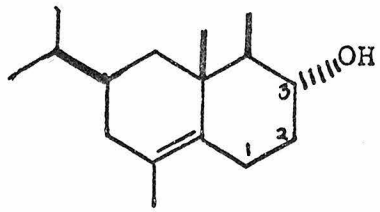

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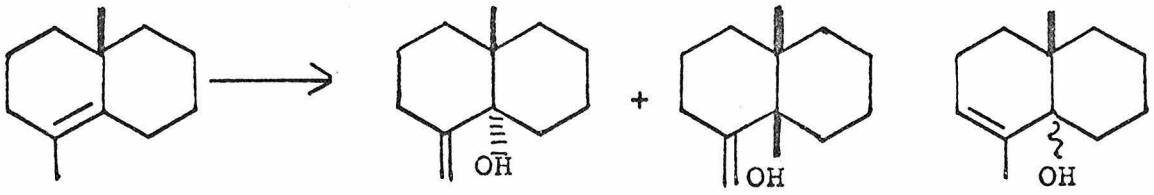
Conversion of Alcohol 43 to cis-Tetrahydroeremophilone. The transformation of the C-16 alcohol 43 to tetrahydroeremophilone required first the removal of the oxygen function at C_3. In order to remove the sixteenth carbon by ozonolysis, the next step was to convert the methyl substituted double bond into a function containing an exocyclic methylene group by photo-oxidation. Marshall and co-workers (22, 23) used the hematoporphyrin sensitized photo-oxidation of methyl substituted double bonds in pyridine followed by lithium aluminum hydride reduction of

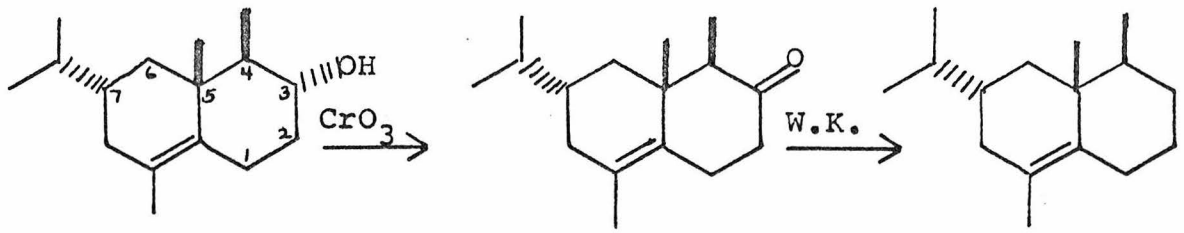
the hydroperoxides as a means of generating allylic alcohols 45, 46, and 47 from olefin 48. Forbes and Griffiths (24) reported a method of photo-oxidation that



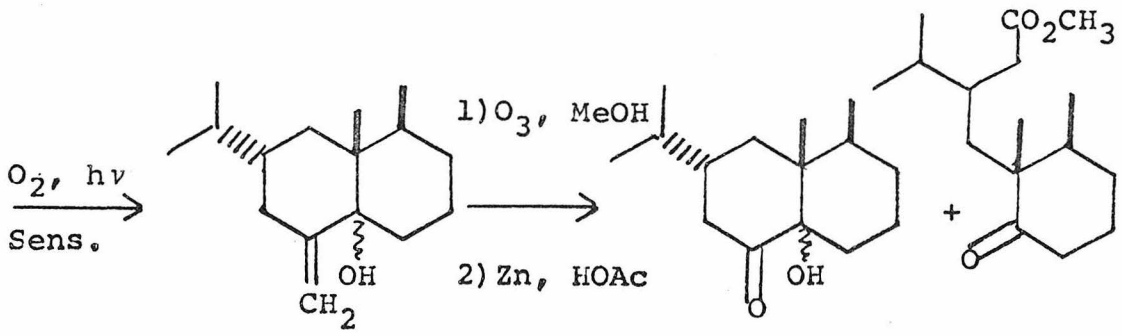
48		45		46		47
	product ratio	9	:	5	:	6

used rose bengal or hematoporphyrin as sensitizer in a solvent system composed of carbon disulfide, methanol, and ether in a ratio of 28:2:3. The advantages of this modification were the shorter reaction time (one to two hours) that was required for tetrasubstituted double bonds, the use of an incandescent light source, and the excellent yields of allylic peroxides obtained.

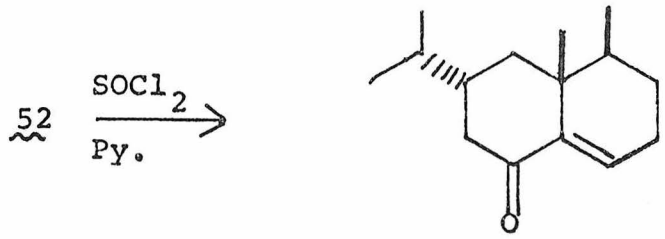
In the first series of reactions the isomeric alcohol 42 was oxidized with chromic acid (25) to the ketone 49, which was reduced (26) to the olefin 50. When olefin was photo-oxidized with hematoporphyrin in pyridine, a very complex mixture of products was obtained. However, when the modification of Forbes and Griffiths (24) was



42 49 50



51 52 53



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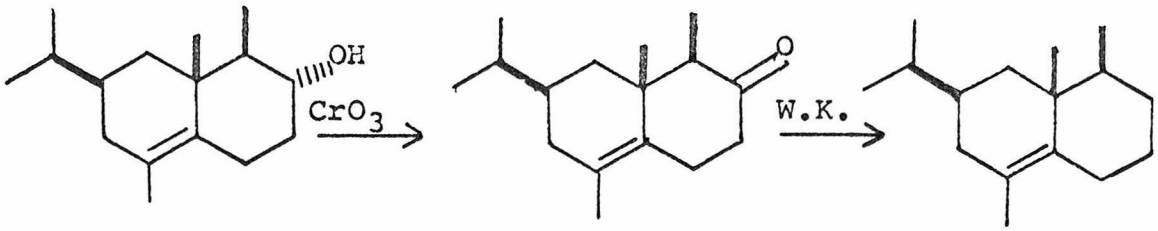
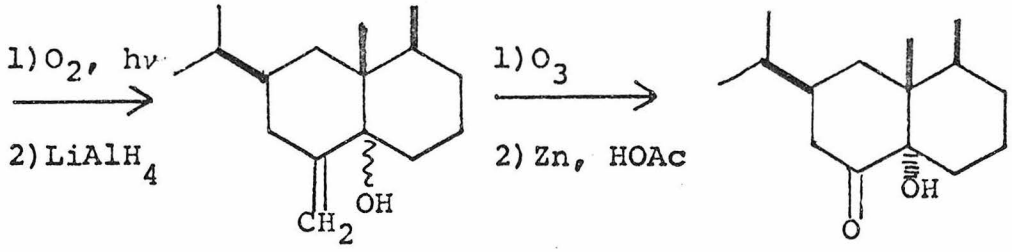
used with rose bengal sensitizer in carbon disulfide-methanol-ether, the oxidation proceeded smoothly within two hours at 10° to give, after lithium aluminum hydride reduction, a mixture that contained two major allylic alcohols. After the most abundant component was purified by chromatography on Florisil, the allylic alcohol 51 was treated with excess ozone in methylene chloride-methanol at -70°. Reduction of the ozonide with zinc dust in acetic acid afforded, after chromatography on Florisil, a low yield of ketol 52, m.p. 98-103°. The major product appeared to be a keto ester 53 resulting from oxidative ring fission. The ketol 52, when stirred with thionyl chloride-pyridine (27), smoothly underwent dehydration to give an α,β-unsaturated ketone 54, which was not dihydro-eremophilone 18 by ir. analysis.

After the model reactions were completed, the isomeric compounds were investigated. Alcohol 43 was oxidized with chromic acid in acetone (25) to afford ketone 57, b.p. 115-120° (1 mm), in 98% yield. Wolff-Kishner reduction (26) of ketone 55 gave olefin 56, b.p. 90-95° (0.8 mm.), in 71% yield.

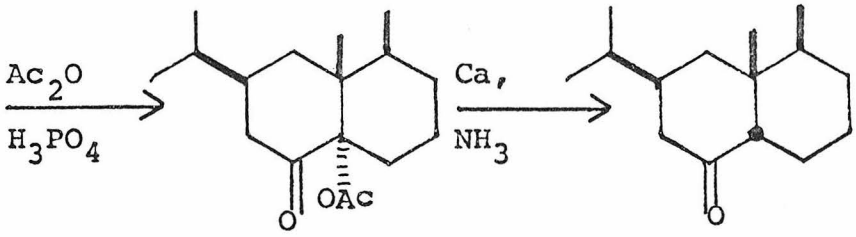
After olefin 56 was photo-oxygenated for two hours with rose bengal sensitizer and a 300-w. tungsten lamp at 8° in carbon disulfide-methanol-ether (24), lithium aluminum hydride reduction of the photoproduct gave a crude



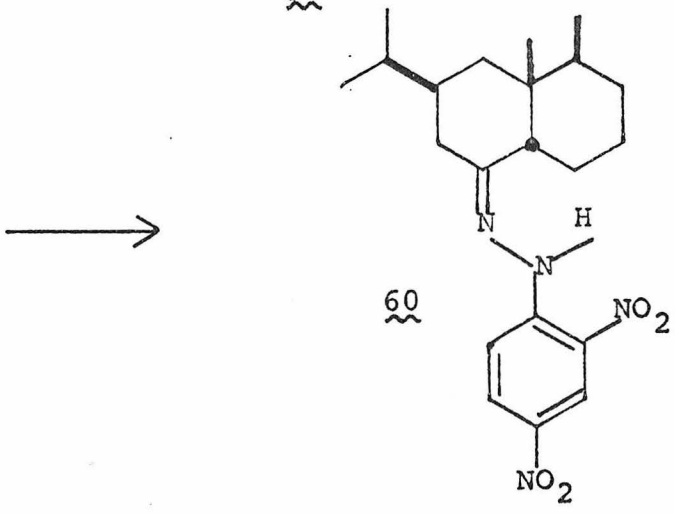
43 55 56



57 58



59 17



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allylic alcohol 57, which was used without further purification. Immediately after the crude alcohol was subjected to ozonolysis by addition to one equivalent of ozone dissolved in methylene chloride at -70° according to the procedure of Johnson and co-workers (28), zinc dust and acetic acid were added to reduce the ozonide. Chromatography on Florisil gave ketol 58, m.p. 70-71°, in 45% yield. The stereochemistry of ketol 58 is based upon previous work (21, 23), which showed that the oxygenation is expected to occur from the less hindered side of the molecule. An attempt to dehydrate the ketol 58 with thionyl chloride-pyridine gave rearranged dehydrated products as evidenced by infrared spectral analysis. Phosphorous oxychloride-pyridine at 25° gave back starting ketol 58. Because the α-isopropyl group at C_7 imposes considerable steric strain on the trans-fused product, the relief of steric strain may be the decisive factor for the trans-diaxial methyl migration to supersede the trans-diaxial removal of a proton. Since the amount of ketol 58 on hand was small, the dehydration or an acetate pyrolysis (29) was not examined in further detail.

Ketol 58 was acetylated with acetic anhydride and phosphoric acid (30) to afford the corresponding keto acetate 59, m.p. 46-48°, in 44% yield. When the keto

acetate 59 was subjected to calcium and liquid ammonia reduction (3), racemic cis-tetrahydroeremophilone (17) was produced in 84% yield. The ir. spectrum of the racemic ketone 17 was identical in all respects to the ir. spectrum of the d-ketone 17 that was prepared according to the procedure of Djerassi and co-workers. (3). The ir. spectra are shown in Figure 1. The v.p.c. retention times of the racemic ketone and the d-ketone 17 were identical by the peak enhancement method. The ir. spectra of the racemic 2,4-dinitro-phenylhydrazone 60, m.p. 141-143°, and d-2,4-dinitro-phenylhydrazone 60; m.p. 181-183°, lit. m.p. 178-179° (1) and 179-180° (31), were identical.

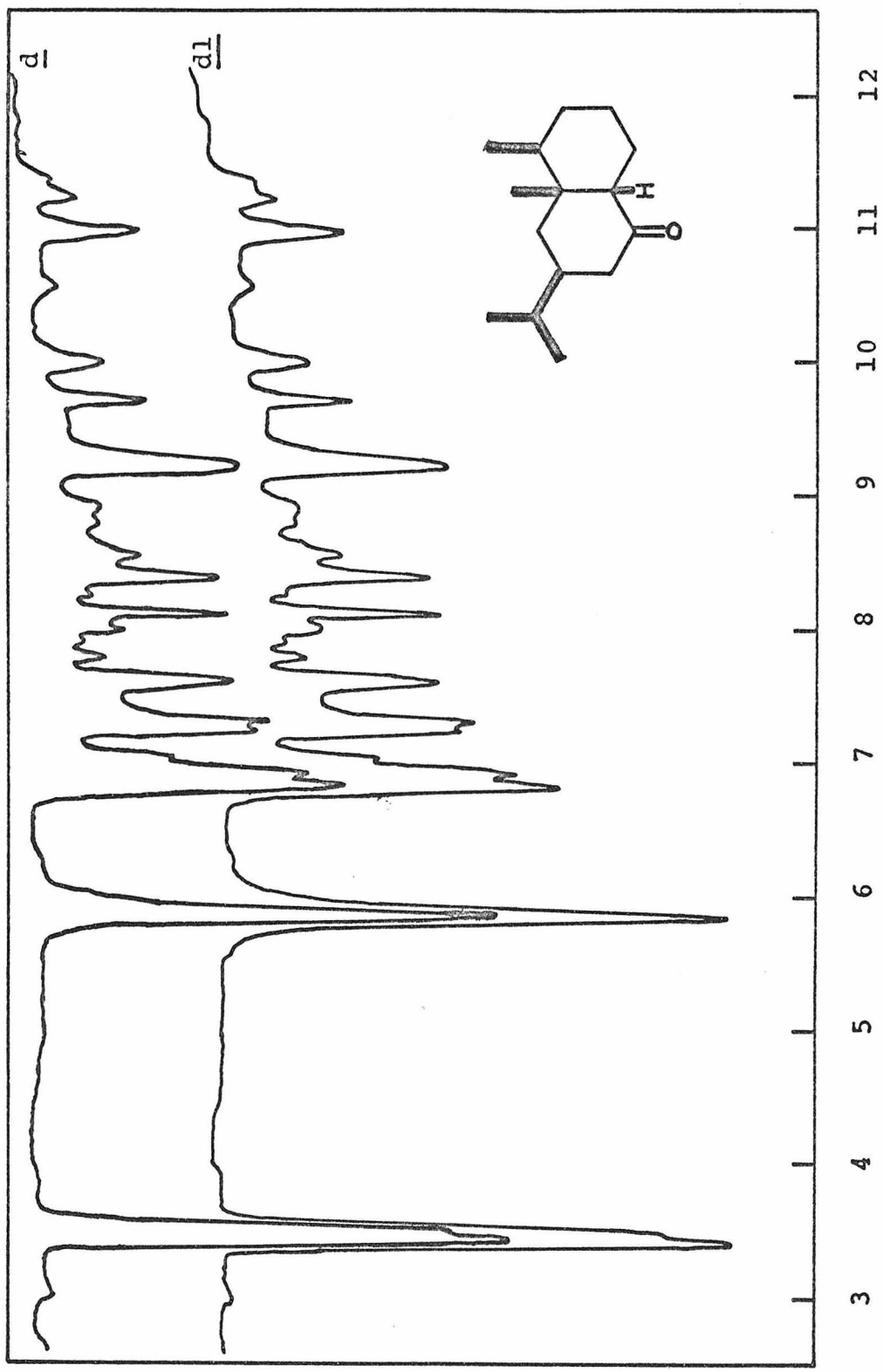

Figure 1. Hand-drawn tracing of the infrared spectra of d- and dl-cis-tetrahydroeremophilone.

CONCLUSION

The total synthesis of racemic cis-tetrahydroeremophilone (17) has been accomplished. The key feature of the synthesis is the solvolytic cyclization, which proceeds through a symmetrical cation 41 and gives rise to two major products. Since one of these products has three cis-alkyl groups, the cyclization reaction can be used to prepare eremophilone-like sesquiterpenes. The ancillary goal of this work to prepare dihydroeremophilone 18 has been unsuccessful to date; however, its preparation from keto acetate 59 may be possible by an acetate pyrolysis reaction.

EXPERIMENTAL

Melting points (m.p.) were determined on a Reichert melting point hot stage and are corrected. Boiling points (b.p.) are uncorrected. Infrared (ir.) spectra were determined on a Perkin-Elmer Infracord Model 137 spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian Associates A-60A spectrometer and are given in delta (δ), parts per million (p.p.m.) downfield from tetramethylsilane. Vapor phase chromatography (v.p.c.) was performed on a Perkin-Elmer Model 881 Chromatograph with a hydrogen flame detector. The activity of the alumina used for chromatography was standardized according to the procedure of Brockmann and Schodder (32). Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Galbraith Laboratories, Inc., Knoxville, Tennessee.

Cyclopropylmethylcarbinol 27.

A. The procedure of Julia and co-workers (17a) was used by Chan (15) to prepare carbinol 27.

B. The procedure of Overberger and Borchert (17b) was used by this author to prepare carbinol 27: b.p. 118-120°, Lit. b.p. 123-123.5° (17b).

Preparation of trans-1-Bromopentene-3 (21). A modification of the procedure of Julia and co-workers (17a) was used. A 76.6-g. (0.89 mole) sample of cyclopropylmethylcarbinol 27 (96% 27, 4% 26 by v.p.c.) in 100 ml. of ether was treated with 200 ml. of 48% hydrobromic acid. After the reaction was stirred for 20 min. at 25°, the aqueous layer was separated and extracted with two 100-ml. portions of pentane. The combined organic extract was washed with water, saturated sodium bicarbonate solution, water, and finally saturated brine. The extract was dried over anhydrous magnesium sulfate, filtered, passed through a short column of alumina (I), and then concentrated by distillation through an eight inch Vigreaux column. The concentrated bromide was distilled through a four inch Vigreaux column to give 94.1 g. (71%) of colorless, crude trans-1-bromopentene-3 (21): b.p. 114-131°, lit. b.p. 125-126° (17a); v.p.c. (6 ft. of 2% Carbowax 20M) 85% bromide 21, 5% ketone 26, and 10% olefin. This bromide mixture was used without further purification.

Preparation of 4-Carbomethoxy-3-methyl-5-isopropyl-2-cyclohexen-1-one (20). The procedure of Horning and co-workers (16) for the preparation of 4-carboethoxy-3-methyl-5-alkyl-2-cyclohexen-1-ones was adapted for the synthesis of the corresponding methyl ester (15).

In each of three 500-ml. flasks were placed 186 ml. (186 g., 1.6 mole) of methyl acetoacetate. The flasks were chilled in an ice-salt bath, and 70 ml. (55.5 g., 0.77 mole) of isobutyraldehyde were added to each flask. The contents were cooled to 0°, and 2 ml. of piperidine in 5 ml. of ethanol were added to each flask with shaking. After the flasks were kept in an ice-salt bath for 6 hr., the contents were combined and placed in a refrigerator. The mixture was kept in the refrigerator for two days and finally kept at 25° for one day; a mixture of 3-ml. piperidine and 5-ml. ethanol was added each day during this time. The crude bis-ester (yellow oil) was added to a mixture of 600 ml. of acetic acid and 40 ml. of concentrated sulfuric acid. A 10-g. portion of boiling chips was added, and the mixture was heated under reflux for 1 hr.; during this time there was a vigorous evolution of carbon dioxide. The mixture was poured with mechanical stirring into 2 l. of ice water and extracted with ether. The organic layer was stirred with 1.2 l. of water and neutralized by the slow addition of solid sodium carbonate. The ethereal solution of the crude material was washed with 100-ml. portion of 5% sodium hydroxide, dried and crudely distilled under reduced pressure. The fraction boiling at 94-110° (0.5-0.7 mm.), 364 g. (78%), was fractionated through a

six inch Vigreaux column yielding 320 g. (69%) of yellow oil: b.p. 92-97° (.15 mm.); v.p.c. (6 ft. of Carbowax 20M) indicated a mixture of 5% of 3-methyl-5-isopropyl-2-cyclohexen-1-one, 17% of 4-carbomethoxy-3-methyl-5-isopropyl-3-cyclohexen-1-one and 78% of cis- and trans-4-carbomethoxy-3-methyl-5-isopropyl-2-cyclohexen-1-one.

Alkylation of 4-Carbomethoxy-3-methyl-5-isopropyl-2-cyclohexen-1-one (20). This preparation was performed by Chan (15). A 8.16-g. (0.34 mole) portion of sodium hydride, which was prepared by washing 13.9 g. of commercial sodium hydride (58.6% mineral oil dispersion) with dry pentane, was suspended in a solution of 300 ml. of dry benzene and 100 ml. of dry dimethylformamide (DMF) and maintained under a nitrogen atmosphere. A 73.56-g. sample (0.35 mole) of 4-carbomethoxy-3-methyl-5-isopropyl-2-cyclohexen-1-one (20) in 30 ml. of dry benzene was added over a period of 45 min. with cooling in an ice bath. After the addition was completed, the resulting solution was stirred for another 45 min., until the reaction was deep red and homogenous. A solution of 50.2 g. (0.34 mole) of trans-1-bromopentene-3 (21) in 25 ml. of benzene was added rapidly, and the resulting mixture was stirred at 25° for 57 hr. The inorganic salt

was removed by filtration, the filtrate was washed with a 300-ml. and 100-ml. portion of water. The aqueous washings were back extracted with three 50-ml. portions of benzene. The combined benzene extract was washed with 100 ml. of water, 100 ml. of brine and dried over anhydrous magnesium sulfate. Distillation gave 50.49 g. (54%) of the desired alkylated products as a pale yellow oil: b.p. 125-133° (0.2 mm.); v.p.c. (6 ft. of Carbowax 20M) 83:17 ratio of C-alkylated to O-alkylated products contaminated by traces of starting materials.

The 50.49-g. (0.18 mole) sample of alkylation products was dissolved in a 100 ml. of methanol, and the solution was cooled in an ice bath. A solution of 14.43 g. of potassium hydroxide in 50 ml. of methanol and 15 ml. of water was added with stirring. Since the solution turned cloudy at the end of the addition, a 20-ml. portion of methanol was added to insure homogeneity. The reaction was stirred at 25° for 15 hr. and then at 46° for 2 hr. The methanol was removed on the rotary evaporator to yield a deep red oil. A 250-ml. portion of water was added, and the resulting solution was extracted with two 100-ml. portions of ether to remove any neutral material. The combined ethereal extract was washed with water, dried over magnesium sulfate, filtered and evaporated on the rotary evaporator to give 14.56 g. (29%) of neutral oil, which was largely

the O-alkylated product on the basis of the n.m.r. spectrum. Distillation gave a forerun of 2.62 g. of low boiling material, b.p. 60-117° (0.8 mm.), and 12.36 g. of the O-alkylated product: b.p. 117° (0.8 mm.); ir. (film) 5.90 (ester), 6.10 (C=C), 6.40 (C=C) and 10.35 (trans C=C); n.m.r. δ0.82 (d., 6, J = 6 Hz, i-propyl CH_3), 1.65 (d., 3, J = 4 Hz., CH_3C=C), 2.13 (s., 3, ring CH_3C=C), 3.62 (s., 3, CH_3O), 3.74 (t., 2, J = 7 Hz., OCH_2CH_2), 4.81 (s., 1, ring CH=C) and 5.45 p.p.m. (m., 1, CH=C).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.24; H, 9.46.

The alkaline, aqueous solution was acidified with cold 7 N hydrochloric acid and extracted with two 100-ml. portions and one 50-ml. portion of ether. The combined ethereal extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated on the rotary evaporator to yield 36 g. (72%) of crude acid 31: ir. (film) 5.78 (COOH), 5.82 (COOH), 6.00 (enone), 6.10 (C=C), and 10.35 μ (trans C=C).

The 36-g. sample of crude acid was heated from 100-140° (20-30 mm.) for a period of 30 min., while carbon dioxide evolution ensued. Distillation gave a forerun of 3.83 g. of low boiling material, b.p. 63-83° (0.5 mm.),

and 23.3 g. (77%, 30% overall from keto ester 20) of monocyclic dienone 19: b.p. 90-92° (0.5 mm.), ir. (film) 6.00 (C=O), 6.13 (C=C), and 10.38μ (trans C=C); n.m.r. 0.92 (d., 6, J = 6 Hz., $C\underline{H}_3CHC\underline{H}_3$), 1.60 (d., 3, J = 3 Hz., $C\underline{H}_3CH=C$), 1.90 (s., 3, ring vinyl $C\underline{H}_3$), and 5.33 p.p.m. (m., 2, $C\underline{H}=C\underline{H}$); v.p.c. (6 ft. Carbowax 20M) 95% purity.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.63: H, 10.83.

Preparation of Dienol 38. A 2.20-g. (10.0 mmoles) sample of dienone 19 was dissolved in 20 ml. of dry ether and treated with a 7.0-ml. (12 mmoles) portion of 1.6 M solution of methyllithium in ether. After the reaction was stirred at 25° for 8 hr., a saturated solution of sodium sulfate was added. After another hour the ethereal solution was filtered and concentrated on the rotary evaporator to give 2.44 g. (100%) of crude dienol 38: ir. (film) 2.97 (OH), 6.03 (C=C), and 10.39 μ (trans C=C). The crude dienol 38 was used without further purification.

Formolysis of Dienol 38. To a 2.12-g. (9.00) mmoles) sample of crude dienol 38 was added with stirring 40 ml. of anhydrous formic acid. After 1.5 min. the reaction was poured into an ice-cold solution of 44 g. of sodium hydroxide in 400 ml. of water. The neutral solution was

extracted with ether; and the ethereal extract was washed successively with saturated sodium bicarbonate solution and saturated brine, was dried over anhydrous magnesium sulfate, filtered, and concentrated on the rotary evaporator to give 2.28 g. of oil. Distillation gave a 0.3-g. forerun of mainly olefin 39: b.p. 75-76° (0.1 mm.); ir. (film) 3.24 (vinyl CH), weak 5.78 (formate contaminant), 6.12 (C=C), 6.21 (C=C), and 10.38 μ (trans C=C). The main distillate was 1.7 g. (72%) of formates 40: b.p. 76-90° (0.1 mm.); ir. (film) 3.66 (formate CHO), 5.78 (C=O), and 8.45μ (C-O).

Preparation of Trienes 39. A 5.00-g. (22.7 mmoles) sample of monocylic dienone 19 (95% pure by v.p.c.) dissolved in 10 ml. of anhydrous ether was treated with 16 ml. (26 mmoles) of 1.6 M ethereal methyllithium at 25°. After being stirred for 30 min., the alcoholate was converted to olefins by the dropwise addition of 2.0 g. (25 mmoles) of dry pyridine and 1.2 g. (8.0 mmoles) of phosphorous oxychloride dissolved in 10 ml. of anhydrous ether; the reaction was cooled in an ice bath. The resulting mixture was stirred overnight. After the mixture was poured into 50 ml. of ice water and extracted with two 50-ml. portions of ether, the combined ethereal extract was washed with dilute hydrochloric acid to remove the

excess pyridine and with three portions of brine, dried over magnesium sulfate, and concentrated on the rotary evaporator. The resulting dark oil was dissolved in ligroin (30-60°) and filtered through a short column of alumina (I) with 200 ml. of ligroin. Concentration of the filtrate on the rotary evaporator gave 3.63 g. (72%) of colorless olefin 39: ir. (film) 3.25 (vinyl CH), 6.12 (C=C), 6.23 (C=C), 10.40 (trans-C=C) and 11.52μ (vinyl $C=CH_2$). The triene mixture was used without further purification. A small sample was molecularly distilled (75°, 0.1 mm.) for an analytical sample.

Anal. Calcd. for $C_{16}H_{26}$: C, 88.00; H, 12.00. Found: C, 87.95; H, 12.09.

Formolysis of Trienes 39. A 3.63-g. (16.6 mmoles) sample of the triene mixture 39 was stirred with 75 ml. of anhydrous formic acid for 20 min. at 25° under nitrogen. The reaction was poured into an ice-cold solution of 100 g. (4.0 moles) sodium hydroxide in 500 ml. of water. The product was extracted with two 100-ml. portions of ether; the combined ethereal extract was washed twice with water and with brine, dried over magnesium sulfate, concentrated on the rotary evaporator to give 3.64 g. (89%) of crude product that was chromatographed on Florisil (Table 1) to give 2.92 g. (67%) of formates which were used without further purification. Molecular distillation at 80°

(0.03 mm.) gave an analytical sample: ir. (film) 3.67 (formate CH), 5.79 (formate C=O) and 8.50μ (C-O).

Table 1. Chromatography of the formolysis products.

Solvent	Vol. (ml.)	Wt. of residue (g.)
Ligroin (30-60°)	200	0.38 (olefin)
1:49 Ether-ligroin	100	0.01 (olefin)
1:49 Ether-ligroin	100	0.66 (formate 40)
1:19 Ether-ligroin	200	2.24 (formate 40)
1:9 Ether-ligroin	100	0.02 (formate 40)
1:4 Ether-ligroin	100	0.03 (diformate)
1:1 Ether-ligroin	100	0.30 (diformate)

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.34; H, 10.83.

Reductive Cleavage of Formates 40. A 2.92-g. (11.2 mmoles) sample of formates 40 obtained from the chromatography of the formolysis products was used without further purification. The ester 40 was dissolved in 100 ml. of anhydrous ether and stirred with 450 mg. (large excess) of lithium aluminum hydride for one hour. The reaction was cooled in an ice bath. After one hour the excess reagent was destroyed with saturated sodium sulfate solution, and was poured into 500 ml. of water. The layers were separated and the aqueous layer was extracted with 100-ml. portion of ether. The combined ethereal extract was washed with twice saturated brine, dried over magnesium sulfate,

filtered, and concentrated on the rotary evaporator to give 2.95 g. of alcohols 42 and 43: ir. (film) 3.00 (OH) and 9.77 μ (C-O); v.p.c. (6 ft. of 2% Carbowax 20M, 170°) two principle alcohols 42 and 43 in a ratio of 3:2.

Chromatographic Separation of Alcohols 42 and 43. A 3.42-g. sample of crude alcohols 42 and 43 was chromatographed on 200 g. of alumina (IV) (Table 2). Isomer 43 obtained from the first 1:99 benzene-ligroin (30-60°) fraction was later purified by means of the 3,5-diniotrobenzoate derivative 44 (see below). The alcohols 42 and 43 obtained from the second 1:99 benzene-ligroin fraction and the 1:19 benzene-ligroin fraction was rechromatographed on alumina. Isomer 42 obtained from the 1:9-1:1 benzene-ligroin fractions was recrystallized from pentane to give colorless alcohol 42: m.p. 91-93°; ir. (KBr) 3.07 (OH) and 9.74 μ (C-O).

Anal. Calcd. for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.18; H, 11.95.

Table 2. Chromatography of the alcohols 42 and 43.

Solvent	Vol. (ml.)	Wt. of residue (g.)
Ligroin (30-60°)	500	0.37 (Olefins)
1:99 Benzene-ligroin	500	0.66 (Alcohol 43)
1:99 Benzene-ligroin	500	0.58 (Alcohols 43 and 42)
1:19 Benzene-ligroin	500	0.49 (Alcohols 43 and 42)
1:9 Benzene-ligroin	500	0.38 (Alcohol 42)
1:4 Benzene-ligroin	500	0.35 (Alcohol 42)
1:1 Benzene-ligroin	1000	0.39 (Alcohol 42)

The benzoate of alcohol 42 was an oil: ir. (film) 3.28 (aromatic CH), 5.81 (C=O), 6.23 (phenyl), and 7.90μ (C-O); n.m.r. (CCl_4) δ 7.98 (m., 2, phenyl hydrogens next to the carboxyl group), 7.38 (m., 3, remaining phenyl hydrogens), 4.98 (sextet, 1, J_1 = 4 Hz., J_2 - 10.5 Hz., axial C<u>H</u>-O), 4.58 (s., 3, = CC<u>H</u>$_3$), and 0.90 p.p.m. (m., 12, four C<u>H</u>$_3$).

Preparation of 3,5-Dinitrobenzoate 44. An 875-mg. (3.7 mmoles) sample of crude alcohol 43 was dissolved in 10 ml. of 1:1 pyridine-benzene. After the solution was cooled to 0°, 1.1 g. (4.8 mmoles) of recrystallized 3,5-dinitrobenzoyl chloride was added with stirring. After 5 min. at 0° the reaction was warmed to 25° and left stirring overnight. The reaction was poured into ice water and extracted with two 70-ml. portions of ligroin (30-60°). The combined ligroin extract was washed with dilute hydrochloric acid, with two portions of water, and with saturated sodium bicarbonate solution. The extract was dried over sodium sulfate, filtered, and concentrated on the rotary evaporator to give 1.89 g. of yellow oil, which crystallized when treated with ligroin. The ester was recrystallized twice from ligroin (60-70°) and finally from n-hexane to give fine needles: m.p. 117-119°; ir. (KBr) 3.23 (aromatic CH), 5.81 (C=O), 6.14 (phenyl), 6.46 (NO_2), 7.43 (NO_2), and 13.95 μ (C-N-O);

n.m.r. (CCl_4) δ 1.67 (s., 3, vinyl $\underline{CH}_3$), 5.21 (sextet, 1, $\underline{J}_1$ = 5 Hz., $\underline{J}_2$ = 10 Hz., axial $\underline{CH}$-O), and 9.09 p.p.m. (m., 3, aromatic $\underline{H}$).

Anal. Calcd. for $C_{23}H_{30}N_2O_6$: C, 64.17; H, 7.02; N, 6.51. Found: C, 64.32; H, 7.02; N, 6.39.

Reductive Cleavage of 3,5-Dinitrobenzoate 44.

An 832-mg. (1.93 mmoles) sample of the dinitrobenzoate 44, m.p. 117-119°, was dissolved in 100 ml. of anhydrous ether and stirred with excess lithium aluminum hydride for 1.5 hr. at 10°. After the reduction complex was destroyed with saturated aqueous sodium sulfate , the mixture was filtered. The filtrate was concentrated on the rotary evaporator to give 431 mg. of yellow oil, which was chromatographed on silica gel. The 1:3 ether-ligroin (30-60°) fractions gave 387 mg. (85%) of alcohol 43, which slowly crystallized. Sublimation at 50° (1 mm.) gave colorless, crystalline alcohol 43: m.p. 47-54°; ir. (CCl_4) 2.76 (OH), 2.99 (OH) and 9.79 μ (C-O); v.p.c. (6 ft. of 2% Carbowax 20M, 170°) one peak with no isomeric alcohol 42 present.

Anal. Calcd. for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.39; H, 12.03

Ketone 49. A 156-mg. (0.662 mmole) sample of alcohol 42 was dissolved in 50 ml. of reagent grade acetone and treated with excess chromic acid (25) at 0°. After 30 min. the excess reagent was destroyed with isopropanol. Anhydrous magnesium sulfate was added to superficially dry the solution, which was then diluted with 100 ml. of ligroin (30-60°). The solution was filtered and concentrated on the rotary evaporator to give a residue that was taken up in 50 ml. of ligroin and redried over anhydrous magnesium sulfate. The solution was re-filtered and reconcentrated as before, and the concentrate was filtered through a column of alumina (III) with 50 ml. of ligroin to yield after concentration on the rotary evaporator 113 mg. (73%) of ketone 49: ir. (film) 5.84μ (C=O); n.m.r. ($CHCl_3$) δ1.62 (s., 3, vinyl $C\underline{H}_3$) and 0.83 p.p.m. (m., 12, four $C\underline{H}_3$).

The semicarbazone was recrystallized from ethanol-water: m.p. 183-189° dec.; ir. (KBr) 2.89 (NH), 3.16 (NH), 5.91 (C=O), and 6.30μ (C=N).

Olefin 50. A 400-mg. (1.38 mmoles) sample of the semicarbazone of ketone 49 was combined with 6.0 g. (60 mmoles) of 100% hydrazine hydrate, 20 ml. of reagent grade diethylene glycol, and 2.6 g. (40 mmoles) of 85% potassium hydroxide. The reaction flask was placed in an oil bath

heated to 200°. After the reaction was heated for 1 hr. under reflux, the lower boiling constituents were removed by distillation. The temperature was then maintained at 220° for 2 hr. After the reaction was allowed to cool to 25°, the distillate and the pot residue were diluted with water, combined, and extracted with pentane. The pentane extract was washed twice with water, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the filtrate on the rotary evaporator gave 275 mg. (91%) of oily olefin 50: ir. (film) 3.40 μ (CH).

Photo-oxidation of Olefin 50. A. Hematoporphyrin-pyridine. A 125-mg. (0.568 mmole) sample of crude olefin 50 was dissolved in 12 ml. of anhydrous pyridine that contained 0.01% hematoporphyrin dihydrochloride. The solution was irradiated with fluorescent lamps for 15 hr., at which time a sample analyzed by the v.p.c. showed the presence of little starting olefin. The reaction was diluted with a large volume of water, and the aqueous solution was extracted with ether. The ethereal extract was washed successively with several portions of water, with dilute hydrochloric acid, and again with water. After decolorizing charcoal and anhydrous magnesium sulfate were added, the solution was filtered and concentrated on the rotary evaporator to give 138 mg. of crude hydroperoxide, which

was reduced in anhydrous ether with excess lithium aluminum hydride. After the reduction complex was destroyed by saturated sodium sulfate solution, the ethereal solution was filtered and concentrated to yield 129 mg. of oil that contained more than 23 components by v.p.c. analysis.

B. Rose Bengal-Carbon Disulfide-Methanol-Ether. An 83-mg. (0.38 mmole) sample of olefin 50 was dissolved in 15 ml. of 28:2:3 carbon disulfide-methanol-ether (24) that contained 1.0 mg./ ml. of rose bengal sensitizer. The sample was irradiated for 2 hr. at 12° with a 300-w. tungsten lamp. After the solvent was removed on the rotary evaporator, the residue was taken up in ether. The ethereal solution was filtered and treated with excess lithium aluminum hydride for 1 hr. After the reduction complex was destroyed with saturated sodium sulfate solution, the ethereal solution was filtered and concentrated to give 80 mg. of crude allylic alcohol 51, which was chromatographed on Florisil. The 1:49 ether-ligroin (30-60°) fraction yielded 21 mg. (24%) of allylic alcohol 51: ir. (film) 2.89 (OH), 3.26 (=CH), 6.08 (C=C), and 11.18μ ($=CH_2$); n.m.r. (CCl_4) δ 4.70 (m., 2, $=C\underline{H}_2$), 0.87 (m., 9, three $CHC\underline{H}_3$), and 0.68 p.p.m. (s., 3, $CC\underline{H}_3$), v.p.c. (6 ft. of Carbowax 20M, 160°) 77% purity.

Ozonolysis of Crude Allylic Alcohol 51. A 21-mg. (0.089 mmole) sample of crude allylic alcohol 51 was used without further purification. The alcohol 51 was dissolved in 5 ml. of methylene chloride and 3 ml. of methanol. After being cooled to -70° in a Dry Ice-acetone bath, the solution was saturated with ozone from a Welsbach generator until a persistent blue color remained. The solution was then flushed with oxygen for 10 min. and warmed to 0° in an ice bath. A 100-mg. portion of zinc dust and 1-ml. portion of acetic acid were added, and the ensuing mixture was stirred for 75 min. The reaction was then diluted with water and extracted with a 50-ml. portion of ligroin (30-60°). The ligroin extract was washed twice with water and then with brine, was dried over anhydrous sodium sulfate, filtered, and concentrated on the rotary evaporator to yield 21 mg. of colorless oil that was chromatographed on alumina (III). The 1:1 benzene-ligroin (30-60°) gave 13 mg. of keto ester 53: ir. (CCl_4) 5.74 (ester C=O) and 5.85μ (ketone C=O); n.m.r. (CCl_4) δ3.52 (s., 3, OCH_3) and 0.80 p.p.m. (m., 12, four CCH_3). The ether-benzene-ligroin fractions gave 6 mg. (30%) of ketol 52: m.p. 98-103°; ir. (CCl_4) 2.87 (OH) and 5.85μ (C=O); n.m.r. ($CHCl_3$) δ0.63 (s., 3, CCH_3), 0.75 (d., 3, J = 7 Hz., $CHCH_3$), and 0.88 p.p.m. (d., 6, J = 5 Hz., CH_3CHCH_3).

Dehydration of Ketol 52. The procedure of Heymann and Fieser (27) was used. A 6-mg. (0.003 mmole) sample of crude ketol 52 was dissolved in 2 ml. of anhydrous pyridine. After the solution was cooled to 0° in an ice bath, a 0.1-ml. portion of thionyl chloride was added. After a period of 1 hr. the reaction was diluted with ice water and extracted with a 30-ml. portion of ligroin (30-60°). The ligroin extract was washed with three 50-ml. portions of water, dried over anhydrous sodium sulfate, filtered, and evaporated on the rotary evaporator to give an oil that was chromatographed on alumina (III). The 1:3 benzene-ligroin (30-60°) fraction gave 4 mg. of (60%) of enone 54: ir. (CCl_4) 592 (C=O) and 6.14 μ(C=C).

Ketone 55. A 345-mg. (1.46 mmoles) sample of alcohol 43 (m.p. 47-54°) was dissolved in 100 ml. of reagent grade acetone, and the solution was cooled to 0° in an ice bath. Excess chromic acid (25) was added, and the solution was stirred for 25 min. A 1-ml. portion of i-propanol was added to destroy the excess reagent, and after 5 min. an aqueous solution of potassium carbonate was added dropwise until the solution was neutral to litmus. A 100-ml. portion of ligroin (30-60°) and some anhydrous magnesium sulfate were added. After the solution was filtered, the filtrate was concentrated on the rotary evaporator. The oily residue was dissolved in 10 ml. of ligroin (30-60°) and filtered through a short column of alumina (V) with 90 ml. of ligroin (30-60°). After the solution was concentrated on

the rotary evaporator, the colorless residue (345 mg.) was distilled to give 337 mg. (98%) of ketone 55: b.p. 115-120° (1 mm.); ir. (film) 5.85μ (C=O); n.m.r. (CCl_4) δ1.68 (s., 3, vinyl CH_3) and 0.85 p.p.m. (m., 12, four CH_3).

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.07; H, 11.22.

Olefin 56. A 327-mg. (1.40 mmole) sample of ketone 55 was dissolved in a mixture of 6 ml. of 95% ethanol and 6.0 g. of 100% hydrazine hydrate. After the mixture was stirred at 25° for 30 min., 20 ml. of reagent grade diethylene glycol and 2.8 g. of 85% potassium hydroxide were added. The reaction was gradually heated under nitrogen to remove the ethanol and the excess hydrazine hydrate by distillation during a period of 1 hr.; the heating bath temperature was raised during this time from 25° to 180°. The bath temperature was raised to 200° and maintained at that temperature for 2 hr. After the reaction flask was cooled, its contents and the distillate were poured into 200 ml. of ice water, which was then extracted with two 50-ml. portions of ligroin (35-40°). The combined ligroin extract was washed twice with water, dried over magnesium sulfate, and filtered through a short column of alumina (I) with 50 ml. of ligroin (35-40°). After the filtrate was concentrated by

distillation through a short Vigreaux column, the concentrate was distilled to give 218 mg. (71%) of olefin 56: b.p. 90-95° (0.8 mm.); n.m.r. (CCl_4) δ 1.60 (s., 3, vinyl CH_3) and 0.83 p.p.m. (m., 12, four CH_3).

Anal. Calcd. for $C_{16}H_{28}$: C, 87.19; H, 12.81. Found: C, 87.13; H, 12.85.

Photo-oxidation of Olefin 56. The procedure of Forbes and Griffiths (24) was used. An 181-mg. (0.822 mmole) sample of the olefin 56 was dissolved in 50 ml. of 28:2:3 carbon disulfide-methanol-ether that contained 1.0 mg./ml. of rose bengal sensitizer. The reaction flask was flushed with oxygen and maintained under a positive oxygen pressure during the course of the reaction. The solution was stirred magnetically. The flask was cooled to 8° in a water bath and irradiated with a 300-w. tungsten lamp for 2 hr. The solvent was removed on the rotary evaporator; ether was added to the residue, and the ether suspension was filtered. The colorless filtrate was stirred with excess lithium aluminum hydride for 30 min. The reduction complex was destroyed by dropwise addition of saturated sodium sulfate solution. After 1 hr. the reaction mixture was filtered. The filtrate was concentrated on the rotary evaporator to give 191 mg.

(98%) of crude allylic alcohol 57: ir. (film) 2.90 (OH), 3.26 (=CH), 6.10 (C=C) and 11.07 μ (=CH_2); v.p.c. (6 ft. of 2% Carbowax 20M, 160°) two alcohols in a ratio of 3:1. The crude alcohol 57 was used without further purification.

The Preparation of dl-Ketol 58. An 191-mg. (0.81 mmole) sample of crude allylic alcohol 57, prepared by the photo-oxidation of the olefin 56, was dissolved in 2 ml. of methylene chloride and cooled to -70° in a Dry Ice-acetone bath. The methylene chloride solution was added with stirring to 31 ml. of methylene chloride saturated with ozone (0.81 mmole) at -70°; an additional 5 ml. of methylene chloride was used to complete the transfer of allylic alcohols to the reaction vessel. A 0.1-g. portion of zinc dust and 1 ml. of acetic acid were added, and the reaction mixture was warmed to 0° in an ice bath. After 15 min. another 0.1 g. of zinc dust and 1 ml. of acetic acid were added, and the mixture was stirred for a total of 1.5 hr. The reaction mixture was poured into sodium bicarbonate solution. The product was extracted with two 75-ml. portions of ether. The combined ethereal extract was washed with water and saturated brine, dried over sodium sulfate, filtered, and concentrated on the rotary evaporator to give 196 mg. of yellow oil, which

deposited a small amount of yellow gum upon trituration with ligroin (30-60°). After the ligroin solution was filtered through cotton, the colorless filtrate was combined with a 23-mg. sample of ketol 58 prepared in a previous run. The ligroin solution was placed on 60 g. of alumina (III) and chromatographed. Ketol 58 was obtained from the 2:9:9 and 1:2:2 ether-benzene-ligroin (30-60°) fractions and was recrystallized from 50% aqueous ethanol to give colorless needles: m.p. 70-71°; ir. (KBr) 2.95 (OH), 5.90 (C=O) and 9.91μ (C-O).

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.59; H, 11.10.

Dehydration of Ketol 58. A. With Thionyl Chloride. A 5.0-mg. (0.021 mmole) sample of ketol 58 was dissolved in 1.5 ml. of dry pyridine. A 0.1-ml. (large excess) portion of thionyl chloride was added dropwise with stirring at 25° under nitrogen. After 1 hr. the reaction was poured on a small amount of ice and diluted with another 50 ml. of ice water. The reaction mixture was extracted with a 50-ml. portion of pentane. The organic extract was washed with two 50-ml. portions of ice water, dried over anhydrous sodium sulfate, filtered, and the filtrate was evaporated on the rotary evaporator giving an oil that had undergone dehydration with rearrangement: ir. (CCl_4) 5.84 (saturated C=O) and 6.10μ (C=C); v.p.c. (6 ft. of 2%

Carbowax 20M, 160°) one peak with a shoulder that was also unresolved at 140°.

B. With Phosphorous Oxychloride. A 5.0-mg. (0.021 mmole) sample of ketol 58 was dissolved in 1.5 ml. of dry pyridine and stirred with 0.1 ml. (large excess) of phosphorous oxychloride at 25° for 17 hr. under nitrogen. The workup described above gave an oil that was 95% starting material: ir. (CCl_4) identical to starting material; v.p.c. (6 ft. of 2% Carbowax 20M, 200°) 95% starting ketol and 5% dehydrated product.

Preparation of Keto Acetate 59. A 56-mg. (0.20 mmole) sample of ketol 58, m.p. 68-70°, was dissolved in a solution of 25 mg. of 85% phosphoric acid and 5 ml. of acetic anhydride. After 16 hr. at 25° the reaction was thrown into ice water, and the product was extracted with a 50-ml. portion of ligroin (30-45°). The ligroin extract was washed successively with water, saturated sodium bicarbonate solution, water and then saturated brine. The extract was dried over anhydrous sodium sulfate, filtered, and concentrated on the rotary evaporator to give an oil, which was chromatographed on Florisil. The keto acetate 59 from the 1:19 and 1:9 ether-ligroin (30-60°) fractions crystallized (m.p. 40-44°). Recrystallization from ethanol (-70°) and sublimation (50°, 1 mm.) gave keto acetate 59:

m.p. 46-48°; ir. CCl_4) 5.74 (acetate) and shoulder at 5.80 μ (C=O).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.74; H, 10.04.

Preparation of dl-cis-Tetrahydroeremophilone (17). A 29-mg. (0.73 mmole) sample (large excess) of calcium metal was dissolved in 20 ml. of liquid ammonia that had been previously distilled from sodium metal. A 6.0-mg. (0.021 mmole) sample of dl-keto acetate 59 dissolved in 0.3 ml. of dry tetrahydrofuran (THF) was added; another 0.3-ml. portion of THF was used to complete the transfer of the keto acetate to the reaction vessel. After a 5 min. reaction time solid ammonium chloride was added, and the reaction was stirred until the blue color was completely discharged. A 20-ml. portion of ether was added, and the ammonia was removed with a stream of nitrogen. After the ethereal slurry was filtered, the filtrate was concentrated on the rotary evaporator. To oxidize any alcohol formed during the reduction, the colorless residue was dissolved in 5 ml. of reagent grade acetone and treated with excess chromic acid reagent (25) at 0°. The reaction was diluted with water and extracted with ligroin (30-60°). The ligroin extract was washed twice with water, dried over sodium sulfate and concentrated on the rotary evaporator.

The oily residue was chromatographed on Florisil. The 4.9 mg. (100%) of ketone obtained from the 1:19 ether-ligroin (30-60°) fraction was molecularly distilled (80°, 32 mm.) giving 4.0 mg. (84%) of dl-cis-tetrahydroeremophilone (17): ir. (film) 5.86 (C=O) and the entire spectrum was superimposable with that of d-cis-tetrahydroeremophilone (17) prepared according to Djerassi and co-workers (31); v.p.c. (6 ft. of 2% Carbowax 20M, 170°) identical retention time (peak enhancement) as d-cis-tetrahydroeremophilone (17).

The racemic 2,4-dinitrophenylhydrazone 60 was prepared and recrystallized from ethanol giving orange needles: m.p. 141-143°; ir. (KBr) 3.00 (NH), 3.23 (aromatic CH), 6.17 (C=N), 6.29 (phenyl), 7.49 (nitro) and 13.48μ (C-N-O), and was superimposable with ir. spectrum of the d-2,4-dinitrophenylhydrazone 60, m.p. 181-183°, lit. m.p. 178-179° (1) and 179-180° (31), prepared according to Djerassi and co-workers (31).

Preparation of d-cis-Tetrahydroeremophilone (17). The procedure of Djerassi and co-workers (31) was used. A 41.5-mg. (0.19 mmole) sample of eremophilone, m.p. 38-40°, was hydrogenated in 5 ml. of methanol with 13.5 mg. of 5% palladium catalyst. After the catalyst was removed by filtration, and the solvent was removed on the rotary

evaporator, the crude cis- and trans-tetrahydroeremophilones were dissolved in 1.5 ml. of methanol and 0.5 ml. of 3 N hydrochloric acid. The solution was heated under reflux for 30 min., cooled, and neutralized with saturated sodium bicarbonate solution. The reaction mixture was extracted with ligroin (30-60°); the extract was dried over anhydrous sodium sulfate, filtered, and concentrated on the rotary evaporator. The residue was chromatographed on Florisil giving 30 mg. of d-cis-tetrahydroeremophilone (17) in the 1:19 ether-ligroin (30-60°) fraction. The oily ketone was molecularly distilled (90°, 32 mm.) to yield 28.5 mg. (68%) of d-cis-ketone 17: ir. (film) 5.86 μ (C=O).

The 2,4-dinitrophenylhydrazone was recrystallized from ethanol: m.p. 181-183°, lit. m.p. 178-179° (1), m.p. 179-180° (31); ir. (KBr) 3.00 (NH), 3.23 (aromatic CH), 6.17 (C=N), 6.29 (phenyl), 7.49 (nitro), and 13.48 μ (C-N-O).

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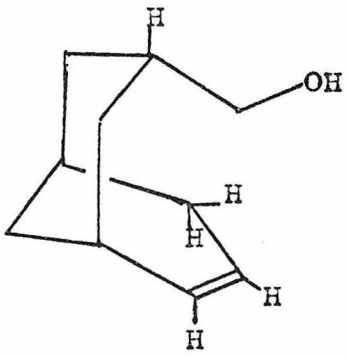
PART II

STUDIES ON SYSTEMS FREE FROM ANGULAR STRAIN

INTRODUCTION

The goals of this investigation were the synthesis of the alcohol 1 and solvolysis of the ester 2. The solvolysis of the ester 2 is expected to generate the



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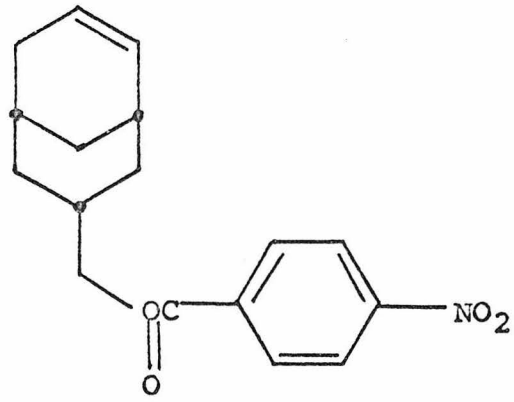

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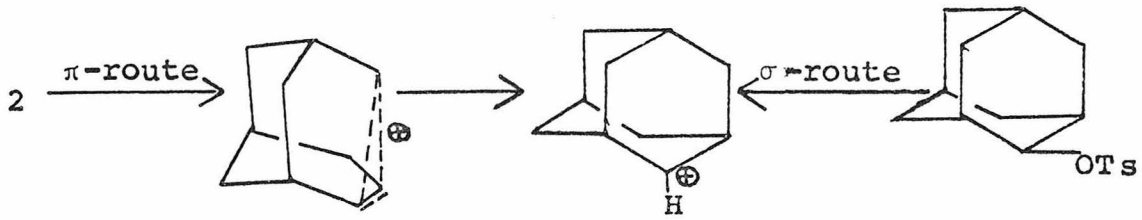
2-adamantyl cation 3 by way of the pi-route, in contrast to the sigma-route used by Schleyer and Nicholas (1). The interest in the possible reactivity of ester 2 arose when



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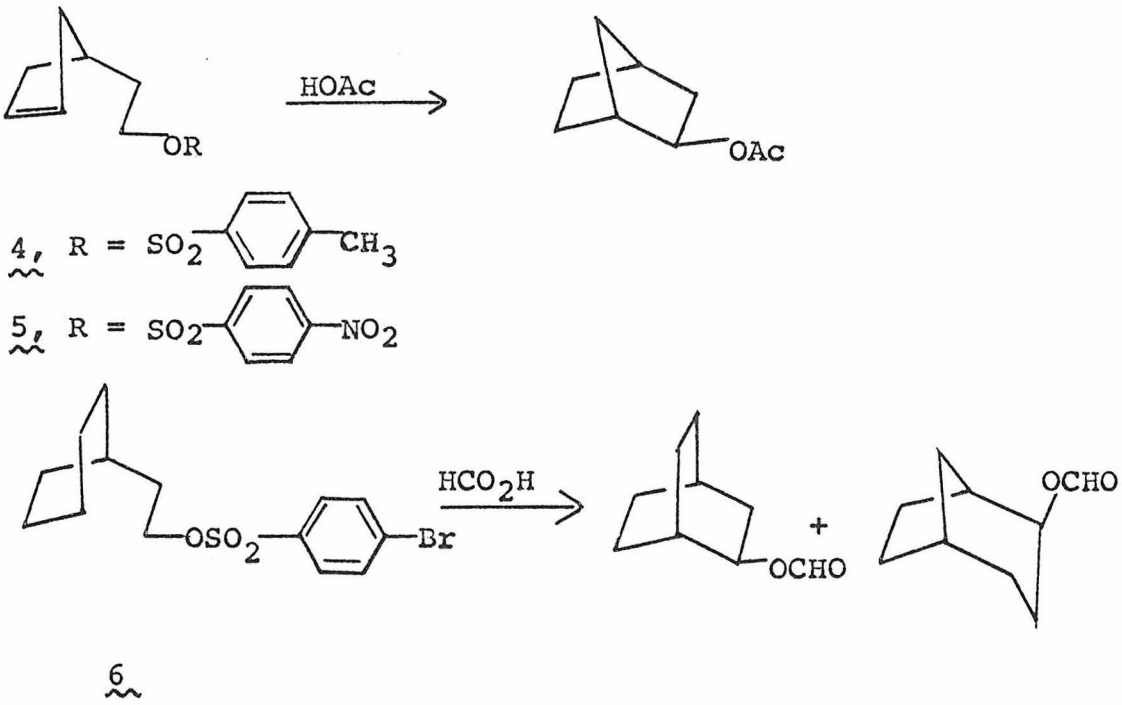
the anchimerically assisted participation of a double bond was observed in the solvolysis of the unsaturated aliphatic

arenesulfonates 4 (2), 5 (3), and 6 (4). If the alcohol 1 can be readily prepared, the solvolytic pi-route could be an useful approach to the preparation of substituted 2-adamantanols.



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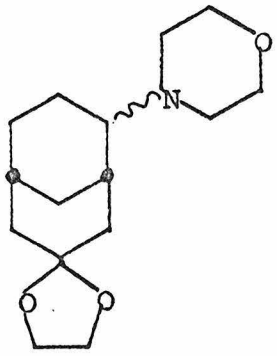
The attempts on the synthesis of alcohol 1 starting from 1,4-dioxaspiro[4.5]decan-8-one (7) is discussed below in three parts. The first section involves the preparation of amine 8 and the pyrolysis of its amine oxide. The second part discusses the preparation of amines 9 and 10. Finally, the third section deals with the preparation of amino acetates 11 and 12 and with the pyrolysis of their corresponding amine oxides.



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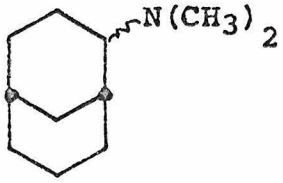

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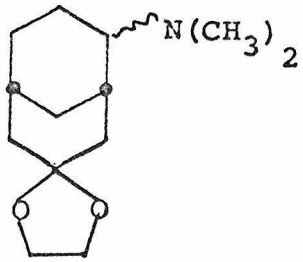

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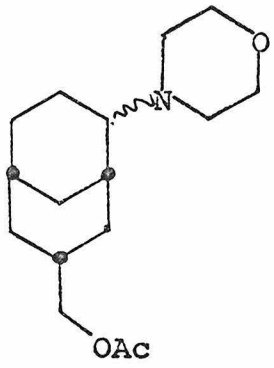

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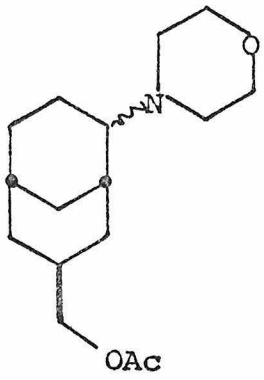

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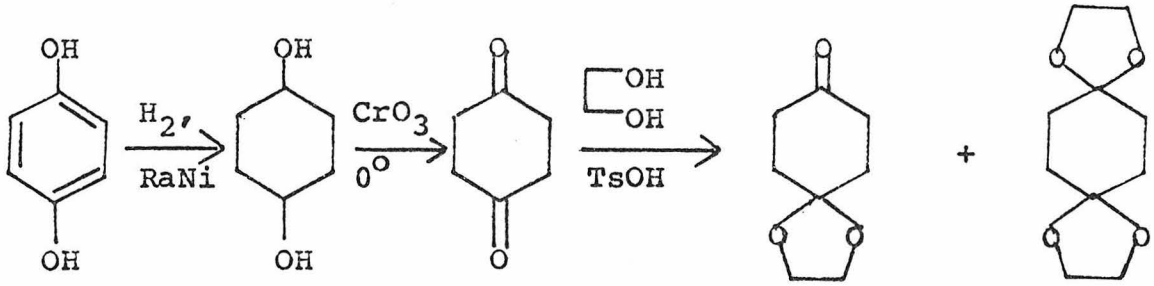
RESULTS AND DISCUSSION

The key intermediate required for all the synthetic efforts was 1,4-dioxaspiro[4.5]decan-8-one (7), which had been prepared previously by several workers (5, 6, 7, 8). The method adopted in this investigation required 1,4-cyclohexadione (13). The large scale preparation of dione 13 was carried out in two steps. Hydrogenation of hydroquinone (14) according to the procedure of Owen and Robins (9) gave cis- and trans-quinitol (15) in 86% yield. The quinitol (15) was then oxidized with chromic acid reagent (10) in acetone at 0°. Because the dione 13 was water soluble, the acetone solution was decanted from the inorganic by-products, and the inorganic sludge was extracted with acetone. The combined acetone extract was superficially dried over calcium chloride and distilled under reduced pressure to give dione 13, b.p. 118-120° (15 mm.), which crystallized from ether affording 51% yield of the desired dione 13, m.p. 77-78° (lit. m.p. 78°) (11).



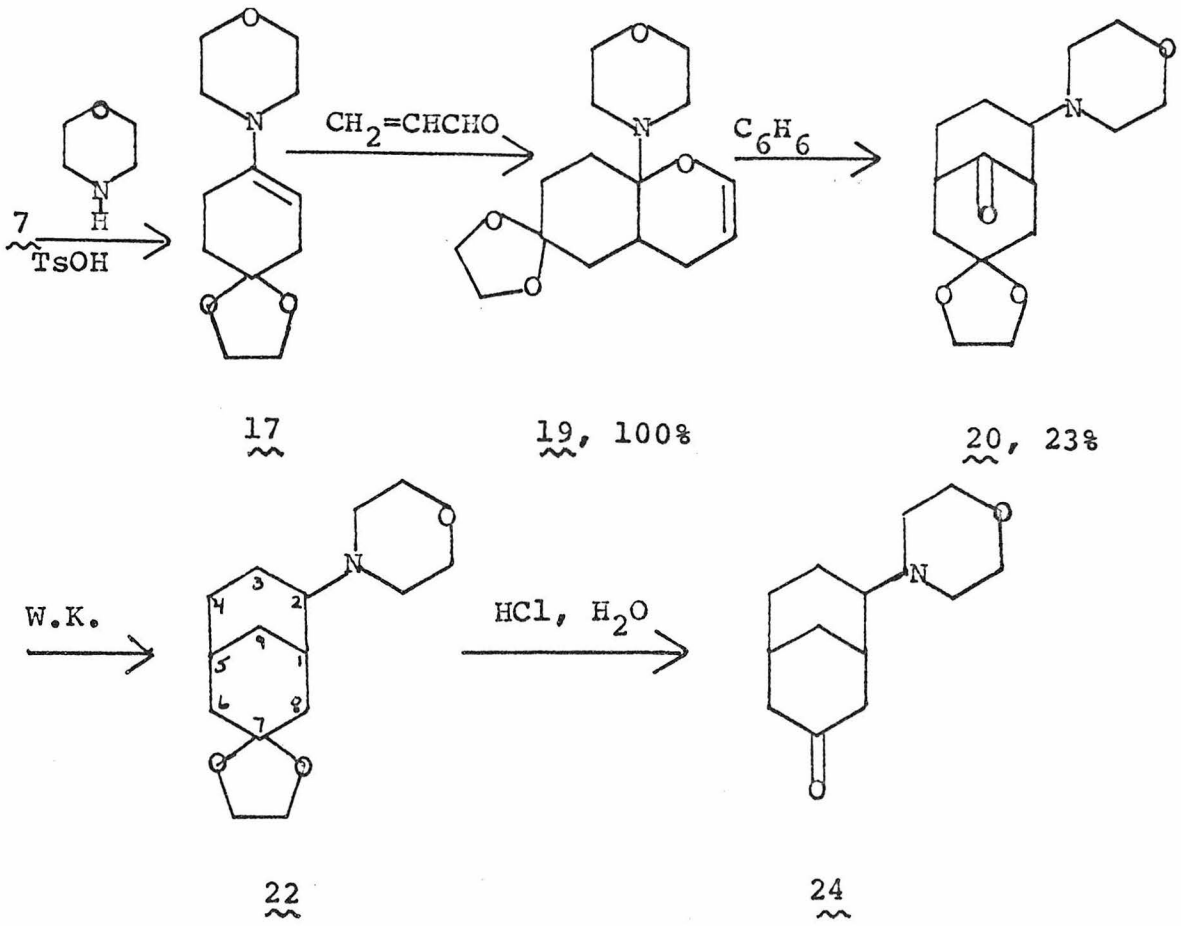
14 15 13 7 16

The method of Courtot (8) was used for the preparation of ketone 7. The dione 13 was ketalized in the presence of 1.5 equivalents of ethylene glycol and a trace of p-toluenesulfonic acid in benzene. The crude product was then stirred with aqueous sodium bisulfite forming the soluble addition compound, and the aqueous solution was extracted with benzene to remove the diketal 16, m.p. 79-80° (lit. m.p. 79-79.5°) (8). The ketone 7 was regenerated from the addition compound by decomposition with potassium carbonate. The ketone 7, m.p. 72-73° (lit. m.p. 72-73°) (5, 8), was subsequently isolated in 35% yield.

Preparation and Reaction of Amine 8 (Scheme 1). The preparation of the amine 8 is outlined in Scheme 1. The ketone 7 was converted to the morpholino enamine 17, b.p. 130° (0.7 mm.), by an adaptation of the procedure of Hunig and co-workers (12) who prepared 1-morpholinocyclohexene (18).

When enamine 17 was alkylated with acrolein in an adaptation of the procedure of Stork and Landesman (13), a quantitative yield of vinyl ether 19, m.p. 80-87°, was obtained. The vinyl ether 19 had infrared (ir.) maxima at 3.29 (vinyl CH) and 6.05 μ (vinyl ether) and the nuclear magnetic resonance (n.m.r.) spectrum showed the presence of two vinylic hydrogens, one at δ 6.16 (doublet, J = 6 Hz., O-CH=CH) and the other at δ 4.65 (multiplet, O-CH=CH).

Scheme 1

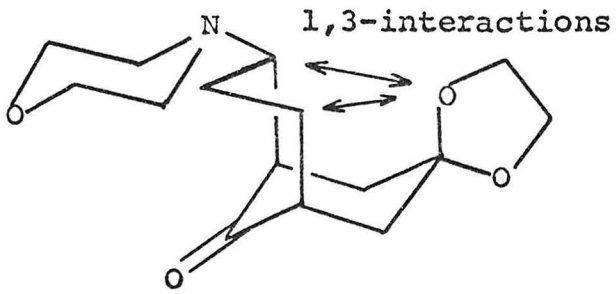


17 19, 100% 20, 23%

22 24

The vinyl ether 19 was heated under reflux for two days in benzene to afford morpholino ketone 20, m.p. 134-135°, in 23% yield. The ir. carbonyl absorption was at 5.80 μ , and the n.m.r. spectrum showed the presence of the ethylenedioxy group at δ 3.92 (singlet) and the morpholino group at δ 3.67 (multiplet, O-CH_2) and δ 2.44 (multiplet, N-CH_2). Since Foote and Woodward (14) converted enamine 18

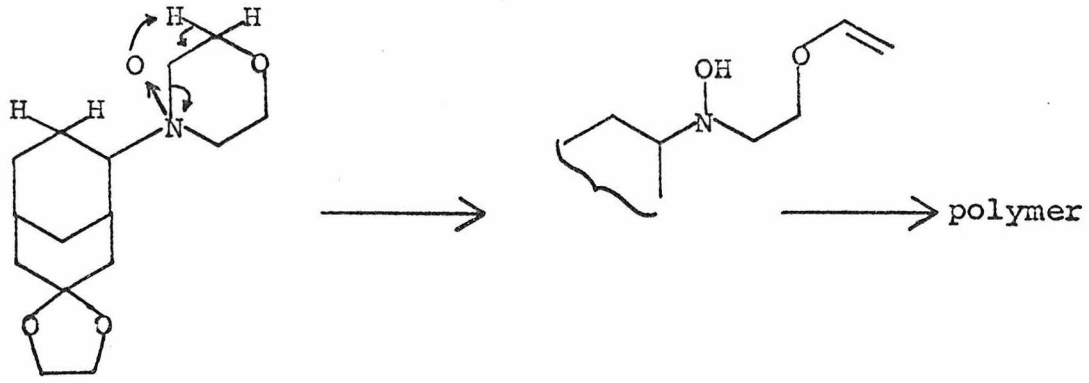
into morpholino ketone 21 in good yield, and this author obtained a 70% yield for the same reaction (see below), the low yield of the ketone 20 in this step was a manifestation of the 1,3-steric interactions presented by the ethylenedioxy group to the development of the three-carbon bridge by way of the reversible Mannich reaction.



20

The ketone 20 underwent Wolff-Kishner reduction (15) affording an 88% yield of amine 22. The n.m.r. spectrum of this amine 22 showed the presence of the ethylenedioxy group at δ 3.48 (singlet) and the morpholino group at δ 3.27 (multiplet, O-C$\underline{H}_2$) and δ 2.05 (multiplet, N-C$\underline{H}_2$). The amine 22 was then oxidized with hydrogen peroxide in methanol until the solution was neutral to litmus. After the excess hydrogen peroxide was destroyed with a trace of catalase, the resultant amine oxide 23 was dried under reduced pressure and pyrolyzed at 180° (20 mm.). The reaction observed was

the transformation of the amine oxide 23 to a black, tarry residue; probably a result of elimination in the morpholino ring and subsequent polymerization. A small amount of distillate obtained appeared to be starting amine 22 by n.m.r. analysis.



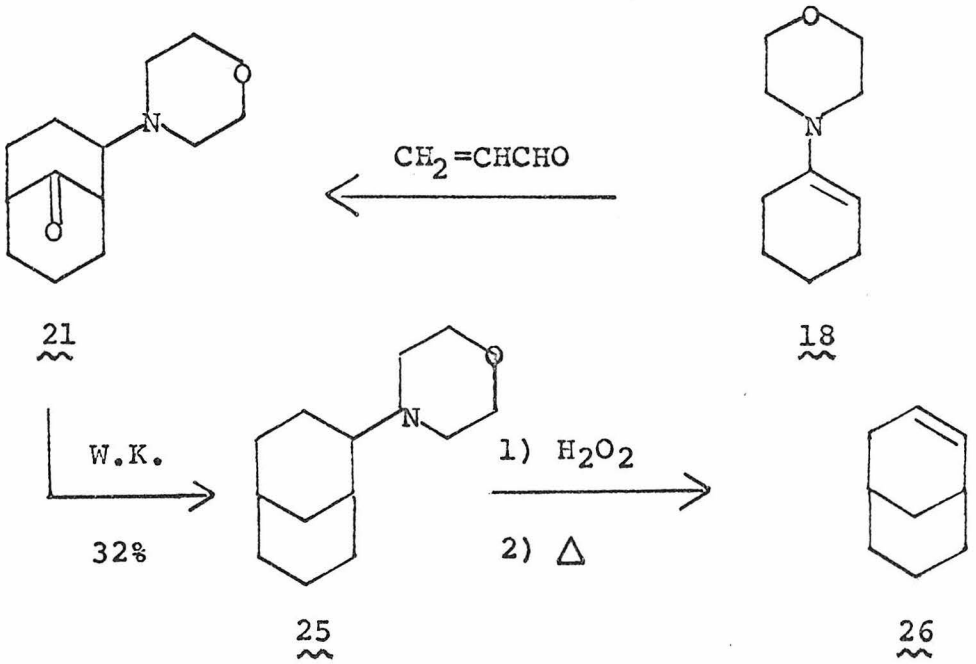
23

Since the amine oxide 23 failed to undergo a Cope elimination upon pyrolysis, the ketal group of the amine 22 was hydrolyzed with hydrochloric acid in aqueous acetone to produce the amino ketone 24. The ir. carbonyl absorption appeared at 5.88 μ, and the n.m.r. spectrum had the morpholino bands at δ 3.70 (multiplet, O-CH_2) and δ 2.35 (multiplet, N-CH_2). The amino ketone 24 was oxidized with hydrogen peroxide, and the resultant N-oxide was residue, and no keto olefin was obtained.

Because these two attempts on the synthesis of olefins from amines 22 and 24 had failed, the structure of these

amines was in doubt. Therefore, an investigation was undertaken to verify the postulated structure of the amine 27. Wolff-Kishner reduction (15) of amino ketone 24 gave amine 25, whose identification was confirmed by an independent synthesis. Morpholino ketone 21, b.p. 123-133° (0.6 mm.) (lit. b.p. 141-147°, 1 mm.) (14), which was prepared in 70% yield according to the procedure of Foote and Woodward (14) by the alkylation of enamine 18 with acrolein, underwent Wolff-Kishner reduction under the condition used for keto amine 24 affording amine 25, b.p. 88-89° (0.2 mm.), in 32% yield. The latter sample of amine 25 had an infrared spectrum identical to the sample prepared from keto amine 24. Hydrogen peroxide oxidation

Scheme 2



of amine 25 prepared from amino ketone 21 gave the corresponding N-oxide, which was pyrolyzed at 125-140° under reduced pressure (20 mm.) to yield bicyclo[3.3.1]non-2-ene (26), m.p. 99-101° (lit. m.p. 103-105°) (16), in 38% yield. The transformation of amino ketone 21 to olefin 26 has also been carried out satisfactorily by Hartmann (16).

Although the N-oxide of amine 25 underwent pyrolysis affording olefin 26 in reasonable yield, the N-oxide of the more substituted amines 22 and 24 gave only undesired black polymer due to elimination in the morpholino ring. If the ethylenedioxy substitution at C_7 was the main cause of the difficulty, then there were two approaches that one could take to circumvent the difficulty in the pyrolysis. The first approach would be the replacement of the morpholino group by the dimethylamino group; if the corresponding amine could be prepared, then the N-oxide elimination would occur in only one direction. The second approach would be the substitution of a less bulky functionality at C_7. The first approach is discussed in the next section, and then the second approach is covered in the final section.

Preparation and Reaction of Amines 9 and 10 (Schemes 3 and 4). The preparation of dimethylamino enamines was investigated. Because the equilibrium:

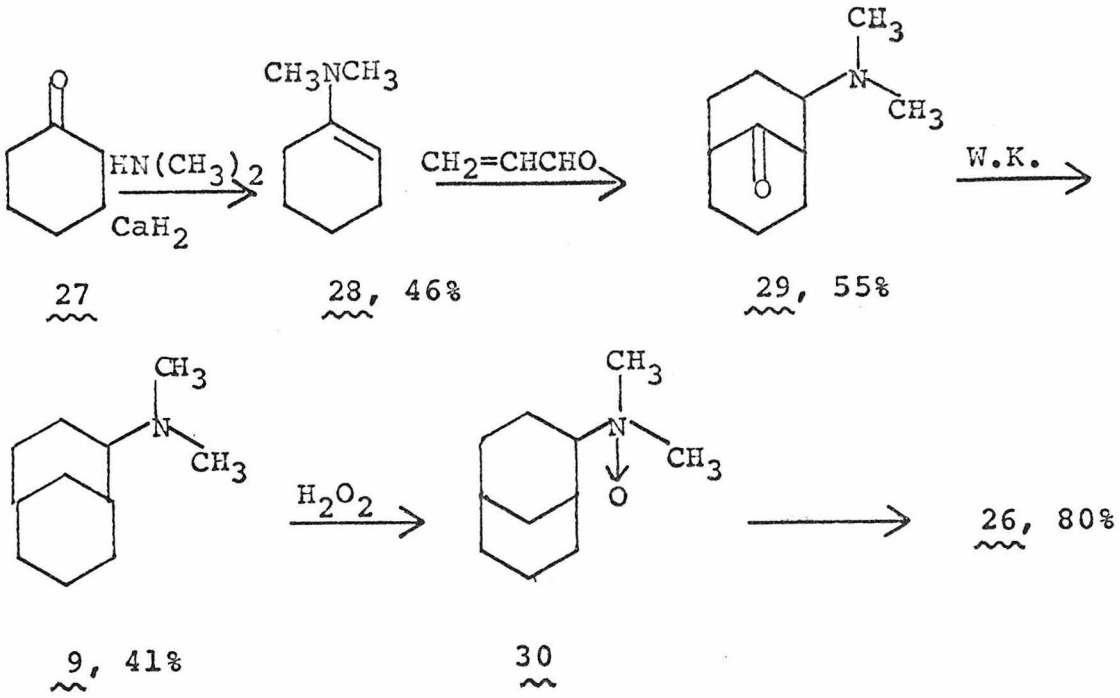
Ketone + Secondary amine $\rightleftharpoons$ Enamine + Water

lies on the side of the ketone, the formation of enamines requires the removal of the water. When morpholine, b.p. 129°, is used, the water-benzene azeotrope can be used to remove the water from the system and, thus, can effect the formation of the desired enamines. However, when dimethylamine, b.p. 7°, is used, water cannot be removed as an azeotrope, and other methods must be applied in order to form the enamines. Drying agents--calcium oxide (17) or molecular sieves (18)--and an acidic catalyst--p-toluene-sulfonic acid (19)--have been employed in the preparation of dimethylamino enamines.

In order to examine the feasibility of the preparation and alkylation of dimethylamino enamines and to investigate the Wolff-Kishner reduction of the resultant amino ketone, a model reaction scheme starting from cyclohexanone (27) was first studied (Scheme 3). When cyclohexanone (27) was stirred with excess dimethylamine in the presence of calcium hydride, as a drying agent, under a Dry Ice condenser, 1-dimethylaminocyclohexene (28), b.p. 168° (760 mm.) (lit. b.p. 175.5°) (20), resulted in 46% yield. Vapor phase chromatography (v.p.c.) indicated the product contained 75% enamine 28 and 25% cyclohexanone (27).

The enamine 28 was not purified further but was transformed in the following four steps to the olefin 26 in

Scheme 3



18% overall yield. Crude enamine 28 (75% pure) was alkylated with acrolein in an adaptation of the procedure of Stork and Landesman (13) to give the amino ketone 29, b.p. 60-90° (0.1 mm.), in 55% yield. The ir. carbonyl absorption occurred at 5.83 μ. Wolff-Kishner reduction (15) of the amino ketone 29 afforded the amine 9, b.p. 50° (0.1 mm.), in 41% yield. The n.m.r. spectrum showed the presence of the dimethylamino group at δ 2.08 (singlet). After the amine 9 was oxidized with hydrogen peroxide in methanol, pyrolysis of the resultant N-oxide 30 at 180° under reduced pressure (20 mm.) resulted in a vigorous decomposition affording the olefin 26 in 80% yield.

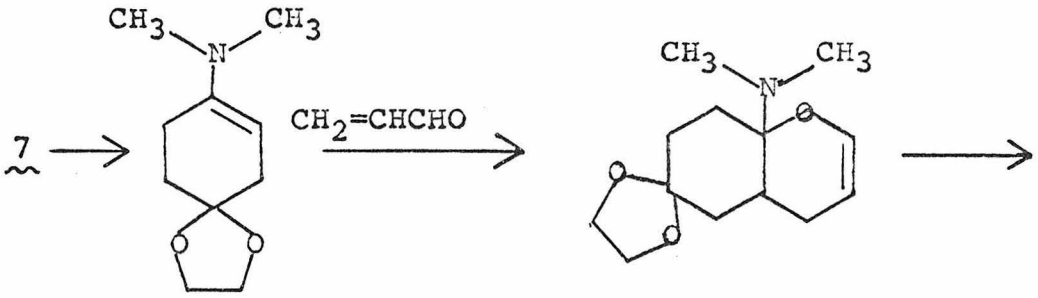
Since the reaction sequence starting from cyclohexanone (27) was reasonably successful, an attempt was made to prepare the dimethylamino enamine of the ketone 7. However, no enamine was formed from the ketone 7 under the conditions used above for cyclohexanone. Therefore, the formation of the enamine 28 was re-examined.

Lithium aluminum hydride (replacing the calcium hydride) and excess dimethylamine were first allowed to form a complex in ether, and then the cyclohexanone (27) was added to the reaction flask. After having been stirred at 25° overnight, the reaction mixture was concentrated by distillation at atmospheric pressure. Further distillation under reduced pressure gave the enamine 28, b.p. 30° (1.5 mm.), in 54% yield. The ir. spectrum had the 3.30 (vinyl CH) and 6.10 μ (C=C) absorptions. However, the absence of a 5.83 μ ir. carbonyl band and an ir. hydroxyl absorption revealed the enamine 28 to be uncontaminated with either cyclohexanone (27) or cyclohexanol (31). Even though the reaction conditions were probably not optimum, the results of this experiment indicated that this method might warrant further study.

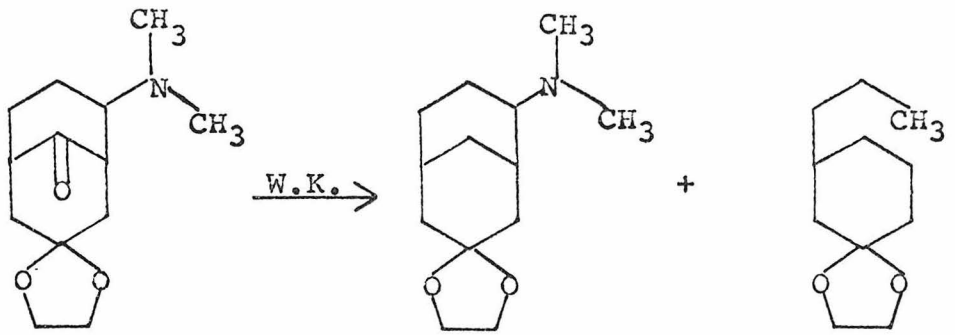
Since a successful method for the preparation of dimethylamino enamines appeared to have been found, the sequence of reactions starting from the ketone 7 was again studied as outlined in Scheme 4. When the ketone 7 was

stirred with the lithium aluminum hydride-dimethylamine reagent, and after the reaction was worked up as described above, the desired enamine 32, b.p. 85-90° (0.8 mm.), resulted in 35% yield. The ir. spectrum had an absorption at 6.09 μ (C=C) and no carbonyl band, which indicated that the enamine 32 was uncontaminated with starting ketone 7.

Scheme 4



32, 35%



33, 48% 10, 4.3% 34, 75%

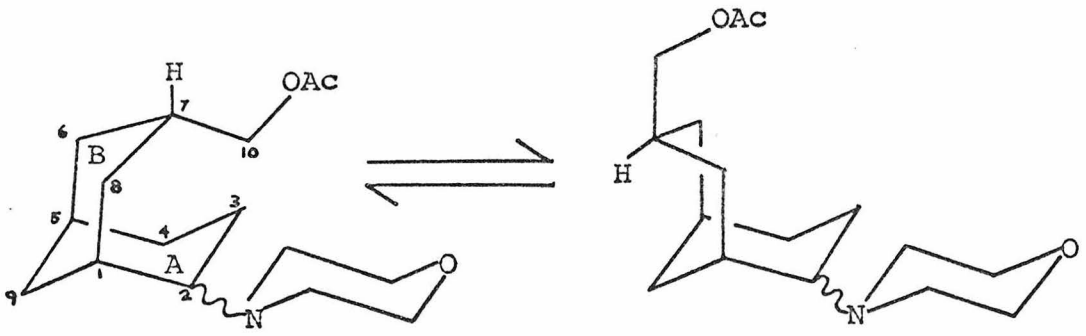
The enamine 32 upon alkylation with acrolein gave the crude amino ketone 33 in 48% yield. The ir. carbonyl absorption appeared at 5.81 μ. The amino ketone 33 underwent Wolff-Kishner reduction (15) giving amine 10, b.p. 103-108° (0.2 mm.), in 4.3% yield and the ketal 34 in

75% yield. The n.m.r. spectrum of the amine 10 showed the presence of the ethylenedioxy group at δ 3.62 (multiplet) and the dimethylamino group at δ 2.04 (multiplet). The n.m.r. spectrum of the ketal 35 indicated the presence of the ethylenedioxy group at δ 3.70 (singlet) and a methyl group adjacent to two hydrogens at δ 0.98 (triplet, J = 6 Hz.).

The formation of ketal 34 in the Wolff-Kishner reduction of amino ketone 33 was a manifestation of a retro-Mannich reaction that occurred under the conditions of the reduction and that was enhanced because a dimethylamino Mannich base is a stronger base than a morpholino Mannich base. Since the yield of amine 10 from the amino ketone 33 was so low, this synthetic route was abandoned, and attention was redirected toward the morpholino derivatives.

Preparation and Reactions of Amines 11 and 12 (Schemes 5, 6, and 7). The use of the morpholino group as the amino moiety in the synthesis of the bicyclic structures was reinvestigated. The purposes of these experiments were the replacement of the ethylenedioxy group by a methylene group to relieve some of the steric interaction that hindered the formation of amino ketone 20 and the investigation of the amine oxide pyrolysis with an acetoxymethyl group at C_7 instead of the ethylenedioxy group. Although the syn-acetoxymethyl group of amino acetate 11 could exert a

steric interaction with C_3, this effect could be relieved by ring B assuming a boat conformation.



11

In the sequence of reactions outlined in Scheme 5, the ketone 7 was first transformed into 8-methylene-1,4-dioxa-spiro[4.5]decane (35) by an adaptation of the procedure of Greenwald and co-workers (21), who modified the Wittig reaction (22) by employing dimethylsulfoxide (DMSO) as solvent and its conjugate base for the formation of phosphorous ylides. Methylsulfinyl carbanion was formed *in situ* by the action of sodium hydride on DMSO and was used to generate methylenetriphenylphosphorane (36) from methyl-triphenylphosphonium iodide (37). The ketone 7 was added to the DMSO solution of the ylide 36 forming the olefin 35, b.p. 89-90° (22 mm.), in 65% yield. The ir. spectrum had absorptions at 3.28 (vinyl CH), 6.08 (C=C), and 11.02 μ (exocyclic methylene); and the n.m.r. spectrum showed the

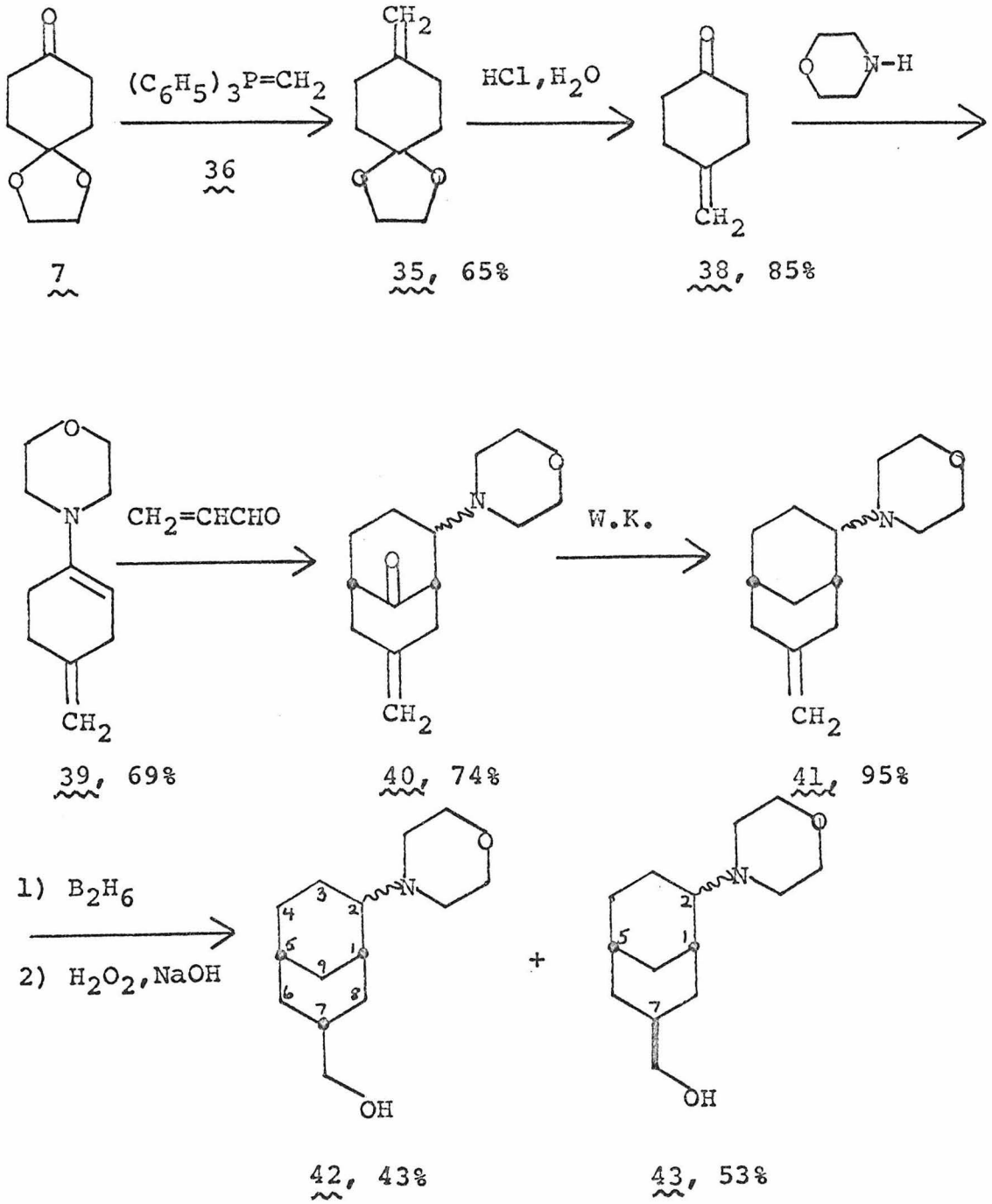
presence of the exocyclic methylene hydrogens at δ 4.58 (broad band) and the ethylenedioxy hydrogens at δ 3.83 (singlet).

The olefin 35 was heated in aqueous acetone with dilute hydrochloric acid in order to hydrolyze the ketal group. The 4-methylenecyclohexanone (38), b.p. 87-90° (50 mm.), resulted in 85% yield. The ir. spectrum had bands at 3.28 (vinyl CH), 5.82 (C=O), 6.05 (C=C), and 11.13 μ (exocyclic methylene); and the n.m.r. spectrum showed the presence of the exocyclic methylene hydrogens at δ 4.58 (broad band) and the ring hydrogens at δ 2.16 (broad band). The 2,4-dinitrophenylhydrazone melted at 154-155°.

The preparation of the morpholino enamine 39 was carried out in the same manner that was used in Scheme 1 for the preparation of enamine 17. The enamine 39, b.p. 80-84° (0.4 mm.), was prepared in 69% yield from the enone 38. The ir. spectrum had absorptions at 3.27 (vinyl CH), 6.08 (C=C), and 11.18 μ (exocyclic methylene); the n.m.r. spectrum confirmed the presence of the exocyclic methylene hydrogens at δ 4.82 (broad band), the ring vinyl hydrogen at δ 4.58 (triplet, J = 3.5 Hz.), and the morpholino hydrogens at δ 3.67 (multiplet, O-CH_2) and δ 2.30 (multiplet, N-CH_2).

The enamine 39 was alkylated in benzene with freshly distilled acrolein that was stabilized with a trace of hydroquinone. The vinyl ether intermediate was dissolved in tetrahydrofuran (THF), and the THF solution was heated

Scheme 5


(C6H5)3P=CH2
36
HCl, H2O
N-H
7
35, 65%
38, 85%
CH2=CHCHO
W.K.
39, 69%
40, 74%
41, 95%
1) B2H6
2) H2O2, NaOH
OH
OH
42, 43%
43, 53%

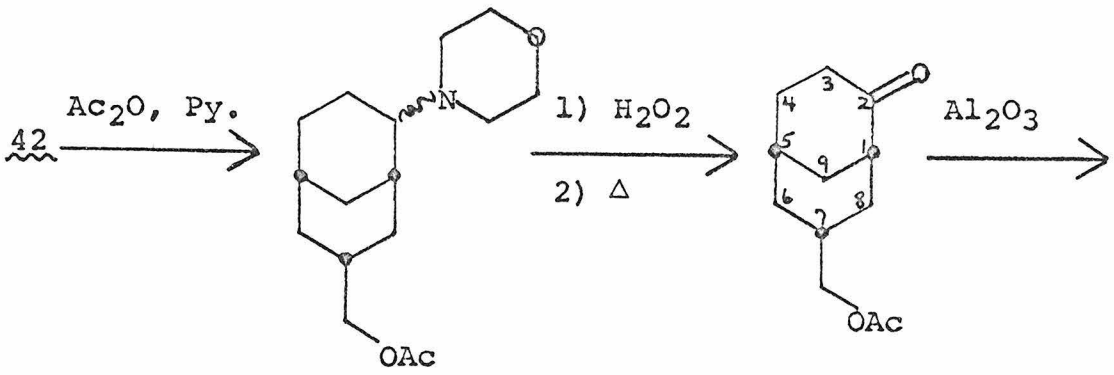
under reflux for 60 hr. Molecular distillation (75-100°, 0.05 mm.) of the crude product afforded the morpholino enone 40 in 74% yield. The ir. carbonyl band appeared at 5.80 μ in addition to the bands at 3.27 (vinyl CH), 6.09 (C=C), and 11.36 μ (exocyclic methylene). The n.m.r. spectrum indicated the presence of the exocyclic methylene hydrogens at δ 4.75 (broad band) and the morpholino hydrogens at δ 3.52 (multiplet, O-CH_2) and at δ 2.28 (multiplet, N-CH_2).

The enone 40 underwent Wolff-Kishner reduction under the conditions used for the preparation of amine 25 (Scheme 2). A 95% yield of morpholino olefin 41, b.p. 69° (0.06 mm.), resulted, and its ir. spectrum had absorptions at 3.28 (vinyl CH), 6.10 (C=C), and 11.40 μ (exocyclic methylene). The n.m.r. spectrum demonstrated the presence of the exocyclic methylene hydrogens at δ 4.61 (broad band) and the morpholino hydrogens at δ 3.55 (multiplet O-CH_2) and at δ 2.27 (multiplet, N-CH_2).

Hydroboration of the morpholino olefin 41 with diborane in THF (23) produced a crystalline amino alcohol 42, m.p. 104-105°, in 43% yield from ether. Evaporation of the mother liquors gave a 53% yield of an oily amino alcohol 42. The ir. spectrum of alcohol 42 had a hydroxyl absorption at 3.10 μ (KBr), and the hydroxyl band of alcohol 43 appeared at 2.93 μ (film). The assignment

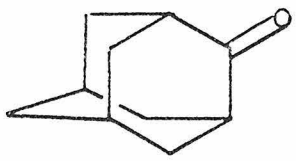
of the configuration of the hydroxymethyl group at C_7 of the alcohol 42 rested upon the subsequent conversion of this alcohol to adamantanone (44) (Scheme 6). The configuration at C_2 will be discussed later. The configuration at C_7 of the alcohol 43 was assigned on the basis that this alcohol was converted to the hydroxy olefin 45 (Scheme 6) that did not give 2-adamantanol upon solvolysis. The configuration at C_2 of the alcohol 43 will also be treated later.

Scheme 6



46, 100%

48, 28%



44

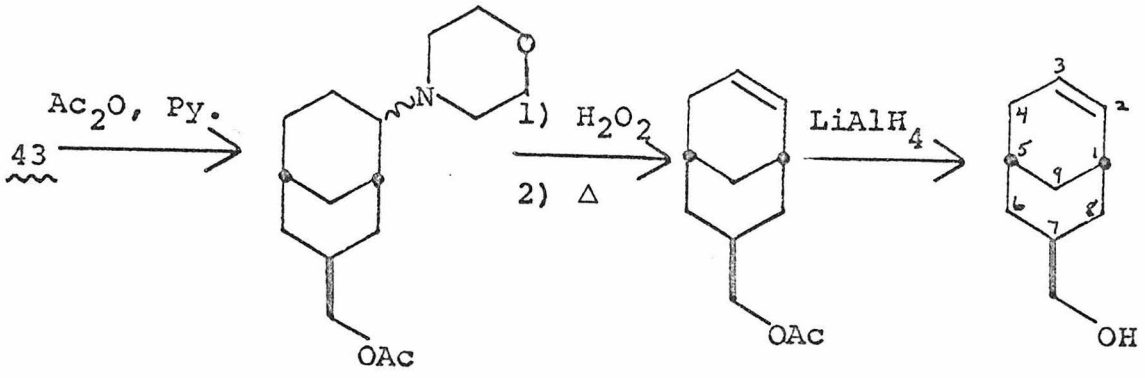
Acetylation of the crystalline amino alcohol 42 with acetic anhydride in pyridine afforded a quantitative yield of the amino acetate 46, m.p. 57-60°; the ir. spectrum had acetate bands at 5.72 (C=O) and 8.05 μ (C-O). Hydrogen peroxide oxidation of the amino acetate 46 gave the corresponding amine oxide 47.

The amine oxide 47 was dissolved in toluene, and the solution was heated under reflux for 12 hr. The toluene was diluted with pentane and washed with dilute hydrochloric acid to remove any basic material. The product was then chromatographed on alumina (I). The ether fraction of the chromatogram gave a 37% yield of a crystalline ketone that was identified as adamantanone (44) by its ir. spectrum (5.79 μ C=O band) (lit. ir. 5.79 μ) (24), and by comparison with an authentic sample (25). The mass spectrum, which had a M^+ peak of m/e 150 (base peak, 100%) and peaks of m/e 151 (11%) and m/e 152 (0.8%), also supported a molecular formula of $C_{10}H_{14}O$. However, if the product in the toluene-pentane solution was chromatographed on Florisil, the ether fraction gave a 28% yield of the keto acetate 48. The ir. spectrum had acetate bands at 5.74 (C=O) and 8.08 μ (C-O) and had a ketone band at 5.85 μ. The n.m.r. spectrum revealed the presence of the acetate methyl hydrogens at δ 2.03 (singlet) and the presence of two hydrogens on carbon adjacent to oxygen at δ 3.90

(doublet, J = 5 Hz., CH-CH_2-O). When the keto acetate 48 was chromatographed on alumina (I), adamantanone (44) was produced. A DMSO solution of amine oxide 47 was heated at 80-90° for 4 hr. (26), and the crude product was chromatographed on alumina (I) giving a 9% yield of adamantanone (44).

In a corresponding sequence of reactions (Scheme 7) the crude alcohol 43 was acetylated with acetic anhydride in pyridine giving an oily amino acetate 49 in 81% yield. The ir. spectrum of this acetate had absorptions at 5.75 (C=O) and 8.06 μ (C-O).

Scheme 7



49 50 45

The oily amino acetate 49 prepared from alcohol 43 was oxidized with hydrogen peroxide, and the resultant amine oxide dissolved in dry DMSO (26) was heated under nitrogen for 4.5 hr. at 80° to afford the crude acetate 50 in 35%

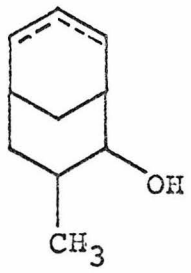
yield. Analysis by v.p.c. revealed a mixture of acetates containing 84% of acetate 50 and 16% of another acetate 51, whose structure is discussed below. Chromatography of the acetate mixture on Florisil gave the acetate 50, which was rechromatographed on Florisil and molecularly distilled at 50° (5 mm.) to yield the colorless acetate 50 of 99% purity (v.p.c. analysis). The ir. spectrum of the acetate 50 had absorptions at 3.34 (vinyl CH), 5.74 (acetate C=O), 6.08 (C=C), and 8.04 μ (acetate C-O). The first chromatogram also gave a 10% yield of keto acetate 48, which probably arose from the presence of the amino acetate 46 in the amino acetate 49 preparation. The acetate 51 was not obtained pure by further rechromatography on Florisil.

The crude acetate 50 was transformed into the alcohol 45 by reduction with lithium aluminum hydride. The p-nitrobenzoate derivative 52, m.p. 71-77°, was prepared and stirred in 50% aqueous acetone at 25° for 24 hr. in an attempted solvolysis that gave back starting ester 52. When the ester 52 was stirred in 67% aqueous dioxane at 70° for 80 min., the starting ester 52 was again isolated, m.p. 77-79°. The ir. spectrum of the ester 52 had bands at 3.32 (vinyl and aromatic CH), 5.78 (ester C=O), 6.55 (nitro), 7.45 (nitro), and 7.88 μ (ester C-O).

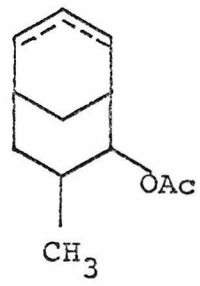
The crude alcohol 45 was purified by chromatography on Florisil, and the purified alcohol 45 had ir. and

n.m.r. spectral properties that were in accord with either structure 45 or structure 1. The ir. spectrum had bands at 3.00 (hydroxyl), 3.33 (vinyl CH), and 6.07 μ (C=C); the n.m.r. spectrum showed the presence of two vinyl hydrogens at δ 5.65 (multiplet, C<u>H</u>=C<u>H</u>) and the presence of the hydroxymethyl hydrogens at δ 3.50 (doublet, <u>J</u> = 5 Hz., CH-C<u>H</u>$_2$-O) and at δ 2.83 (singlet, O<u>H</u>). However, because the ester 52 was unreactive under solvolytic conditions, the <u>anti</u>-configuration was assigned to C_7 of alcohol 45.

The minor alcohol 53 obtained from the Florisil chromatogram above was rechromatographed on Florisil. The alcohol 53 (99% pure by v.p.c. analysis) had ir. absorptions at 3.00 (hydroxyl), 3.33 (vinyl CH), and 6.07 μ (C=C) and produced a n.m.r. spectrum that revealed the presence of two vinyl hydrogens at δ 5.52 (multiplet, C<u>H</u>=C<u>H</u>), the presence of three methyl hydrogens at δ 0.92 (doublet, <u>J</u> = 6 Hz., CH-C<u>H</u>$_3$), and the presence of a hydrogen on carbon adjacent to oxygen at δ 3.13 (multiplet, C<u>H</u>-O). These data suggested the structure of alcohol 53 as that illustrated below, and, thus the acetate 51 had the structure also illustrated. These products are a manifestation of the migration of the exocyclic double bond into the ring at some stage prior to the hydroboration of olefin 41. The amount of alcohol 53 available was too small to determine the position of the double bond.



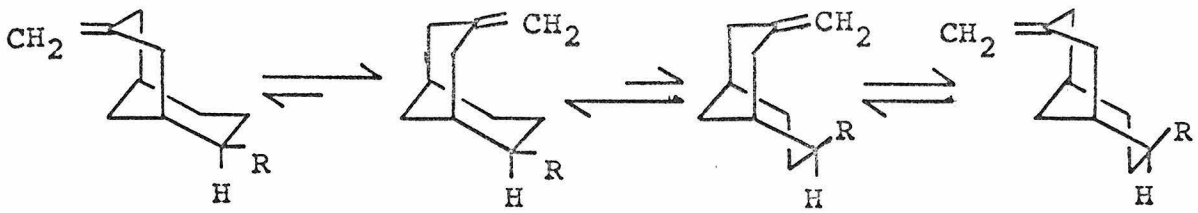
53



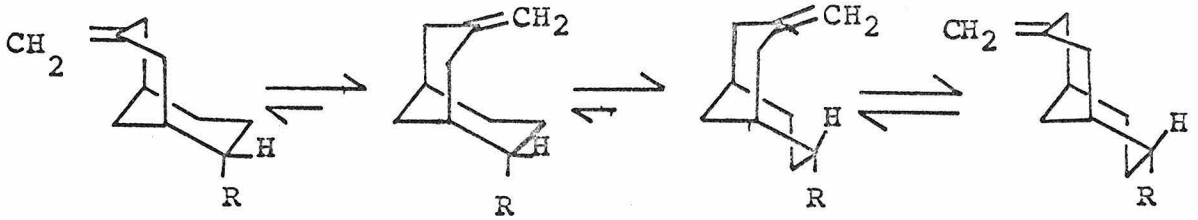
51

In order to formulate the stereochemistry of the morpholino group of the alcohols 42 and 43, the eight possible conformers 41a-h of the two isomers of the olefin 41 are examined. The most stable conformer of each isomer should have the bulky morpholino group equatorial. In the isomer 41a-d, which has a cis-morpholino group on ring A, conformer 41b has both rings in the more favorable chair conformation. Thus, conformer 41b should be the predominate species of the isomer 41a-d.

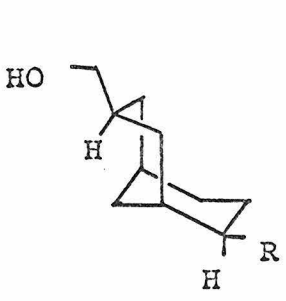
The isomer 41e-h, which has a trans-morpholino group on ring A, requires ring A to be in a boat conformation, if the morpholino group is to be equatorial. Ring B should assume the chair conformation as in conformer 41g; however, if this ring also takes on the boat conformation, as in conformer 41h, the bicyclo[3.3.1]nonane skeleton loses its rigidity and becomes flexible. By becoming twist-boats, both rings can be relieved of some of the eclipsing interactions that are produced in the boat conformation. Thus, the conformer 41h may either be approximately equal in



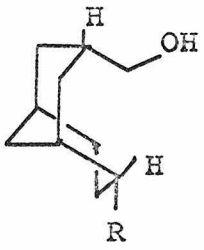
41a 41b 41c 41d



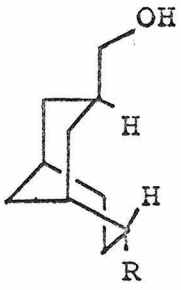
41e 41f 41g 41h



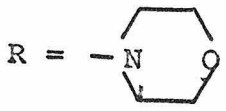
42a



42b



43a

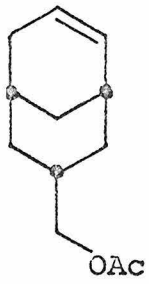


stability to conformer 41g or be even more energetically favorable than conformer 41g. Thus both conformers 41g and 41h may be present in the mixture of the olefin 41.

When the olefin 41 is hydroborated, the borane should attack the double bond from the less hindered side. Hydrogen peroxide oxidation of the alkylborane then should give the alcohol 42a from conformer 41b, alcohol 42b from conformer 41g, and alcohol 43a from conformer 41h.

CONCLUSION

Attempts on the synthesis of the alcohol 1 starting from 1,4-dioxaspiro[4.5]decan-8-one (7) have been unsuccessful to date. The main difficulty that arose in two reaction sequences (Schemes 1, 5, and 6) was the removal of the morpholino group by an amine oxide pyrolysis reaction. In the case where amine 8 was oxidized, and the resultant amine oxide was pyrolyzed, no elimination products were obtained. In the case where amine 11 was carried through the same reactions sequence (oxidation followed by pyrolysis), the keto acetate 48 was obtained instead of the desired acetate 54. The keto acetate 48, however, afforded adamantanone (44) upon chromatography on alumina (I).



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In a third reaction sequence (Scheme 4) the dimethylamino moiety replaced the morpholino group. A reasonably good general method for the preparation of dimethylamino enamines was developed, but, since the Wolff-Kishner reduction of amino ketone 33 afforded amine 10 in only 4.3% yield, the sequence was abandoned.

EXPERIMENTAL

Melting points (m.p.) were determined on a hot stage and are corrected. Boiling points (b.p.) are uncorrected. Infrared (ir.) spectra were determined on a Perkin-Elmer Infracord Model 137 spectrometer. Nuclear magnetic resonance (n.m.r.) spectra were obtained on Varian Associates A-60 and A-60A spectrometers and are reported in delta (δ), parts per million (p.p.m.) downfield from tetramethylsilane. Vapor phase chromatography (v.p.c.) was performed on Loenco Model 15B and Model 70 chromatographs with a thermal conductivity detector and on a Perkin-Elmer Model 881 chromatograph with a hydrogen flame detector. The activity of the alumina used for chromatography was standardized according to the procedure of Brockmann and Schodder (27). Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan, and Galbraith Laboratories, Inc., Knoxville, Tennessee.

Preparation of cis- and trans-Quinitol (15). Hydroquinone was hydrogenated under 146 atm. pressure for 5 hr. at 100° according to the method of Owen and Robins (9) to afford in 86% yield cis- and trans-quinitol (15); ir. (KBr) 3.08 μ (OH).

Preparation of 1,4-Cyclohexadione (13). A 200-g. (1.72 mole) sample of cis- and trans-quinitol (15) dissolved

in 800 ml. of reagent grade acetone was oxidized at 0° by dropwise addition of 858 ml. (2.29 moles) of 2.67 F chromic acid reagent (10) to the stirred solution of the diol 15. After the addition of oxidant was completed, the reaction mixture was stirred for 1 hr., and then the acetone supernatant was decanted from the inorganic sludge, which was washed with two portions of acetone and discarded. The combined acetone solution was dried superficially over calcium chloride and was reduced in volume on the rotary evaporator. The concentrate was treated with sodium bicarbonate to neutralize any acid present, was filtered, and was distilled to give 136 g. of crude dione 13, b.p. 118-120° (15 mm.), which upon crystallization from ether afforded 98.0 g. (51%) of dione 13: m.p. 77-78°, lit. m.p. 78° (11); ir. ($CHCl_3$) 5.80 μ (C=O); n.m.r. ($CHCl_3$) δ 2.38 p.p.m. (s.).

Preparation of 1,4-Dioxaspiro[4.5]decan-8-one (7). The procedure of Courtot was used (8). A 56.0-g. (0.500 mole) sample of 1,4-cyclohexadione (13), a 47.5-g. (0.766 mole) portion of ethylene glycol, 0.50-g. (2.5 mmole) sample of p-toluenesulfonic acid monohydrate, and a 100-ml. portion of benzene were placed in a 500-ml. flask fitted with a magnetic stirring bar and a water separator under the condenser. After the reaction was stirred for 1.5 hr. at

25°, the solution was heated under reflux for 15 min., and the water was removed with the aid of the separator. The solution was cooled to 25°, and washed with a dilute solution of potassium carbonate to remove the acidic catalyst, was washed with water, dried over anhydrous magnesium sulfate, filtered, and was concentrated on the rotary evaporator to give 82.5 g. of crystalline residue, which was shown to be a mixture of ketone 7 and diketal 16 by v.p.c. analysis.

The mixture was divided into two approximately equal portions, and each portion was dissolved in a 200-ml. portion of ethanol (95%). Each ethanol solution was added to a stirred solution of 120 g. (0.57 mole) of sodium bisulfite in 90 ml. of water. The crystalline addition compound was removed by filtration, washed with ethanol, and then dissolved in water. The aqueous solution was extracted with benzene to remove any remaining diketal 16. The ethanol filtrates were concentrated on the rotary evaporator, and the residues were combined with the combined benzene extract, which was washed with brine, dried over anhydrous magnesium sulfate, and was concentrated to afford 42.2 g. (42%) of diketal 16: m.p. 79-80°, lit. m.p. 79-79.5° (8); ir. ($CHCl_3$) 3.38 μ (CH); n.m.r. ($CHCl_3$) δ 3.48 (s., 8, ethylenedioxy CH_2) and 1.30 p.p.m. (s., 8, carbocyclic CH_2).

The aqueous solutions of the bisulfite addition compound were made basic with potassium carbonate and extracted with three portions of benzene. The combined benzene extract was washed with brine, dried over magnesium, and was concentrated on the rotary evaporator to give 36.9 g. of crystalline residue, which was recrystallized from ether-ligroin (30-60°) affording 27.4 g. (35%) of ketone 7: m.p. 72-73°, lit. m.p. 72-73° (5, 8); ir. ($CHCl_3$) 5.82 μ (C=O); n.m.r. ($CHCl_3$) δ 3.59 (s., 4, ethylenedioxy $C\underline{H}_2$), 2.05 (m., 4, $CH_2C\underline{H}_2C{=}O$), and 1.57 p.p.m. (m., 4, $C\underline{H}_2CH_2C{=}O$).

Preparation of Enamine 17. A 5.20-g. (33.3 mmoles) sample of ketone 7 was dissolved in 50 ml. of benzene. A 5.60-g. (66.6 mmoles) portion of morpholine and 0.1-g. portion of p-toluenesulfonic acid monohydrate were added, and the reaction mixture was heated under reflux overnight under a water trap. After the benzene and excess morpholine were removed by distillation, the product was distilled to give 5.54 g. (74%) of colorless enamine 17: b.p. 130° (0.7 mm.); n_D^{24} 1.5134; ir. (film) 3.28 (=CH) and 6.08 μ (C=C); n.m.r. (benzene) δ 4.43 (m., 1, =C$\underline{H}$), 3.82 (s., 4, O-$C\underline{H}_2C\underline{H}_2$-O), 3.60 (m., 4, (O-$C\underline{H}_2CH_2$-N), and 2.68 p.p.m. (m., 4, O-$CH_2C\underline{H}_2$-N).

Alkylation of Enamine 17 with Acrolein. A 2.5-g. sample (45 mmoles) of freshly distilled acrolein (Matheson, Coleman, and Bell) containing a trace of hydroquinone was added slowly to a solution of 9.84 g. (43.7 mmoles) of enamine 17 in 50 ml. of dry methanol under a nitrogen atmosphere. The reaction was stirred at 25° for 24 hr., then the methanol was removed under reduced pressure. The residue crystallized upon trituration with methanol, and the solid was recrystallized from dry methanol to give 12.2 g. (100%) of vinyl ether 19: m.p. 80-87°; ir. ($CHCl_3$) 3.29 (=CH) and 6.05 μ (C=C); n.m.r. (benzene) δ 6.16 (d., 1, J = 6 Hz., O-C<u>H</u>=CH), 4.65 (m., 1, C<u>H</u>=CH-O), and 3.67 p.p.m. (s., 4, O-C<u>H</u>$_2$C<u>H</u>$_2$-O).

Preparation of Morpholino Ketone 20. A 12.2-g. (43.5 mmoles) sample of vinyl ether 19 prepared above was dissolved in 20 ml. of dry methanol and heated under reflux for 1.5 hr. under nitrogen. After the methanol was removed on the rotary evaporator, the residue, which was examined by ir. spectroscopy, showed no change in composition. The residue was dissolved in 20 ml. of benzene and heated under reflux for two days under nitrogen. The reaction mixture was concentrated on the rotary evaporator to give an oil that deposited 2.79 g. (23%) of crystalline material upon trituration with ether. Recrystallization from acetonitrile gave colorless morpholino ketone 20: m.p. 134-135°; ir (KBr)

5.80 μ (C=O); n.m.r. ($CHCl_3$) δ 3.92 (s., 4, O-$C\underline{H}_2C\underline{H}_2$-O), 3.67 (m., 4, O-$C\underline{H}_2CH_2$-N), and 2.44 p.p.m. (m., 4, O-$CH_2C\underline{H}_2$-N).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.13; H, 8.32; N, 5.26.

Preparation of Amine 22. A 1.00-g. (3.6 mmoles) sample of morpholino ketone 20 was combined with 1.0 ml. (16 mmoles) of 85% hydrazine hydrate, 10 ml. of redistilled diethylene glycol, and 3 ml. of benzene. After the mixture was heated under reflux for 30 min. under nitrogen, a 0.50-g. portion of 85% potassium hydroxide was added. The bath temperature was raised to 180°, and the lower boiling constituents were removed by distillation. After 1 hr. the reaction mixture was cooled to 25° and was poured into 30 ml. of water. The aqueous solution was extracted repeatedly with ether. The ethereal solution was washed with brine, was dried over anhydrous magnesium sulfate, filtered, and was concentrated on the rotary evaporator to give 0.92 g. (88%) of oily amine 22: ir. (film) 3.40 μ (CH); n.m.r. ($CHCl_3$) δ 3.48 (s., 4, O$C\underline{H}_2C\underline{H}_2$O), 3.27 (m., 4, O$C\underline{H}_2CH_2$N), and 2.05 p.p.m. (m., 4, O$CH_2C\underline{H}_2$N).

Amine Oxide 23 Pyrolysis. A 0.92-g. (3.4 mmoles) sample of amine 22 dissolved in 5 ml. of methanol was oxidized with 1.0 g. (8.9 mmoles) of 30% hydrogen peroxide. The reaction was heated under reflux for 1.5 hr. The

solution was concentrated on the rotary evaporator, and the residue dissolved in water in order to decompose the excess peroxide with a trace of catalase. The water was removed by azeotropic distillation with ethanol and benzene on the rotary evaporator to give a residue, which was heated under reduced pressure (20 mm.) at 100° for 30 min., at 150° for 15 min., and finally at 180-200° for 2 hr. When the temperature reached 180°, the contents of the pyrolysis flask very quickly turned black, and the small amount of distillate collected still had the morpholino group: n.m.r. (CCl_4) δ 3.81 (s., 4, OCH_2CH_2O), 3.68 (m., 4, OCH_2CH_2N), and 2.48 p.p.m. (m., 4, OCH_2CH_2N); the rest of the spectrum closely resembled that of the starting amine 22.

Preparation of Morpholino Ketone 24. A 1.5-g. (5.6 mmoles) sample of morpholino ketal 22, which was prepared by the Wolff-Kishner reduction of the crystalline morpholino ketone 20, was dissolved in a 10-ml. portion of 1:1 acetone-water. A 0.5-ml. portion of concentrated hydrochloric acid was added, and the reaction was heated under reflux for 5 min. After the acetone was removed by evaporation on the rotary evaporator, the acidic solution was neutralized with potassium hydroxide. The solution was extracted with ether, and the ethereal extract was washed

with brine, dried over anhydrous magnesium sulfate, filtered, and was concentrated on the rotary evaporator to give an oily residue. Molecular distillation of the residue at 160° (0.4 mm.) yielded 1.1 g. (90%) of morpholino ketone 24: ir. (film) 5.88 (C=O) and 8.93 μ (C-O); n.m.r. (benzene) δ 3.70 (m., 4, O-CH_2CH_2-N) and 2.35 p.p.m. (m., 4, O-CH_2CH_2-N).

Amine Oxide Elimination on Amino Ketone 24. A 0.31-g. (1.4 mmole) sample of amino ketone 24 was dissolved in 1 ml. of methanol. A 0.45-g. (4 mmoles) portion of 30% hydrogen peroxide was added, and the solution was allowed to stand at 25° for 19 hr. After the methanol was removed on the rotary evaporator, and after the residue was dissolved in water, a trace of catalase was added to destroy the excess peroxide. The water was removed by azeotropic distillation with ethanol and benzene on the rotary evaporator, and the residue was pyrolyzed at 200° (20 mm.). The contents of the pyrolysis flask turned black, and nothing was collected in the receiving traps.

Morpholino Ketone 21. Morpholino ketone 21 was prepared in 70% yield from 1-morpholinocyclohexene (18) according to the procedure of Foote and Woodward (14): b.p. 106-110° (0.1 mm.), lit. b.p. 141-147° (1 mm.) (14); $n^{20}D$ 1.5202, lit. $n^{25}D$ 1.5182 (14); ir. (film) 5.83 μ (C=O), lit. ir. ($CHCl_3$) 5.84 μ (14).

Preparation of Amine 25. A. From Morpholino Ketone 21. A 23.6-g. (0.106 mole) sample of morpholino ketone 21 prepared from 1-morpholinocyclohexene (18) was combined with 48.5 g. (1.0 mole) of 100% hydrazine hydrate and 300 ml. of reagent grade diethylene glycol. The mixture was heated under reflux for 2 hr., and a 30.0-g. portion of 85% potassium hydroxide was added. The lower boiling solvents were removed by distillation, while the temperature of the heating bath was raised to 240°. After 3 hr. a 240° the reaction was cooled to 25°, diluted with water, and extracted with four 50-ml. portions of benzene. The benzene extract was washed twice with brine, was dried over anhydrous sodium sulfate, filtered, and was concentrated on the rotary evaporator to give an oily residue. Distillation of the residue gave 7.04 g. (32%) of amine 25: b.p. 85-86° (0.3 mm.); $n^{25}D$ 1.5109; n.m.r. (benzene) δ 3.70 (m., 4, O-CH_2CH_2-N) and 2.35 p.p.m. (m., 4, OCH_2CH_2-N); ir. (film) 3.43 (CH) and 8.92 μ (C-O or C-N).

Anal. Calcd. for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.88; H, 11.10; N, 6.89.

B. Preparation from Morpholino Ketone 24. A 1.00-g. (4.48 mmoles) sample of morpholino ketone 24 prepared from morpholino ketal 22 was combined with 2.43 ml. of 100% hydrazine hydrate and 20 ml. of reagent grade diethylene

glycol. The reaction was carried out as described above to give after molecular distillation (80°, 0.6 mm.) 0.50 g. (53%) of colorless amine 25: ir. (film) 3.43 (CH), and 8.92 μ (C-O or C-N), identical to the ir. spectrum of amine 25 prepared from morpholino ketone 21; n.m.r. (benzene) δ 3.70 (m., 4, O-CH_2CH_2-N) and 2.35 p.p.m. (m., 4, O-CH_2CH_2-N).

Bicyclo[3.3.1]non-2-ene (26). A. From Amine 25. A 5.2-g. (25 mmoles) sample of amine 25, which was prepared from morpholino ketone 21 was combined with a 4.0-g. (36 mmoles) portion of 30% hydrogen peroxide and 10-ml. portion of methanol. The solution was heated under reflux for 5 hr., and the excess peroxide was then destroyed with platinum black. The solution was filtered and concentrated on the rotary evaporator to yield a colorless residue. The residue was heated at 125-140° (20 mm.) with a receiver cooled to -70° until no more decomposition was observed. The residue in the receiver was dissolved in ether. The ethereal solution was washed in succession with water, dilute hydrochloric acid, dilute sodium bicarbonate solution, and brine. The solution was dried over anhydrous magnesium sulfate, filtered, and was carefully concentrated by distillation yielding 1.15 g. (38%) of olefin 26: m.p. 99-101°, lit. m.p. 103-105° (16); ir. (CCl_4) 3.33 (=CH), 5.98 (C=C), and 14.25 μ (cis CH=CH); n.m.r. ($CHCl_3$) δ 5.84 p.p.m. (m., 2, CH=CH).

Preparation of 1-Dimethylaminocyclohexene (28).

A. Calcium Hydride Method. A benzene suspension of 9.8 g. (0.10 mole) of cyclohexanone, 2.1 g. (0.050 mole) of calcium hydride, and 10 g. of dimethylamine was stirred for 6 hr. under a Dry-ice condenser. The solution was distilled to give after a forerun of benzene 5.8 g. (46%) of the enamine 28: b.p. 168° (760 mm.), lit. b.p. 175.5° (15); ir. (film) 3.30 (=CH), 3.60 (CH), and 6.10 μ (C=C), v.p.c. (6 ft. of 5% Carbowax 20M) 75% purity (25% cyclohexanone).

B. Lithium Aluminum Hydride Method. In a flask fitted with a Dry-ice condenser, a 1.9-g. (50 mmoles) sample of lithium aluminum hydride (95%, Metal Hydrides, Inc.) was dissolved in 25 ml. of dry ether. Excess dimethylamine was added, and after 1 hr. a 9.80-g. (0.100 mole) sample of cyclohexanone was added with stirring. The reaction was stirred overnight, and the excess dimethylamine was allowed to escape through a drying tube. Distillation of the residue, after removal of the solvents, gave 6.8 g. (54%) of colorless enamine 28: b.p. 30° (1.5 mm.); ir. (film) 3.30 (=CH), 3.60 (CH), and 6.10 μ (C=C).

Preparation of Amino Ketone 29. A 11.0-g. (65 mmoles) sample of 1-dimethylaminocyclohexene (28) (75% pure by v.p.c.) prepared by the calcium hydride method was dissolved in 10 ml. of dry methanol. A 3.65-g. (65 mmoles) portion

of freshly redistilled acrolein was added dropwise while the reaction flask was cooled in an ice bath. After the reaction was stirred at 25° for 15 hr., the solution was concentrated on the rotary evaporator, and the residue was distilled to give 6.7 g. (55% based on acrolein) of dimethylamino ketone 29: b.p. 60-90° (0.1 mm.); ir. (film) 3.62 (CH) and 5.83 μ (C=O).

Preparation of Amine 9. A solution of 6.7 g. (37 mmoles) of the ketone 29, 25 g. (0.50 mole) of 100% hydrazine hydrate, 150 ml. of reagent grade diethylene glycol, and 10 g. of 85% potassium hydroxide was heated for 3 hr. under reflux. After the lower boiling liquids were removed by distillation, the reaction was heated for 1.5 hr. at 200°. The usual workup as described for amine 25 gave 2.5 g. (41%) of the amine 9: b.p. 50° (0.1 mm.); ir. (film) 3.62 μ (CH); n.m.r. (benzene) δ 2.08 p.p.m. (s., 6, $C\underline{H}_3NC\underline{H}_3$).

Bicyclo[3.3.1]non-2-ene (26). B. From Amine 9. A methanol solution of 2.5 g. (15 mmoles) of amine 9 and 2.2 g. (20 mmoles) of 30% hydrogen peroxide was stirred overnight at 25° and then heated under reflux for 1 hr. After the excess peroxide was destroyed with platinum catalyst, the solution was filtered, and concentrated on the rotary evaporator, to give the amine oxide 30 that was dried under

reduced pressure in a desiccator. The dried amine oxide 30 was heated to 180° under reduced pressure (20 mm.) while vigorous decomposition took place. The distillate was dissolved in pentane, and the pentane solution was washed with dilute hydrochloric acid and water, dried, and was filtered through a short column of alumina (I). Distillation through a 12 in. Widmer column removed most of the pentane, and the residual solvent was removed at 0° under slightly reduced pressure (about 100 mm.) to give 1.45 g. (80%) of crystalline olefin 26 : m.p. 99-101°, lit. m.p. 103-105° (16).

Preparation of Enamine 32. A 15.6-g. (0.100 mole) sample of ketone 7 was added to a mixture of 1.9 g. (50 mmoles) of lithium aluminum hydride (95%, Metal Hydrides, Inc.) in 25 ml. of dry ether and excess dimethylamine as described in the preparation of enamine 28. Distillation of the reaction residue gave 6.61 g. (36%) of enamine 32, b.p. 75-88° (0.8 mm.), which was redistilled to yield 6.44 g. of enamine 32: b.p. 85-90° (0.5 mm.); ir. (film) 6.09 μ (C=C).

Dimethylamino Ketone 33. A 1.97-g. (35.2 mmoles) sample of freshly distilled acrolein stabilized with a trace of hydroquinone was added slowly to a solution of 6.44 g.

(35.2 mmoles) of enamine 32 in 10 ml. of dry methanol with cooling in an ice bath. After the reaction was stirred for two days at 25°, the solvent was removed on the rotary evaporator, and the residue was distilled to give 3.92 g. of oil, b.p. 110-142° (0.2 mm.), which had an infrared band at 6.05 μ (C=C) due to the vinyl ether. The distillate was dissolved in methanol and heated under reflux with 100 mg. of dimethylamine hydrochloride. After 3 hr. the reaction was cooled to 25°, and potassium carbonate was added to neutralize the amine hydrochloride. The solution was filtered and was concentrated on the rotary evaporator to give a residue that was dissolved in ether and centrifuged to remove inorganic solids. The clear supernatant was concentrated on the rotary evaporator to give 4.0 g. (48%) of a dimethylamino ketone 33: ir. (film) 3.61 (CH) and 5.81 μ (C=O).

Wolff-Kishner Reduction of Dimethylamino Ketone 33. A mixture of 3.71 g. (15.5 mmoles) of dimethylamino ketone 33 and 20 g. (0.40 mole) of 100% hydrazine hydrate was stirred at 25° for 2 hr. A 3.31-g. portion of 85% potassium hydroxide and 60-ml. portion of reagent grade diethylene glycol were added. After the reaction was heated under reflux for 4 hr., the temperature of the heating bath was raised to 200°, and the lower boiling liquids were removed

by distillation. Steam distillation of the reaction mixture gave a cloudy distillate, which was extracted with ether. The ethereal extract was washed with water and brine, dried over anhydrous magnesium sulfate, and was concentrated on the rotary evaporator to give 2.14 g. (75%) of ketal 34; ir. (film) 3.42 μ (CH); n.m.r. (benzene) δ 3.70 (s., 4, O-$\underline{CH_2}\underline{CH_2}$-O) and 0.98 p.p.m. (t., 3, $\underline{J}$ = 6 Hz., $CH_2\underline{CH_3}$).

The pot residue from the steam distillation was diluted with water and extracted with chloroform. The extract was washed with water and brine, was dried over anhydrous magnesium sulfate, and was concentrated on the rotary evaporator to give 1.47 g. of dark oil, which was distilled to yield an oil, b.p. 98-115° (0.2 mm.). Redistillation of the oil gave 0.13 g. (4.3%) of amine 10: b.p. 103-108° (0.2 mm.); ir. (film) 3.62 μ (CH); n.m.r. ($CHCl_3$) δ 3.70 (m., 4, O-$\underline{CH_2}\underline{CH_2}$-O) and 2.04 p.p.m. (m., 6, $\underline{CH_3}$-N-$\underline{CH_3}$).

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 68.97; H, 10.26; N, 6.50, 6.47.

Preparation of 8-Methylene-1,4-dioxaspiro[4.5]decane (35). An adaptation of the procedure of Greenwald and co-workers (21) was employed. A 20.5-g. (12.0-g. sodium hydride, 0.500 mole) portion of 58.6% sodium hydride

dispersion (Metal Hydrides, Inc.) was added to a 1-l. flask fitted with a magnetic stirring bar. After the hydride was washed with 50 ml. of anhydrous ether, a 250-ml. portion of dry dimethylsulfoxide (DMSO, Baker Analyzed Reagent) was added. The reaction was heated in a nitrogen atmosphere at 55° (oil bath) for 4 hr. with stirring and then was cooled to 25°. A solution of 202 g. (0.500 mole) of methyltriphenylphosphonium iodide (37) prepared from triphenylphosphine and methyliodide in 500 ml. of DMSO was added, and the resulting solution was stirred for 30 min. at 25°. A 76.0-g. (0.487 mole) portion of 1,4-dioxaspiro[4.5]decan-8-one (7) was added slowly, while the flask was cooled in an ice bath. After the addition was completed, the ice bath was removed; and the solution was stirred overnight at 25°. The DMSO solution was extracted with five 200-ml. portions of a solvent composed of equal parts of ether and pentane. The extract was washed once with water and then with brine, was dried over anhydrous magnesium sulfate, and was concentrated on the rotary evaporator at 5° to yield 56.8 g. of oil. The DMSO solution was then diluted with 500 ml. of ice water and was re-extracted with five 200-ml. portions of ether-pentane. After being washed, dried, and concentrated as described above, the second extract gave an additional 16.5 g. of oil. The combined crude product (73.3 g.) was distilled to yield

48.7 g. (65%) of olefin 35: b.p. 89-90° (22 mm.); ir. (film) 3.28 (=CH), 6.08 (C=C), and 11.02 μ ($=CH_2$); n.m.r. (CCl_4) δ 4.58 (broad band, 2, $=C\underline{H}_2$), 3.83 (s., 4, $OC\underline{H}_2C\underline{H}_2O$), 2.25 (m., 4, C_7 and C_9 allylic hydrogens), and 1.59 p.p.m. (m., 4, C_6 and C_{10} hydrogens).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.15; H, 9.06.

Preparation of 4-Methylenecyclohexanone (38). To a solution of 23.0 g. (0.15 mole) of 8-methylene-1,4-dioxaspiro[4.5]decane (35) in 70 ml. of acetone was added 60 ml. of 2 N hydrochloric acid. After having been heated under reflux for 5 min., the solution was cooled and neutralized with 4.81 g. of sodium hydroxide pellets (pH 7). The solution was diluted with brine and extracted with four 70-ml. portions of methylene chloride. The organic extract was dried over anhydrous magnesium sulfate and concentrated to yield 22.5 g. of oil, which was distilled through a six inch Vigreux column to give 15.8 g. of enone 38 : b.p. 86-95° (50 mm.). To remove traces of ethylene glycol, the distillate was diluted with pentane and was washed with water. The organic layer was dried and concentrated to yield 14.0 g. (85%) of enone 38 that was contaminated with 10% (v.p.c. analysis) of the starting ketal. The crude enone 38 was satisfactory for the preparation of the morpholino

enamine 39. An analytical sample was purified by a second hydrolysis and distillation to give enone 38: b.p. 87-90° (50 mm.); $n^{22}D$ 1.4729; ir. (film) 3.28 ($=CH_2$), 5.82 (C=O), 6.05 (C=C), and 11.13 μ ($=CH_2$); n.m.r. (CCl_4) δ 4.58 (broad band, 2, $=CH_2$) and 2.16 p.p.m. (broad band, 8, ring hydrogens).

Anal. Calcd. for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.43; H, 9.11.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol: m.p. 154-155°.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.94; H, 4.84; N, 19.24.

Preparation of Enamine 39. A benzene solution of 13.0 g. (0.12 mole) of crude 4-methylenecyclohexanone (38) that contained 10% (v.p.c. analysis) of 8-methylene-1,4-dioxaspiro[4.5]decane (36), 30.5 g. (0.35 mole) of morpholine and a trace of p-toluenesulfonic acid was heated under reflux overnight with a water trap in a nitrogen atmosphere. Most of the benzene was removed by distillation at atmospheric pressure. A small quantity of powdered barium hydroxide was added to the flask to neutralize the acidic catalyst, and the remaining solvent was removed under reduced pressure (1 mm.). Distillation of the residue gave 14.9 g. of oil: b.p. 77-84° (0.4 mm.). Redistillation of the oil gave

14.5 g. (69%) of colorless enamine 39: b.p. 80-84° (0.4 mm.); ir. (film) 3.27 ($=CH_2$), 6.08 (C=C-N), and 11.18 μ ($=CH_2$); n.m.r. (C_6H_6) δ 4.82 (broad band, 2, $=C\underline{H}_2$), 4.58 (t., 1, $\underline{J}$ = 3.5 Hz., $C\underline{H}$=C-N), 3.67 (m., 4, $C\underline{H}_2$-O), 2.30 (m., 4, $C\underline{H}_2$-N), 2.92 (m., 2, C_3 allylic hydrogens), and 2.70 p.p.m. (m., 4, C_5 and C_6 allylic hydrogens).

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.70; H, 9.71; N, 7.72.

Preparation of Morpholino Enone 40. In a nitrogen atmosphere a 4.54-g. (81.0 mmoles) portion of freshly redistilled acrolein (Matheson, Coleman and Bell) stabilized with a trace of hydroquinone was added to a solution of 14.5 g. (81.0 mmoles) of 1-morpholino-4-methylenecyclohexene (39) in 30 ml. of dry benzene. After the reaction had been stirred at 25° for 5 hr., the solution was concentrated on the rotary evaporator, the residue was redissolved in 70 ml. of dry tetrahydrofuran (THF). The THF solution under nitrogen was heated under reflux for 60 hr., during which time the course of the reaction was followed by the removal of small aliquots that were examined by ir. and n.m.r. spectroscopy until the 5.80 μ ir. band no longer increased in relative intensity. The solvent was removed on the rotary evaporator, and the residue was purified by a single molecular distillation (75-100°, 0.05 mm.) to yield 14.1 g.

(74%) of colorless morpholino ketone 40: ir. (film) 3.27 (=CH_2), 5.80 (C=O), 6.09 (C=C), and 11.36 μ (=CH_2); n.m.r. (C_6H_6) δ 4.75 (broad band, 2, =$C\underline{H}_2$), 3.52 (m., 4, $C\underline{H}_2$-O), and 2.28 p.p.m. (m., 4, $C\underline{H}_2$-N).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.43; H, 8.91; N, 6.12.

Preparation of Morpholino Olefin 41. A solution of 8.27 g. (35.2 mmoles) of the enone 40, 124 g. (2.48 moles) of 100% hydrazine hydrate and 40 ml. of ethanol was allowed to stand at 25° for 1 hr. A 330-ml. portion (3.5 moles) of diethylene glycol and a 51-g. (0.78 mole) portion of 85% potassium hydroxide pellets were added. The reaction was heated for 5 hr. in a nitrogen atmosphere at a bath temperature of 200°, while the lower boiling constituents were removed by distillation. The pot residue and the distillate were each diluted with water and separately extracted with ether. The extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated to yield 5.13 g. of oil from the pot residue and 2.63 g. of oil from the distillate. The combined crude product was distilled to give 7.33 g. (95%) of amine 41: b.p. 69° (0.06 mm.); ir. (film) 3.28 (=CH_2), 6.10 (C=C), and 11.40 μ (=CH_2); n.m.r. (C_6H_6) δ 4.61 (broad band, 2, =$C\underline{H}_2$),

3.55 (m., 4, CH_2-O), and 2.27 p.p.m. (m., 4, CH_2-N).

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.02; H, 10.40; N, 6.41.

Hydroboration of Morpholino Olefin 41. In a nitrogen atmosphere a 52-ml. (17 mmoles) portion of 0.33 M diborane in tetrahydrofuran (THF) (23) was added dropwise to a THF solution of 7.18 g. (32.5 mmoles) of morpholino olefin 41. After the solution was stirred at 25° for 12 hr., a 13-ml. portion of 3 N sodium hydroxide and 13-ml. portion of 30% hydrogen peroxide were added. After having been stirred for 45 min., the solution was extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and concentrated to give 7.93 g. of viscous oil, which partially crystallized. The solid was recrystallized from ether yielding 3.36 g. (43%) of colorless amino alcohol 42: m.p. 104-105°; ir. (KBr) 3.10 μ (OH).

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.32; H, 10.50; N, 5.77.

The mother liquors gave 4.13 g. (53%) of oily amino alcohol 43, which was molecularly distilled at 100° (0.03 mm.) to yield an analytical sample: ir. (film) 2.93 μ (OH).

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.35; H, 10.41; N, 5.82.

Acetylation of Crystalline Amino Alcohol 42. A 500-mg. (2.08 mmoles) sample of crystalline amino alcohol 42 was dissolved in 4.8 ml. of dry pyridine. After a 1.6-ml. (large excess) portion of acetic anhydride was added, the reaction was heated at 95° for 10 min. The solution was cooled and was concentrated on the rotary evaporator. In order to remove the residual reagents, the residue was dissolved in toluene, and the solution reconcentrated on the rotary evaporator to give an oil, which crystallized upon standing to afford 622 mg. (100%) of amino acetate 46: m.p. 57-60°; ir. (CCl_4) 5.72 (acetate) and 8.05 μ (C-O).

Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.07; H, 9.59; N, 5.14.

Amine Oxide Elimination on Crystalline Amino Acetate 46. A. In Toluene at 110°. A 1.00-g. (3.56 mmoles) sample of crystalline amino acetate 46 dissolved in 10 ml. of n-propanol was oxidized with 1.0 ml. (9.6 mmoles) of 30% hydrogen peroxide. The reaction was heated under reflux for 12 hr., and the excess hydrogen peroxide was destroyed with platinum catalyst, which was then removed by centrifugation. The supernatant was concentrated on the rotary evaporator to give an oil, which was dissolved in 10.0 ml. of dry benzene. Aliquots of this solution (solution A) were used under the following conditions to study the amine oxide elimination.

A 1.0-ml. portion of solution A was concentrated on the rotary evaporator, and the resulting oil was redissolved in 15 ml. of toluene. The toluene solution was heated under reflux for 10 hr. under nitrogen. After the toluene solution was cooled at 25°, diluted with pentane, washed with dilute hydrochloric acid, water and brine, was dried over anhydrous magnesium sulfate, and filtered, the organic product was chromatographed on alumina (I). Ether gave 20 mg. (37%) of crystalline ketone, which was identified as adamantanone (44): ir. (CCl_4) 5.79 μ (C=O), spectrum was identical to an authentic sample (25); mass spectrum (70 eV.) m/e (rel. intensity) 150 (100), 151 (11), 152 (0.8), 79 (82), mol. formula $C_{10}H_{14}O$.

In order to determine whether the adamantanone (44) was produced in the thermal reaction or whether it was formed in the chromatography of the crude product, a 2.0-ml. portion of solution A was concentrated, and the resulting oil was heated under reflux in toluene as before. The product was isolated as before except that after the dried toluene-pentane solution was filtered, its volume was adjusted to 50.0 ml. with pentane. One-half of this solution was chromatographed on alumina (I) yielding 14 mg. (26%) of adamantanone (44). The remaining 25-ml. portion of the solution was chromatographed on Florisil giving in the ether fractions 21 mg. (28%) of keto acetate 48: ir. (film)

5.74 (acetate C=O), 5.85 (ketone C=O), and 8.08 μ (acetate C-O); n.m.r. ($CHCl_3$) δ 3.90 (d., 2, J = 5 Hz., CH_2OAc) and 2.03 p.p.m. (s., 3, CH_3CO). When a 4-mg. sample of keto acetate 48 was chromatographed on alumina (I), 2 mg. of adamantanone (44) was obtained.

B. In DMSO at 90°. A 200-mg. (0.712 mmole) sample of crystalline amine acetate 46 was oxidized with 0.50 ml. (4.8 mmoles) of 30% hydrogen peroxide in 4 ml. of n-propanol. The reaction was heated under reflux for 12 hr., and the resultant oily amine oxide obtained as before was dissolved in a 5-ml. portion of dry DMSO. The DMSO solution was heated at 80-90° for 4 hr. under nitrogen. The solution was diluted with water and was extracted with ether. The ethereal extract was washed twice with water, once with brine, dried over anhydrous magnesium sulfate, filtered, and was concentrated on the rotary evaporator to give 153 mg. of oil, which was chromatographed on alumina (I). The ether fractions afforded 13 mg. (9.4%) of adamantanone (44) identified by its ir. spectrum.

Acetylation of Liquid Amino Alcohol 43. The mother liquors from the hydroboration product were concentrated, and the crude alcohol 43 was used without further purification. A 4.13-g. (17.3 mmoles) sample of crude amino alcohol 43 was dissolved in 40 ml. of dry pyridine. After a 14-ml.

portion of acetic anhydride was added, the reaction was heated at 100° for 10 min. The excess reagents were removed on the rotary evaporator with the aid of toluene to give 5.05 g. of yellow oil. The oil was dissolved in ether, treated with charcoal, filtered, and concentrated to yield 4.77 g. of pale yellow oil, which was molecularly distilled at 90° (0.05 mm.) to afford 3.94 g. (81%) of viscous colorless amino acetate 45: ir. (film) 5.75 (acetate) and 8.06 μ (C-O).

Anal. Calcd. for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.42; H, 9.66; N, 4.92.

Amine Oxide Elimination on Crude Amino Acetate 49. The acetate 49 prepared from the crude amino alcohol 43 was used without further purification. A 2.59 g. (9.24 mmoles) sample of oily amino acetate 49 and a 26-ml. (25 mmoles) portion of 30% hydrogen peroxide solution were dissolved in 25 ml. of n-propanol. The solution was heated under reflux until the solution was no longer basic to litmus (4.5 hr.). The reagents were removed on the rotary evaporator with the aid of toluene. The residue was dissolved in 30 ml. of dry DMSO and was heated under nitrogen for 4.5 hr. at 80°. After having been cooled to 25°, the solution was poured into 125 ml. of ice water. The aqueous solution was extracted with four 50-ml. portions of ether. The combined ethereal

extract was washed first with a 50-ml. portion of water, then with several portions of 0.01 M hydrochloric acid until the aqueous layer remained acidic to litmus. The ethereal layer was rewashed with water and was dried over anhydrous magnesium sulfate. After the solution was concentrated on the rotary evaporator at 10°, the residue was dissolved in 50 ml. of pentane. The pentane solution was dried over anhydrous magnesium sulfate and was filtered through a column of 20 g. of silicic acid with a total of 100 ml. of pentane. Evaporation of the solvent afforded 0.649 g. (35%) of crude acetate 49: ir. (film) 3.32 (=CH), 5.73 (acetate) and 8.05 μ (C-O); v.p.c. (6 ft. of Carbowax 20M) two compounds, the one with the shorter retention time (acetate 50) amounted to 16% of the mixture, the compound with the longer retention time (acetate 49) amounted to 84%.

Purification of the Acetate Mixture 50. A 198-mg. sample of crude acetate 50 was chromatographed on Florisil (60/100 mesh), and the results are summarized in Table 1. Each fraction was analyzed by v.p.c. on Carbowax 20M. The mixture of acetates 50 and 51 obtained from the 1:99 ether-pentane was rechromatographed on Florisil (Table 2).

Table 1. Chromatography of crude acetate 50.

Solvent	Vol. (ml.)	Wt. of residue (mg.)
Pentane	150	20 (Hydrocarbons)
1:99 Ether-pentane	50	0
1:99 Ether-pentane	50	42 (Acetates 50 and 51)
1:99 Ether-pentane	50	34 (Acetate 50)
1:19 Ether-pentane	50	45 (Acetate 50)
1:9 Ether-pentane	50	23 (Acetate 50)
1:3 Ether-pentane	25	
1:1 Ether-pentane	25	23 (Keto acetate 48)
Ether	50	
Ether	50	0

Table 2. Chromatography of acetate mixture 50 and 51.

Solvent	Vol. (ml.)	Wt. of residue (mg.)
Pentane	200	0
1:99 Ether-pentane	200	0
1:49 Ether-pentane	100	11 (Acetates 50 and 51)
1:19 Ether-pentane	100	21 (95% Acetate 50)
1:9 Ether-pentane	50	3 (99% Acetate 50)
1:4 Ether-pentane	50	
1:1 Ether-pentane	50	0
Ether	50	

The combined acetate 50 fractions from both chromatograms were rechromatographed on Florisil (Table 3). The acetate 50 of 99% purity obtained from the third chromatogram was molecularly distilled at 50° (5 mm.) to yield a colorless oil: ir. (film) 3.34 (=CH), 5.74 (acetate), 6.08 (C=C), and 8.04 μ (C-O).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.03; H, 9.44.

Table 3. Rechromatography of the acetate 50.

Solvent	Vol. (ml.)	Wt. of residue (mg.)
Pentane	100	0
1:99 Ether-pentane	100	0
1:99 Ether-pentane	100	18 (93% Acetate 50)
1:99 Ether-pentane	100	28 (97% Acetate 50)
1:49 Ether-pentane	100	25 (98% Acetate 50)
1:49 Ether-pentane	100	14 (99% Acetate 50)
1:19 Ether-pentane	100	9 (99% Acetate 50)
1:9 Ether-pentane	50	2

Reductive Cleavage of Crude Acetate 50. To an ether solution of 174 mg. (0.90 mmole) of crude acetate 50 obtained from the amine oxide elimination reaction, was added, by way of a soxhlet extractor, a 31-mg. (0.78 mmole) portion of 95% lithium aluminum hydride. After the reaction was heated under reflux for 2 hr., the excess hydride was decomposed with wet ether and powered sodium sulfate decahydrate. The mixture was stirred for another 30 min. The solution was filtered and concentrated to yield 183 mg. of oil that was molecularly distilled at 90° (20 mm.) to afford 128 mg. (94%) of oily alcohol 45: ir. (film) 3.00 μ (OH).

The p-nitrobenzoate derivative was prepared by the addition of 75 mg. (0.40 mmole) of p-nitrobenzoyl chloride and 0.063 ml. (0.80 mmole) of dry pyridine to a toluene solution of 30 mg. (0.20 mmole) of alcohol 48. The reaction was heated to 100° for 5 min. The product was extracted

with pentane; the pentane solution was washed with water, dried over anhydrous magnesium sulfate, filtered, and was concentrated to give the ester 52: m.p. 71-77°; ir. (CCl_4) 3.32 (=CH), 5.78 (C=O), 6.55 (NO_2), 7.45 (NO_2), and 7.88 μ (C-O). The ester 52 was stirred in 1:1 acetone-water at 25° for 24 hr. The product was worked up by extraction with pentane. The pentane solution was washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to give a solid that was identified as starting ester 52 by its infrared spectrum. Ester 52 was then stirred in 3:2 dioxane-water at 70° for 80 min. After the workup described above and purification by thin-layer chromatography was performed, ester 52 was again isolated: m.p. 77-79°; ir. (CCl_4) same as the spectrum summarized above.

Purification of Crude Alcohol 45. A 300-mg. sample of crude alcohol 45 that was obtained from the reductive cleavage of the crude acetate 50 was chromatographed on Florisil (Table 4). The composition of the fractions was monitored by v.p.c. (6 ft. of 5% Carbowax 20M, 180°). The 99% alcohol 45 fractions were combined and molecularly distilled at 80° (25 mm.) to yield a colorless, oily alcohol 45: ir. (film) 3.00 (OH), 3.33 (=CH), and 6.07 μ (C=C); n.m.r. ($CHCl_3$) δ 5.65 (m., 2, C<u>H</u>=C<u>H</u>), 3.50 (d., 2, <u>J</u> = 5 Hz., C<u>H</u>$_2$OH), and 2.83 p.p.m. (s., 1, OH).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.90; H, 10.59; Found: C, 78.94; H, 10.80.

The crude alcohol 53 was rechromatographed on Florisil to give the purified alcohol 53: ir. (film) 3.00 (OH), 3.33 (=CH), and 6.07 μ (C=C); n.m.r. ($CHCl_3$) δ 5.52 (m., 2, C<u>H</u>=C<u>H</u>), 3.13 (m., 1, C<u>H</u>OH), 2.78 (s., 1, O<u>H</u>), and 0.92 p.p.m. (d., 3, <u>J</u> = 6 Hz., CHC<u>H</u>$_3$); v.p.c. (6 ft. of 5% Carbowax 20M, 180°) 99% purity.

Table 4. Chromatography of crude alcohol 45.

Solvent	Vol. (ml.)	Wt. of residue (mg.)
1:19 Ether-pentane	100	5
1:9 Ether-pentane	100	2
1:9 Ether-pentane	200	53 (95% Alcohol 53)
1:9 Ether-pentane	100	78 (95% Alcohol 45)
1:9 Ether-pentane	100	57 (99% Alcohol 45)
1:3 Ether-pentane	200	76 (99% Alcohol 45)
1:1 Ether-pentane	100	8 (99% Alcohol 45)

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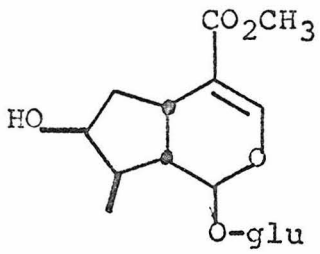
PROPOSITIONS

Proposition 1

An investigation of the biogenesis of the iridoid, loganin (1), is proposed in order to determine if farnesol is a precursor of this family of terpenoids.

The iridoids (1) are a family of plant constituents with a cyclopentane monoterpenoid skeleton. A few representative members of this family are iridodial (2) (2), asperuloside (3) (1), loganin (1) (3), and nepetalactone (4) (4). Aucubin (5) (5, 6, 7) is a nine-carbon iridoid and unedoside (6) (8) is an eight-carbon iridoid. Gentiopricroside (7) (9) and swertiamarin (8) (10) are seco-iridoids. Skytanthine (9) (11), actinidine (10) (12) and gentianine (11) (13) are alkaloids that are related to the iridoids. Fulvoplumierin (12) (14), plumierid (13) (15), and plumericin (14) (16) are thirteen- and fourteen-carbon compounds that are structurally related to the iridoids.

Although the carbon skeleton of the ten-carbon iridoids can be divided into two isoprenoid units, the iridoids as a group possess several properties that are unique among the monoterpenes. The 1,2-dimethyl-3-isopropylcyclopentane-carbon skeleton is almost unknown to the monoterpenes. Monoterpenes are usually hydrocarbons or mono-oxygenated compounds with three to five degrees of



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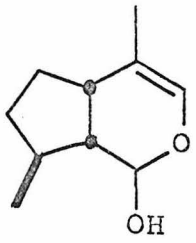

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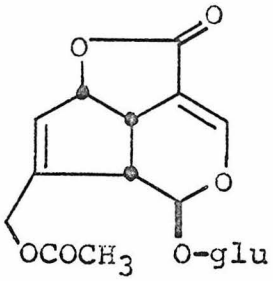

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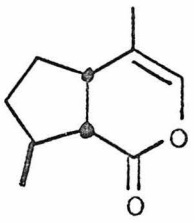

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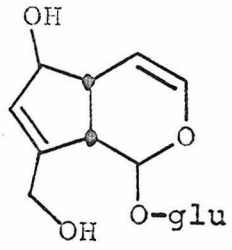

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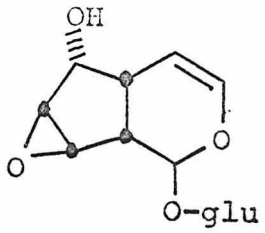

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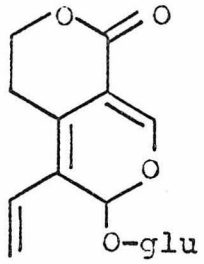

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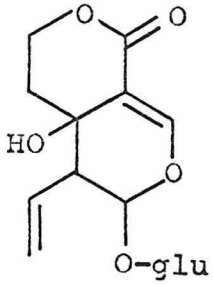

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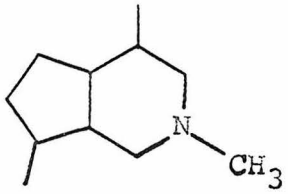

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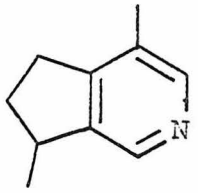

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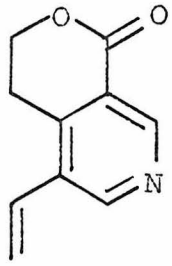

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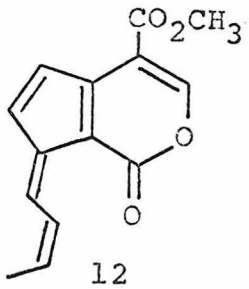

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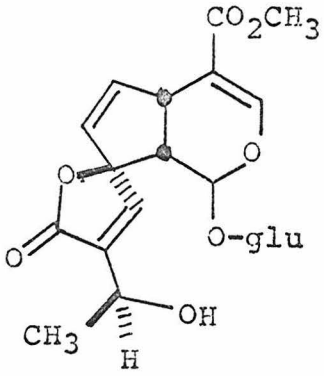

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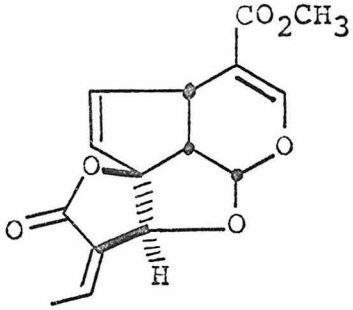

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unsaturation, but the iridoids are usually poly-oxygenated substances with five to eleven degrees of unsaturation. Several iridoids exist as enol hemiacetal glucosides, an unusual linkage for a monoterpene. The existence of eight-, nine-, ten-, thirteen-, and fourteen-carbon homologues is also unique in terpene chemistry. The characteristics mentioned above do not exclude the iridoids from the realm of the monoterpenes, but these points do suggest that the biogenesis of the iridoids may differ from that of the regular monoterpenes and that the iridoids may be degradation products from higher terpenoids.

Although geraniol has been shown to be a precursor of loganin (1) (17, 18) and loganic acid (19) as a result of labelling experiments, these experiments do not rule out the possibility that higher terpenoids derived from geraniol may actually be involved in the biogenesis of the iridoids. Therefore, the use of labelled [^{14}C]-farnesol in feeding experiments similar to those already carried out with geraniol (17, 18, 19) is proposed. Since farnesol is a precursor of all the higher terpenoids, incorporation of label from this precursor into loganin (1) would produce evidence for a degradative biogenesis, and negative results would support a monoterpene biogenesis.

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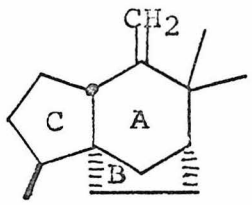
Proposition 2

A synthesis of the sesquiterpene, zizanoic acid (1) (also known as khusenic acid) is proposed.

The structure of zizanoic acid (1) (1), known also as khusenic acid (2), has recently been elucidated. The



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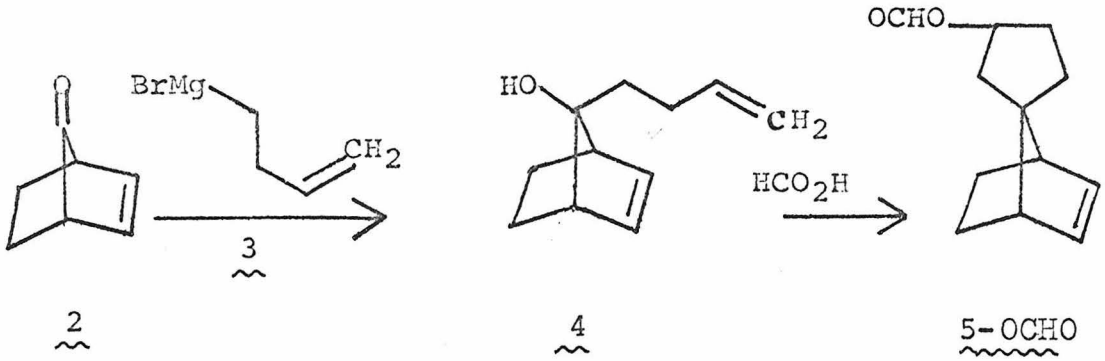
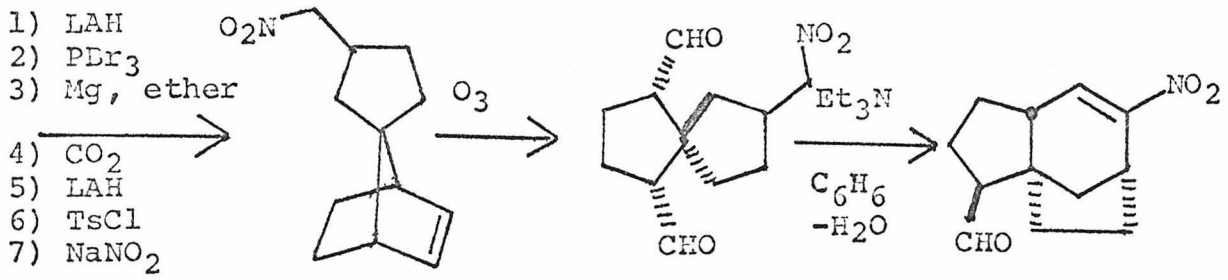
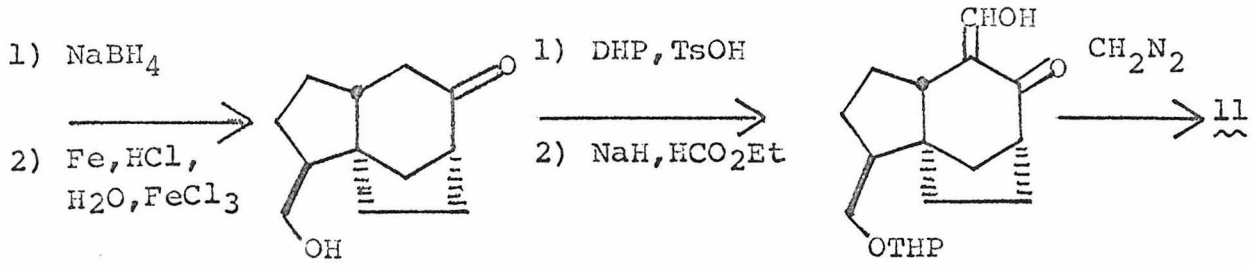
synthesis of this unusual sesquiterpene is proposed starting from norboren-7-one (2). Alkylation of the enone 2 with the Grignard reagent 3 should occur from the less hindered side of the carbonyl group to yield the unsaturated carbinol 4. If the carbinol 4, when solvolyzed in formic acid, gives the cyclized formate 5-OCHO, reductive cleavage of the formate 5-OCHO with lithium aluminum hydride followed by transformation of the resultant alcohol 5-OH with phosphorous tribromide should afford the corresponding bromide 5-Br. The bromide 5-Br is converted to the Grignard reagent, which is carboxylated with carbon dioxide. The resultant acid 5-COOH is reduced with lithium aluminum hydride to the alcohol 6-OH, which is then converted to the tosylate 6-OTs.



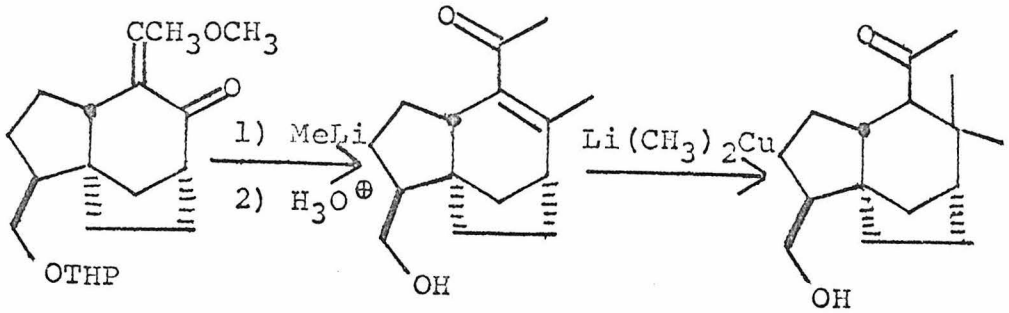
2 4 5-OCHO



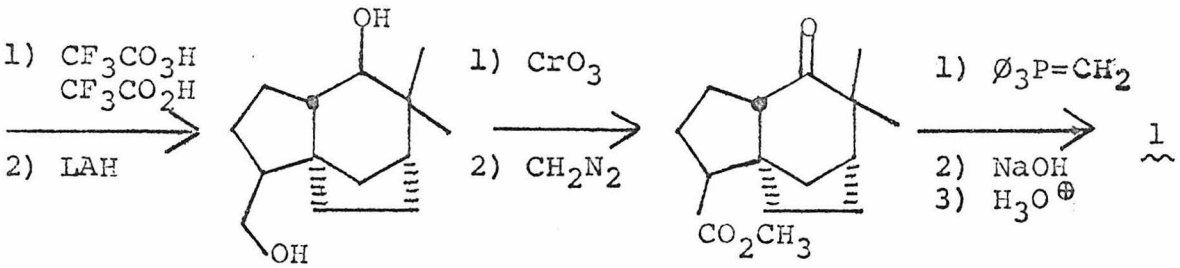
6-NO2 7 8



9-OH 10



11 12 13



14 15-CO_2CH_3

Reaction of the tosylate 6-OTs with sodium nitrite (3) should produce the nitroalkene 6-NO_2. After the nitroalkene 6-NO_2 is converted upon ozonolysis (4) to the dialdehyde 7, base-catalyzed condensation (5) should give the tricyclic nitro-olefin 8, whose aldehyde group will probably have the more stable beta orientation.

Since the nitro group is stable to sodium borohydride (6), this reagent can be used to reduce the remaining aldehyde group to an alcohol function. Then, reduction of the unsaturated nitro function with iron in aqueous hydrochloric acid (5) should give the ketol 9-OH. At this point it is necessary to protect the alcohol group of the ketol 9-OH with a tetrahydropyranyl ether linkage (7). The carbonyl group of the resulting ketone 9-OTHP is converted into the hydroxymethylene derivative 10 with sodium hydride and ethyl formate (8). The enol 10 is then treated with excess diazomethane (9) to give the ketone 11. Addition of methyllithium to the ketone 11 followed by acidic workup (10) of the crude product is expected to give the enone 12. The enone 12 should undergo methylation with lithium dimethylcopper (I) (11) to yield the ketol 13. If a Baeyer-Villiger oxidation (12, 13) of the ketone 13 is followed by reductive cleavage of the crude product with lithium aluminum hydride, the diol 14 should be obtained. Oxidation of the diol 14 with excess chromic

acid reagent (14) to the keto acid 15-COOH gives after methylation with diazomethane the keto ester 15-$COOCH_3$. The keto ester 15-$COOCH_3$ is then converted into the unsaturated ester 16 by reaction with methylenetriphenylphosphorane (15). Saponification of the ester 16 followed by acidification of the salt should give zizanoic acid (1).

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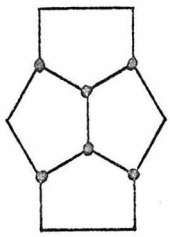
Proposition 3

A synthesis of the quadricyclic hydrocarbon 1 is proposed. The synthetic scheme also yields intermediates that can be used in solvolytic routes to compounds related to birdcage hydrocarbon 2-H.

The quadricyclic hydrocarbon 1 is a homologue of the tricyclo[5.2.1.$0^{4,10}$]decane (3) (1), which has been used as an intermediate in the synthesis of the triquinacene (4) (2). The original purpose (1, 2) in preparing the triquinacene (4) was its use as a potential intermediate in the synthesis of the dodecahedrane (5). The interest in the hydrocarbon 1 stems from its relationship to the hydrocarbons 3 and 5.



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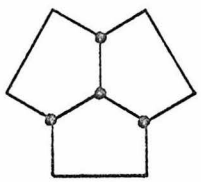

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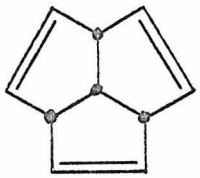

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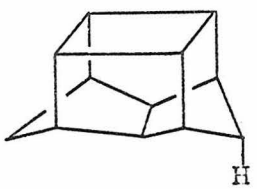
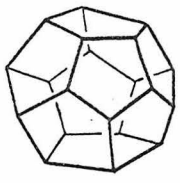


2-H



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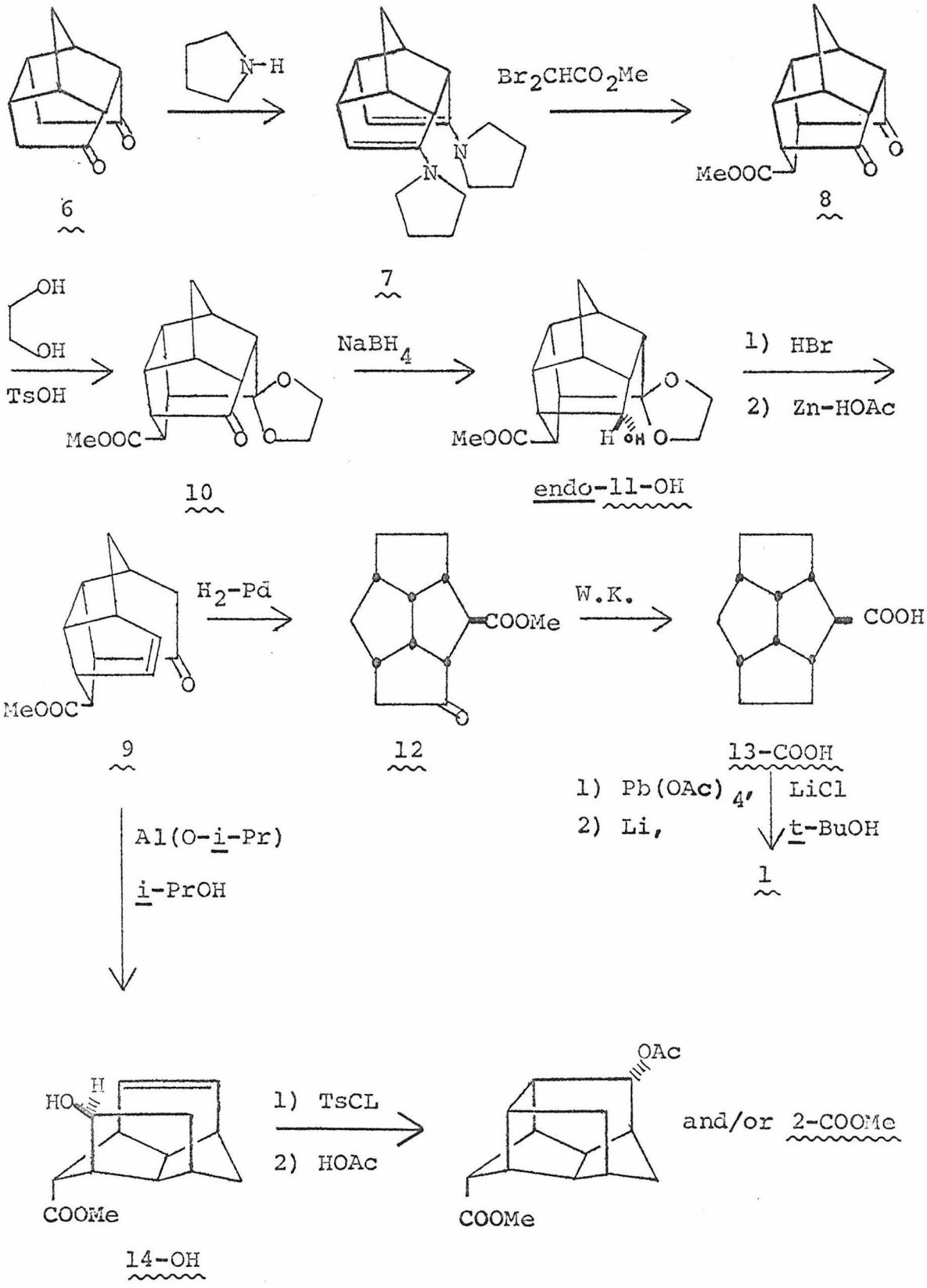
The synthetic route proposed begins with the diketone 6 (3), which when converted to the bis-enamine 7 and alkylated with methyl dibromoacetate is expected to yield the diketone 8 by analogy to a series of reactions carried out by Stetter and Thomas (4) who prepared 4-carbomethoxyadamantan-2,6-dione. The following conversion of the diketone 8 to the enone 9 is analogous to a series of reactions that were reported by Eaton (3). Mono-ketalization of the diketone 8 with ethylene glycol gives the ketone 10, which can be reduced with sodium borohydride to the alcohol endo-11-OH. The alcohol endo-11-OH after treatment with hydrobromic acid is expected to yield the bromide exo-11-Br, which upon zinc-acetic acid reduction leads to the enone 9.

Catalytic hydrogenation of the enone 9 should give the ketone 12, which upon Wolff-Kishner reduction is expected to afford the acid 13-COOH. The acid 13-COOH after chlorodecarboxylation is expected to give the chloride 13-Cl, which can then be reduced with lithium (6) to give the hydrocarbon 1.

The synthetic intermediates can also be used in other interesting studies. The enone 9 upon aluminum isopropoxide reduction can produce the alcohol 14-OH. The solvolysis of the tosylate 13-OTs can then be investigated as another possible solvolytic route to compounds related to bird-cage hydrocarbon 2-H.



6

7

8

10

endo-11-OH

9

12

13-COOH

1

14-OH

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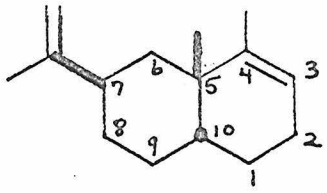
Proposition 4

A synthesis of the sesquiterpene eremophilene 1 is proposed.

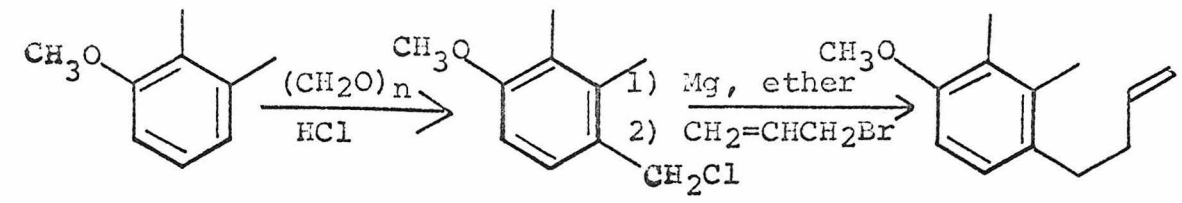
The sesquiterpene eremophilene 1 (1) has three asymmetric centers which are all common to one six-membered



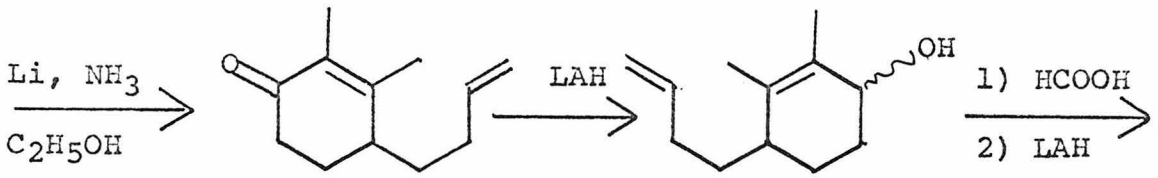
1

ring of a cis-octalin carbon skeleton. Since the olefinic cyclization procedure of Johnson and co-workers (2, 3) is ideally suited to establish this cis-fused octalin skeleton, a relatively simple synthesis of eremophilene (1) is proposed.

Chloromethylation (4) of the ether 2 should give the benzyl chloride 3-Cl, which is used to prepare the corresponding Grignard reagent 3-MgCl. If the Grignard reagent 3-MgCl is coupled with allyl bromide, the ether 4 should be obtained. Birch reduction (5, 6) of the ether 4 is expected to give the dienone 5. Lithium aluminum hydride reduction to the allylic alcohol 6 followed by olefinic cyclization in formic acid (2, 3) is expected to give the hydroxy olefin 7-OH after lithium aluminum hydride reduction of the formate ester 7-OCHO. After the alcohol 7-OH is



2 3-Cl 4



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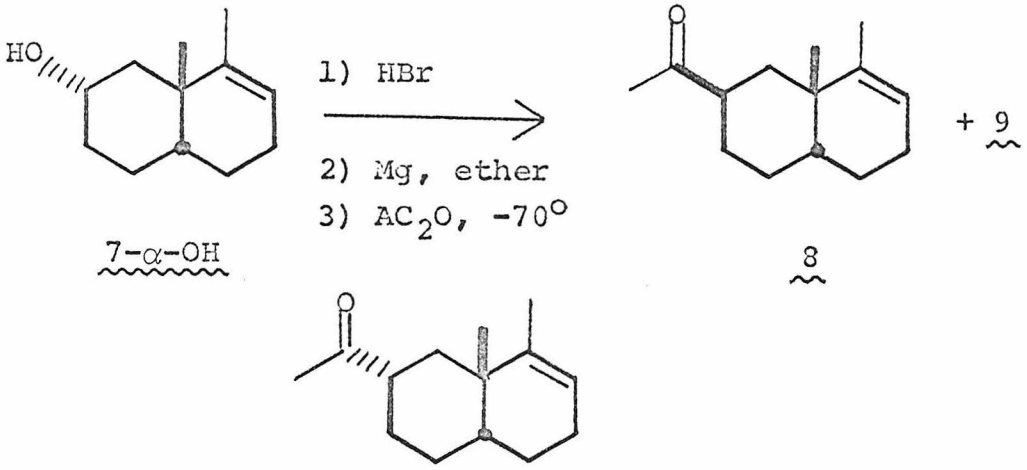

7-α-OH 8

9

converted to the bromide 7-Br with 48% hydrobromic acid, the corresponding Grignard reagent 7-MgBr can be prepared and converted to the ketones 8 and 9 upon addition to acetic anhydride at -70° (7).

The ketones 8 and 9 will probably require some type of chromatographic separation. If the mixture can be successfully separated, the undesired isomer 9 can be re-equilibrated with acid to produce more of the desired ketone 8. The identity of the two ketones can be established by conversion of each isomer to the corresponding methylene derivatives with methylenetriphenylphosphorane (8); and the isomer 8 will yield the desired eremophilene (1), which can be compared to an authentic sample. Although this synthetic scheme suffers from a nonstereospecific introduction of the substituent at C_7, the problem may be easily overcome by finding a suitable scheme to separate the ketones 8 and 9. The ketone 8 may serve also as a useful intermediate in the synthesis of derivatives of eremophilane.

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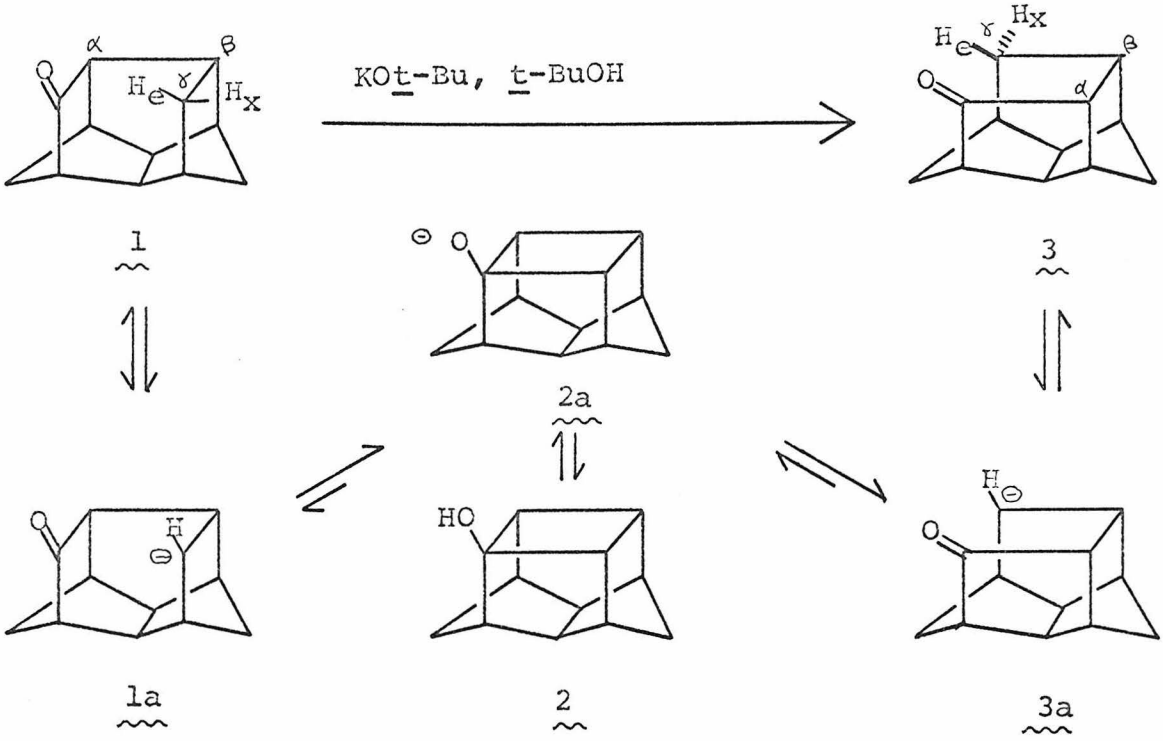
Proposition 5

An investigation into the mechanism of the base-catalyzed rearrangement of the half-cage ketone 1 is proposed. A study into the stereochemistry of the protonation of the birdcage alkoxide 2a should clarify the mechanism of the rearrangement.

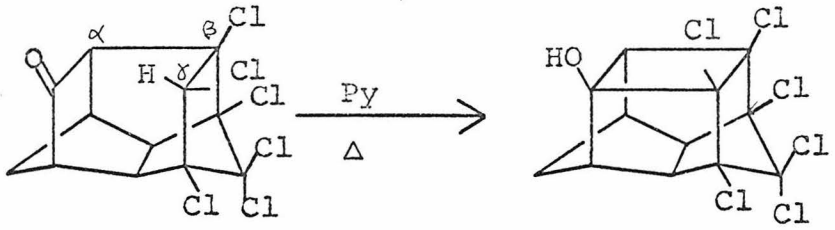
The half-cage ketone 1 undergoes base-catalyzed rearrangement to the half-cage ketone 3 (1, 2). Furthermore, since the birdcage alcohol 2 upon treatment with base also has been transformed to the ketone 3, the anion 2a has been established as an intermediate in the overall homoenolization-homoketonization, which begins by the formation of the homoenolate 1a, and continues by the rearrangement of 1a into the alkoxide 2a and then by the rearrangement of 2a into the homoenolate 3a, and finally concludes by the protonation of 3a to yield the ketone 3.

Howe and Winstein (1) have suggested that the outside hydrogen H_x at C_γ of 1 is abstracted by the base. If this mechanism is applicable, the protonation of the homoenolate 3a should also occur from the outside direction to give ketone 3 with the new hydrogen H_x at C_γ. However, in another communication Winstein and co-workers (3) reveal that the chlorinated half-cage ketone 4 rearranges to the birdcage alcohol 5 upon heating with pyridine. Furthermore,



1 2a 3

1a 2 3a



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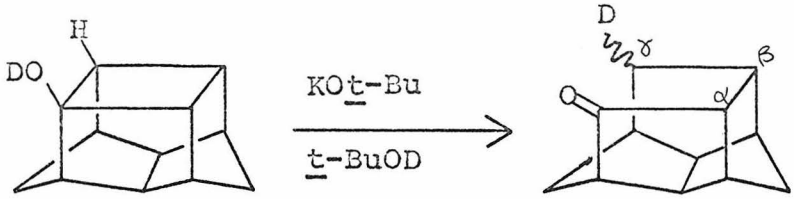

2-OD 3-CγD

when ketone 4 was treated with an equivalent of lithium aluminum hydride, the birdcage alcohol 5 was also produced (4). In both cases the inside hydrogen at C_γ has been abstracted by the base. Therefore, either the mechanism of this homoenolization differs from that of the half-cage ketone 1 or the mechanism of the latter rearrangement requires further examination.

In order to remove the ambiguity in the mechanism of the homoketonization of alcohol 2, it is proposed that the alcohol 2-OD be prepared and rearranged in deuterated t-butanol and potassium t-butoxide. If the homoenolate 3a is deuterated stereospecifically, then, nuclear magnetic resonance analysis of the deuterated ketone 3-C_γD should reveal the orientation of the C_γ proton and, thereby, clarify the mechanism of the homoketonization.

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