I. THE ISOLATION AND STRUCTURE OF AN α,β-UNSATURATED SESQUITERPENIC KETONE

II. SYNTHESIS AND CONFIGURATIONAL STUDIES OF SUBSTITUTED CYCLOPENTANE-1,2-DICARBOXYLIC ACIDS

By

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GENERAL INTRODUCTION

This thesis consists of two parts. The first describes the isolation and structure determination of a new α,β-unsaturated terpenic ketone. The second part reports a study of the base-catalyzed rearrangement of substituted bromo keto esters to cyclopentane-1,2-dicarboxylic acids. Because the two parts are not directly related, each has its own subdivisions: introduction, historical, discussion and results, conclusion, and experimental.

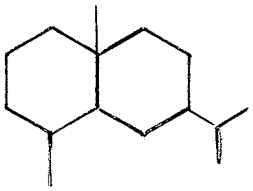
PART I

THE ISOLATION AND STRUCTURE OF AN α,β-UNSATURATED SESQUITERPENIC KETONE

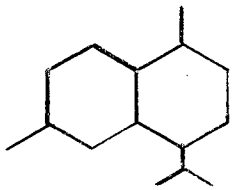
INTRODUCTION

The major fraction, 40%, of the steam volatile oil obtained from Bothriochloa intermedia varieties gangetica and indica, plants of Indian origin, was a sesquiterpenic ketone, $C_{15}H_{24}O$. The infrared spectrum of the ketone showed α,β-unsaturation, and the n.m.r. spectrum showed a methyl group α to the keto group.

At first, it appeared as if the compound possessed a selinane (1) or cadinane (2) skeletal structure.

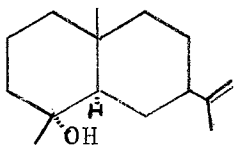


1 selinane

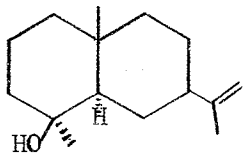


2 cadinane

The physical properties of the unsaturated ketone, such as the boiling point and the retention time on the gas chromatogram, were typical of ketones of the selinane (1) or cadinane (2) configuration. Moreover, two selinane sesquiterpenes, intermedeol (3)[1] and neo-intermedeol (4),[2] have been isolated from the same species of plants, Bothriochloa intermedia.



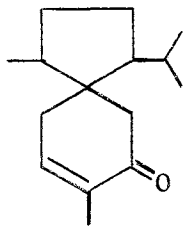
3 intermedeol



4 neo-intermedeol

Attempts to correlate the hydrocarbon from the unsaturated ketone with either selinane (1) or cadinane (2) failed.

A comparison of the thick-film infrared spectrum of the unsaturated ketone with spectra of known sesquiterpenes[3,4] showed that the unsaturated ketone was similar to acorenone (5) obtained by Vrkoc and coworkers in 1961.[5,6] The physical properties of the unsaturated ketone



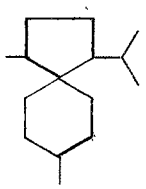
5 acorenone

and the analysis of its degradation products gave further evidence of its similarity with acorenone. However, the optical rotation of the dihydro ketone was not the same as that of dihydroacorenone. Moreover, R. McClure[7] compared the dihydro ketone with an authentic sample of dihydroacorenone by gas-liquid chromatography. He found that they were each mixtures of one major (80%) and one minor component but the two mixtures were not identical. In addition, he found that the ozonolysis product of the new unsaturated ketone gave a dibasic acid which had the same melting point and molecular formula as the ozonolysis product from acorenone (5). Thus it was concluded that the unsaturated ketone, now

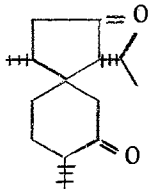
designated as epiacorenone, has the same gross structure as acorenone (5) but a different stereochemistry at the spiro carbon.

HISTORICAL

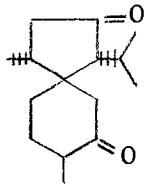
In 1956 Sykora and co-workers isolated[8] from sweet-flag oil (Acorus calamus L.) and characterized[9,10] the first acorane-type (6) sesquiterpenes -- acorone (7), isoacorone (8), and neoacorone, which was later found to be a mixture of acorone (7) and cryptoacorone (9).[11]



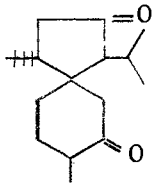
6 acorane



7 acorone



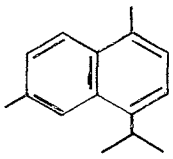
8 isoacorone



9 cryptoacorone

The absolute configurations of acorone (7) and its isomers were determined in 1964 by optical rotatory dispersion, the Hudson-Klyne Rule, and dipole moment measurements.[12] The latest report of an acorane-type sesquiterpene, acorenone (5), appeared in 1961.[5,6]

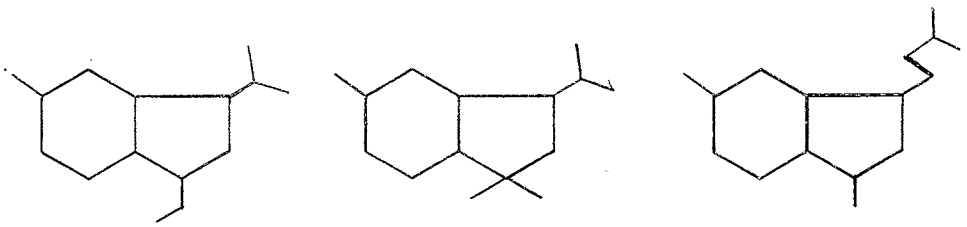
The first degradation studies on acorone (7)[9] indicated that it had a cadalene-type structure (10).



10 cadalene

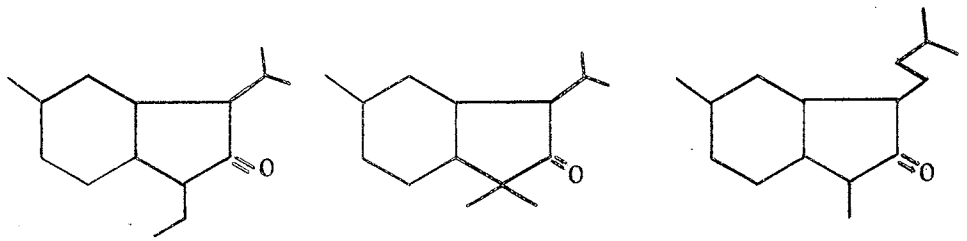
However, the infrared spectrum of 7 showed a carbonyl group in a five-membered ring, ν_{max} 1736 cm^{-1}. The absorption peak was inconsistent with the cadalene structure. In addition, acorane (6) obtained from

the Clemmensen reduction of 7 did not correspond to cadinane (2). Sykora suggested the following structures for acorane.



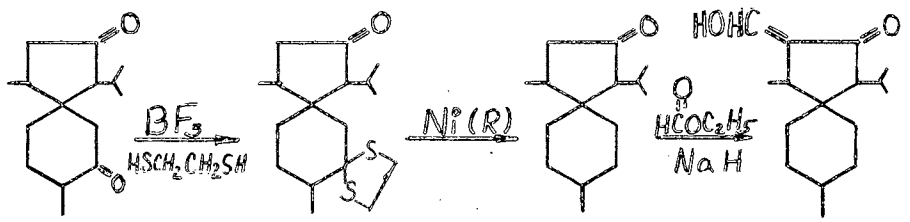
11 12 13

He then proved that none of the corresponding ketones



14 15 16

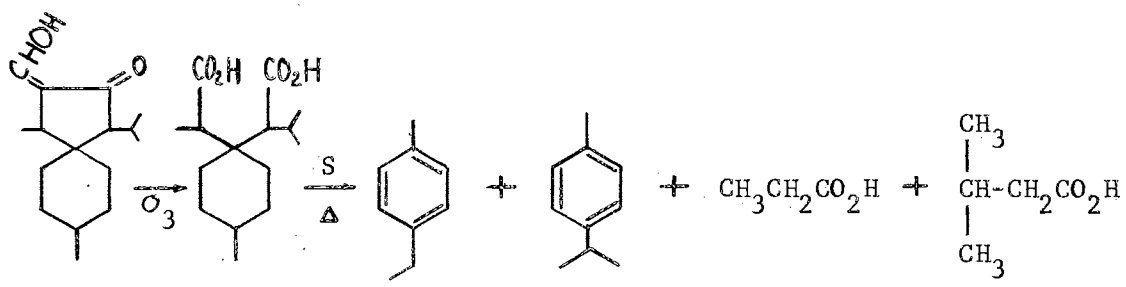
could be acorone (7). By selectively removing the carbonyl group in the six-membered ring and adding a formyl group α to the ketone in the five-membered ring he showed that structures 14, 15, and 16 were not correct for acorone.



7 17 18 19

Since no methylene group exists α to the carbonyl in the five-membered ring in structures 14, 15, and 16, Sykora postulated structure 7 for acorone.

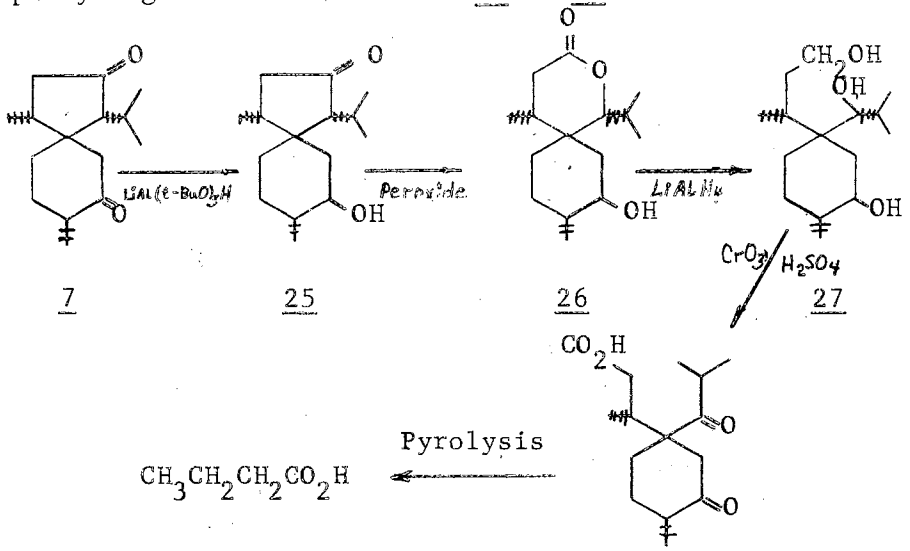
The final proof of the relative configuration of acorone (7) was obtained by ozonizing the formyl compound (19) and dehydrogenating the corresponding diacid (20) with sulfur.



19 20 21 22 23 24

The fragments -- 4-ethyltoluene (21), 4-methyl-1-isopropylbenzene (22), propionic acid (23), and isovaleric acid (24) -- led to the structure 7 for acorone.[8,9]

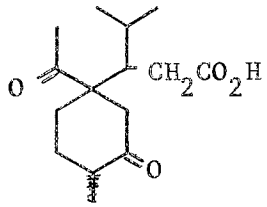
The position of the carbonyl group in the five-membered ring was confirmed by reducing acorone (7) selectively to acoronol (25), Baeyer-Villiger oxidation of 25 to a hydroxy lactone (26), reduction of 26 to the triol (27), oxidizing 27 to the diketo carboxylic acid (28), and finally prolyzing the barium salt of 28 to 29.[11]



7 25 26 27

29 28

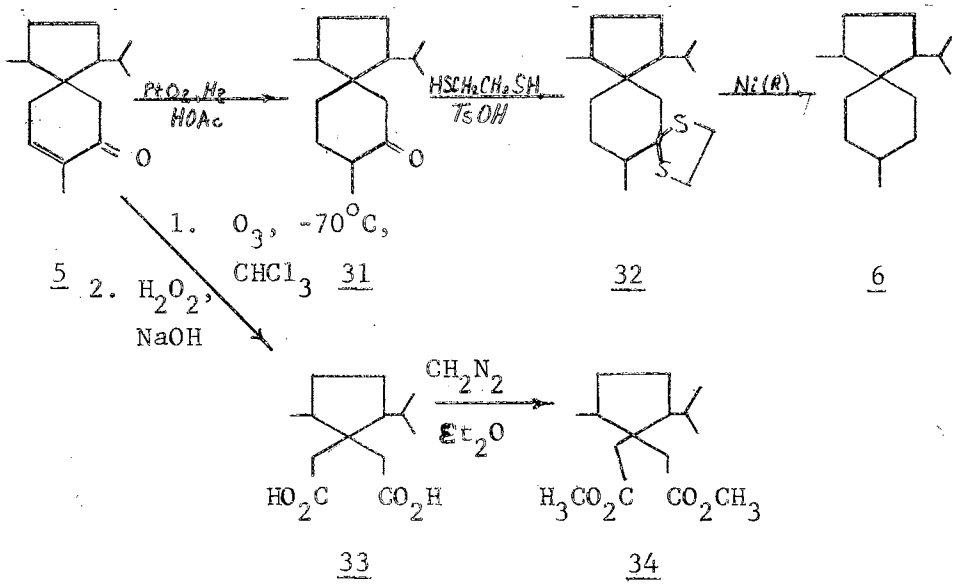
Thus it was shown that the carbonyl group in the five-membered ring was next to the isopropyl group instead of the methyl group. If the carbonyl had been adjacent to the methyl group, instead of 28 the methyl ketone 30 should have been isolated.



30

Moreover, pyrolysis of the barium salt of 28 gave n-butyric acid (29) and not isocaproic acid as would be expected from 30.

In 1961 Vrkoc and co-workers[5] isolated an α,β-unsaturated sesquiterpenic ketone, acorenone (5), from sweet-flag oil. The relative configuration of 5 was characterized by relating acorenone (5) to acorane (6) and then determining the position of the keto group by oxidation of 5 to the diacid (33).[6]



5 31 32 6

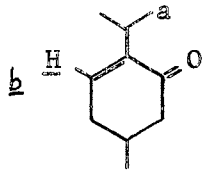
33 34

DISCUSSION AND RESULTS

The Department of Agronomy at Oklahoma State University in their search for new range grasses for livestock feeds grew different varieties of Bothriochloa intermedia and gangetica of Indian origin on their experimental research plots in Stillwater, Oklahoma. The Chemistry Department of Oklahoma State University obtained the grasses from the Agronomy Department in an attempt to classify the plants according to their steam-volatile compounds.

The major constituent of the essential oil was isolated by steam distillation of the ground grasses, ethereal extraction of the steam distillate, and chromatography on alumina.

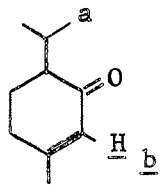
The infrared spectrum of the major constituent, epiacorenone, showed an α,β-unsaturated carbonyl group, ν_{max} 1674 cm^{-1}. The nuclear magnetic resonance spectrum showed an olefinic proton signal at 6.75 δ. The olefinic proton signal was similar to that of carvone (35),[13]



a. 1.75 δ
b. 6.75 δ

35

rather than piperitone (36),[14]



a. 1.93 δ
b. 5.87 δ

36

The elemental analysis of the unsaturated ketone together with its retention time on the gas-liquid chromatogram indicated that the compound had a molecular formula of $C_{15}H_{24}O$.

The mass spectra of the unsaturated ketone and its dihydro derivative confirmed the molecular weight by showing molecular ion peaks of mass 220 and 222 respectively.

The infrared spectrum of epiacorenone was identical to that of acorenone in the region between 5.5 and 7.5μ.[15] The physical properties of epiacorenone (Table I) are in good agreement with those of acorenone.[6]

TABLE I

PHYSICAL PROPERTIES OF EPIACORENONE (37) AND ACORENONE (5)

Compound	n_D^{20}	d_D^{20}	$(\alpha)_D$	ν_{max}
Epiacorenone	1.5039	0.9664	-22.6° (25°C, EtOH)	1674 cm^{-1}
Acorenone	1.5039	0.9599	-22.3° (25°C, neat)	1674 cm^{-1}

Vrkoc and co-workers[6] could not prepare a solid derivative of acorenone but prepared a crystalline semicarbazone from dihydroacorenone. Solid dinitrophenylhydrazones were prepared for both epiacorenone and dihydroepiacorenone but a crystalline semicarbazone could not be prepared for either compound.

Epiacorenone was reduced in the manner described by Vrkoc.[6]

$$C_{15}H_{24}O \xrightarrow{PtO_2,\ H_2,\ HOAc} C_{15}H_{26}O$$

37 epiacorenone — 38 dihydroepiacorenone

The optical rotation of dihydroepiacorenone was +13° (25°C, neat), whereas Vrkoc reported -10.6° (20°C, neat)[16] for dihydroacorenone (31). Moreover, it has been reported recently that when dihydroepiacorenone (38) was mixed with dihydroacorenone (31) two peaks were observed in the gas chromatogram.[7] Thus dihydroepiacorenone (38) was not dihydroacorenone (31).

To establish the relative configuration of epiacorenone (37) attempts were made to convert it to the parent aromatic and saturated hydrocarbons for comparison with known sesquiterpenic hydrocarbons, to degrade epiacorenone oxidatively to a known derivative, and to synthesize a degradation product, 3-(2-isopropyl-5-methylcyclopentyl)glutaric acid.

Two methods of synthesis of the aromatic hydrocarbon were investigated. First, dihydroepiacorenone (38) was reduced with lithium aluminum hydride to an alcohol (39).

$$\underset{\underline{38}}{C_{15}H_{26}O} \xrightarrow{LiAlH_4,\ \text{anhydrous } Et_2O} \underset{\underline{39}}{C_{15}H_{28}O}$$

The resulting alcohol (39) was dehydrogenated by heating with 10% palladized charcoal for 10 hours at 200°C.

$$\underset{\underline{39}}{C_{15}H_{28}O} \xrightarrow{10\%\ Pd/C,\ 200^{\circ}C,\ 10\ hours} \text{Mixture}$$

The gas-liquid chromatogram showed that the product contained three components. The n.m.r. spectrum showed only traces of aromatic protons at 7.2 δ. However, the infrared spectrum showed that the alcoholic

group (ν_{max} 3350 cm^{-1}) had disappeared. A second attempt was made to prepare the aromatic hydrocarbon. The alcohol (39) was dehydrated with phosphorus oxychloride to a mixture of two olefins (40) as indicated by vapor-phase chromatography. The olefins (40) were heated at 300°C with selenium for 20 hours. Strong bands appeared in the infrared spectrum at ν_{max} 1525 and 818 cm^{-1}; these were attributed to an aromatic group.

$$\underset{\underline{39}}{C_{15}H_{28}O} \xrightarrow{POCl_3,\ pyridine} \underset{\underline{40}}{C_{15}H_{26}} \xrightarrow[24\ hours]{Se,\ 300^{\circ}C} \text{Mixture of three components}$$

The product was u.v.-active, but attempts to prepare a derivative failed.

Two procedures were followed for preparing the saturated hydrocarbon. First, the olefins (40) on hydrogenation in acetic acid in the presence of platinum oxide consumed one equivalent of hydrogen. The gas-liquid chromatogram showed a mixture of two products.

$$\underset{\underline{40}}{C_{15}H_{26}} \xrightarrow{H_2,\ PtO_2,\ HOAc} \underset{\underline{41}}{C_{15}H_{28}}$$

Next the thioketal (42) was prepared from dihydroepiacorenone (38) and reduced to the hydrocarbon (41) with lithium in ethylamine.

$$\underset{\underline{38}}{C_{15}H_{26}O} \xrightarrow{HSCH_2CH_2SH,\ TsOH} \underset{\underline{42}}{C_{17}H_{30}S_2} \xrightarrow{Li,\ CH_3CH_2NH_2} \underset{\underline{41}}{C_{15}H_{28}}$$

The products from the reduction of the olefins (40) and that of the thioketal (42) were compared by gas-liquid chromatography. They were

identical. A thick film infrared spectrum of the hydrocarbon mixture was taken and was compared to that of acorane.[17] The spectra were identical in the regions 6 to 8μ and 9.8 to 11.3μ. However, in the region between 9 and 9.8μ a wide variation occurred. The spectra were similar but not identical.

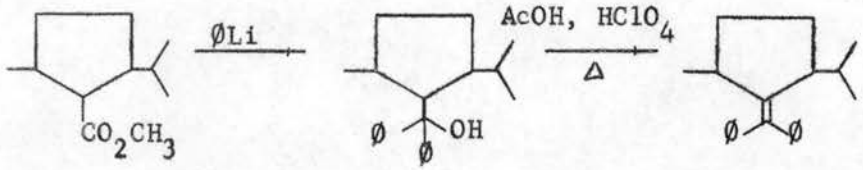
Epiacorenone was ozonized at -70°C in methylene chloride. The ozonide was added to 30% H_2O_2 and 10% aqueous KOH. A six-membered cyclic anhydride (ν_{max} 1820 and 1755 cm^{-1}) was obtained. Cleavage of the anhydride (43) was accomplished by adding 43 to dilute base at reflux temperatures for 1 hour. A liquid acid (44) was obtained. Attempts were made to crystallize this acid but no crystalline material was isolated. However, the acid was crystallized recently by R. McClure.[7] McClure found that the melting point of the acid was identical to that of 33. The acid (44) was added to an ethereal solution of diazomethane to give a dimethyl ester (45).

$$\underset{37}{C_{15}H_{24}O} \xrightarrow[2.\,H_2O_2,\ KOH]{1.\,O_3,\ CH_2Cl_2} \underset{43}{C_{13}H_{20}O_3} \xrightarrow[H^{\oplus}]{NaOH} \underset{44}{C_{13}H_{22}O_4} \xrightarrow{CH_2N_2} \underset{45}{C_{15}H_{26}O_4}$$

Infrared (thick-film) and n.m.r. spectra were taken. The n.m.r. showed 6 integrated carbomethoxy protons at 3.68 δ. The analysis was in agreement with the molecular formula $C_{15}H_{26}O_4$.

A modified version of the Barbier-Wieland oxidation described by Cookson and co-workers[18] was investigated for the degradation of the dimethyl ester (45). First, a model compound, methyl 2-isopropyl-5-methylcyclopentanecarboxylate (46), was treated with phenyllithium. The resulting alcohol (47) was dehydrated with acetic acid and

perchloric acid at steam bath temperatures.



46 47 48

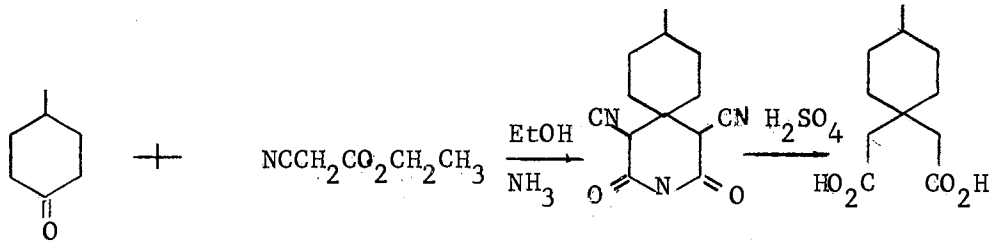
A crystalline white solid (48) was isolated in good yield. Then the dimethyl ester (45) was combined with phenyllithium. The ester carbonyl bands gave way to an alcohol band (ν_{max} 3400 cm^{-1}). The alcohol was dehydrated in refluxing acetic acid. The resulting olefin was oxidized with chromic oxide in acetic acid and esterified with diazomethane. A thin layer chromatographic separation of the products yielded a pure oil which contained aromatic protons as indicated by its n.m.r. spectrum. The desired mono- or diester was not obtained, however. Since the quantity of product was small, additional oxidation steps were not attempted.

Three methods were chosen to synthesize the dimethyl ester (45) -- a modification of the Guareschi reaction,[19,20,21,22] an aldol condensation, and a modified Claisen ester condensation.

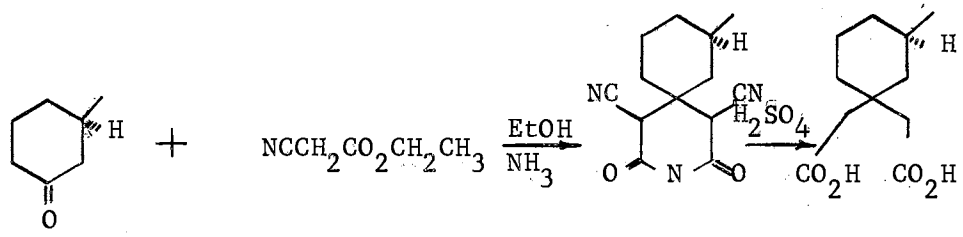
The Guareschi reaction is conducted by adding ethyl cyanoacetate to a ketone in a weak base, usually gaseous ammonia bubbled into anhydrous ethanol. The product of the reaction is a cyano amide. The cyano amide is decomposed in sulfuric acid to give the diacid. The reaction works well with cyclohexanones and poorly or not at all with cyclopentanones. However, the method of J. Varma,[22] a modification of the original Guareschi reaction, gave up to 50% yields for some cyclopentanones. It was hoped that 2-isopropyl-5-methylcyclopentanone would

condense with two moles of ethyl cyanoacetate to obtain the desired glutaric acid derivative.

The Guareschi reaction described by Rice and co-workers[21] was used on model compounds, 4-methylcyclohexanone (49) and (+) 3-methylcyclohexanone (53). Equimolar amounts of 4-methylcyclohexanone (49) or (+) 3-methylcyclohexanone (53) and ethyl cyanoacetate (50) were added to an ethanol solution saturated with ammonia.



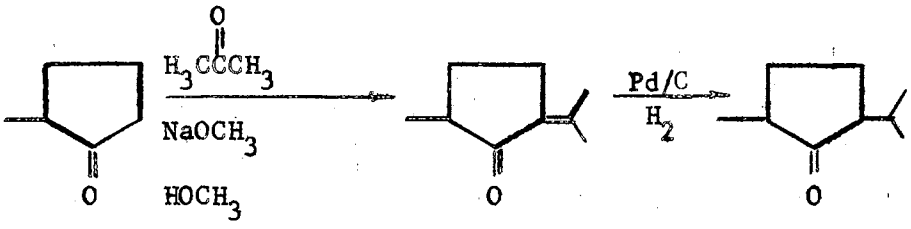
49 50 51 52



53 54 55

The reaction mixtures were placed in a refrigerator for 5 days, then water was added and the amides were filtered out. Each amide was hydrolyzed with 10% aqueous hydrochloric acid and decarboxylated by heating at 170°C for 1 hour in 70% sulfuric acid. The yields of crude products were 85%.

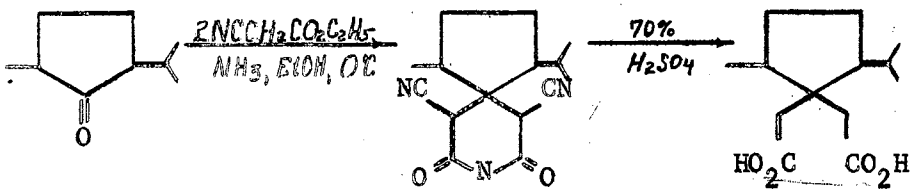
2-Isopropyl-5-methylcyclopentanone (58) was prepared by adding equimolar amounts of acetone and 2-methylcyclopentanone (56) to a solution of sodium methoxide at 0°C.[23]



56 57 58

2-Isopropylidene-5-methylcyclopentanone (57) was isolated in 85% yield. 2-Isopropylidene-5-methylcyclopentanone (57) was reduced to 2-isopropyl-5-methylcyclopentanone (58) with hydrogen on 10% palladium on charcoal.

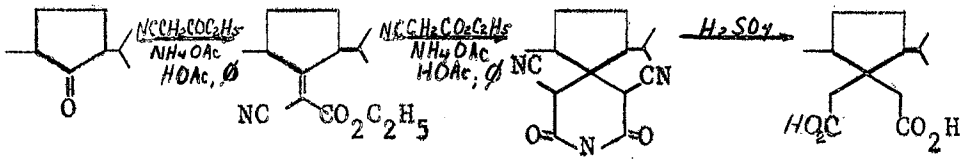
Equivalent amounts of 2-isopropyl-5-methylcyclopentanone (58) and ethyl cyanoacetate were added to an ammoniated ethanol solution.



58 59 60

The mixture was placed in a refrigerator for 5 days. The reaction mixture was worked up in the manner described by Rice and co-workers.[21] Only starting material was isolated.

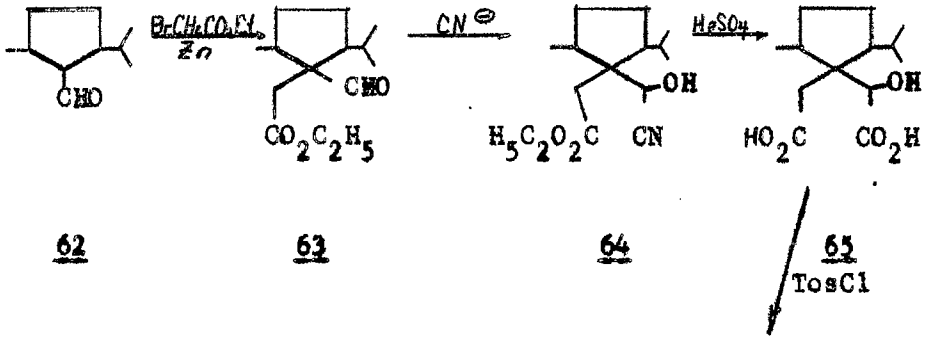
A modification of the Guareschi reaction was attempted. Equimolar amounts of 58 and ethyl cyanoacetate in a mixture of benzene, acetic acid, and ammonium acetate were refluxed for 24 hours under a water separator. Compound 61 was isolated.



58 61 59 60

However, when 61 was treated with a second mole of cyanoacetate only starting material was obtained.

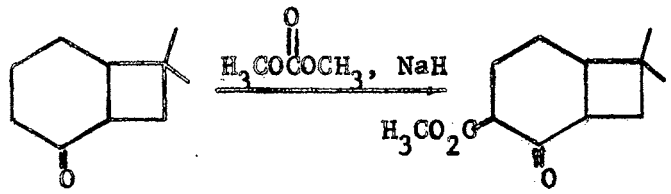
Since the Guareschi reaction failed, the preparation of 3-(2-isopropyl-5-methylcyclopentyl)glutaric acid (60) was attempted by condensing 2-isopropyl-5-methylcyclopentanal with ethyl bromoacetate, then forming the cyanohydrin by adding cyanide ion to the aldehyde (63), hydrolyzing the cyanohydrin to the acid (65), esterifying the alcoholic group as the tosylate (66), and cleaving the tosylate group with lithium aluminum hydride to the acid (60).



60 66

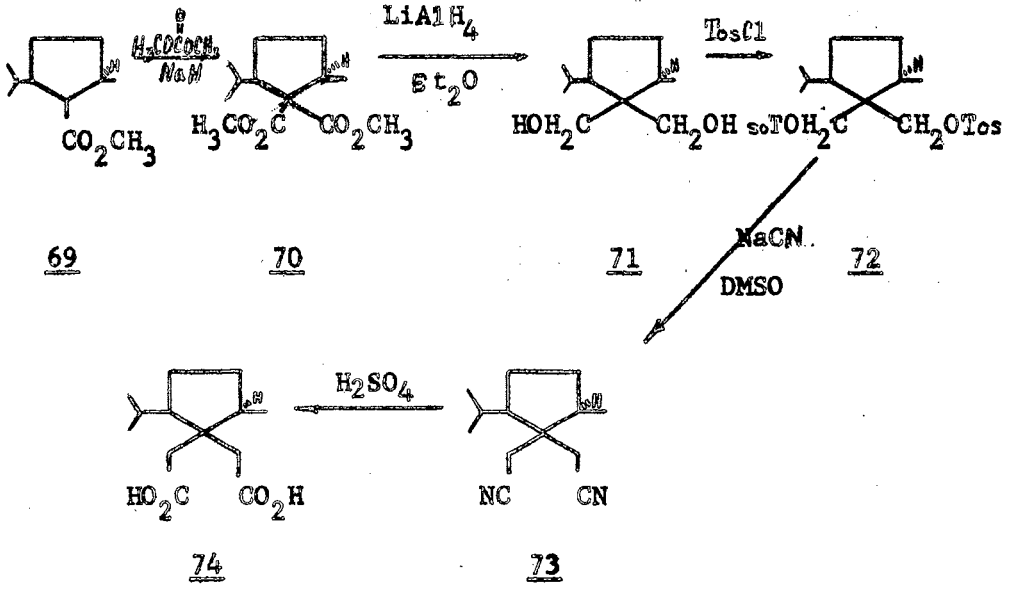
The aldehyde (63) was not isolated.

Next the condensation of dimethyl carbonate with methyl 2-isopropyl-5-methylcyclopentanecarboxylate was attempted according to the method of E. J. Corey[24]. Corey condensed 7,7-dimethylbicyclo-(4.2.0)octan-2-one (67) with dimethyl carbonate using sodium hydride as the base. 3-Carbomethoxy-7,7-dimethylbicyclo[4.2.0]octan-2-one was obtained in 85% yield.



67 68

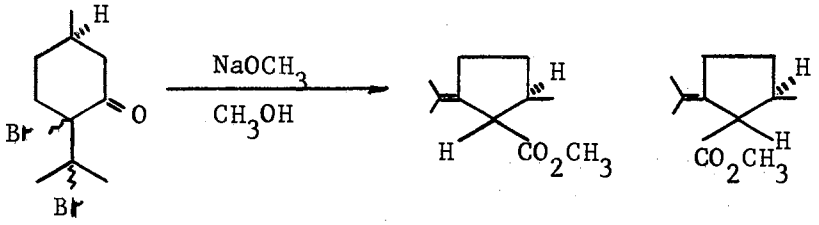
It was hoped that 74 could be prepared by condensing dimethyl carbonate with methyl 2-isopropyl-5-methylcyclopentanecarboxylate, reducing the carbomethoxy groups with lithium aluminum hydride to the diol (71), forming the tosylate (72) of the diol, displacing the tosylate with cyanide ion, and hydrolyzing the dinitrile (73) to 74.



69 70 71 72

74 73

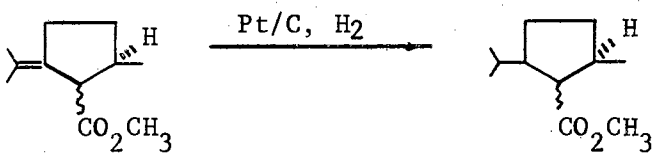
Methyl 2-isopropyl-5-methylcyclopentanecarboxylate (69) has been prepared by a Favorskii-type reaction.[25,26,27,28] The method of J. Wolinsky and D. Chan[28] was chosen for preparing 69. Equimolar amounts of bromine and pulegone were mixed at 0°C. Then the crude pulegone dibromide (75) was added dropwise to sodium methoxide in a solution of



75 76

methanol. A yield of 67% of cis- and trans- methyl pulegenates (76) was obtained.

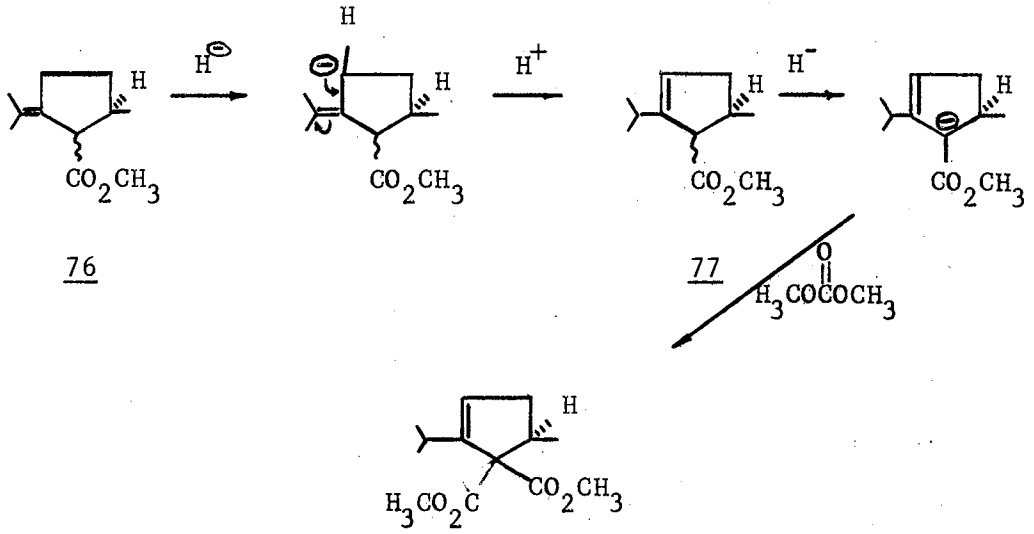
The mixed methyl pulegenates (76) were reduced with hydrogen in the presence of platinum on charcoal.



76 69

The addition of the carbomethoxy group by applying the method of E. J. Corey[24] to 69 failed. However, when methyl pulegenate was combined with dimethyl carbonate, two fractions were obtained on distillation of the final reaction mixture. The first fraction was identified as starting material. The n.m.r. integration for the second fraction showed the presence of two carbomethoxy groups, as well as a proton on

a vinyl carbon atom. The gas-liquid chromatogram indicated that the compound was homogeneous. The elemental analysis was consistent with the structure of compound 78. It was concluded that the isopropylidene double bond had migrated into the five-membered ring β to the carbonyl group, which facilitated the reaction by flattening the five-membered ring.

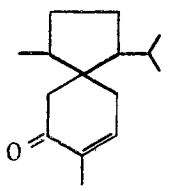


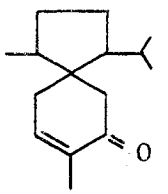
76 77 78

Reduction of 78 with hydrogen over platinum oxide in acetic acid yielded 70. The ester (70) was reduced with lithium aluminum hydride in dry ether to the diol (71). The diol was added to tosyl chloride in dioxane forming the ditosylate (72). The displacement of tosylate group with cyanide ion yielded the dinitrile (73). The synthesis of 73 concludes that part of the research that has been completed. The hydrolysis reaction was attempted. However, the conditions were too vigorous and only tars were obtained.

CONCLUSIONS

So far conclusive evidence for the structure of epiacorenone has not been obtained. However, enough information is available to permit a proposal of structure. First, the compound is an α,β-unsaturated ketone and the carbonyl group is in a six-membered ring as shown by its infrared and ultraviolet spectra. Second, the acorane structure is in agreement with dehydrogenation studies, for an aromatic hydrocarbon is not an expected product of acorenone dehydrogenation. Third, the identities of the various degradation products, such as dihydroepiacorenone and 3-(2-isopropyl-5-methylcyclopentyl)glutaric acid, are in agreement with the acorenone structure. Fourth, the striking similarities of infrared spectra of acorenone and acorane with those of epiacorenone and the saturated hydrocarbon obtained from epiacorenone indicate that epiacorenone is an acorane-type terpene. Finally, the recent reported isolation of 3-(2-isopropyl-5-methylcyclopentyl)-glutaric acid from epiacorenone[7] gives strong support to the acorane-type configuration for epiacorenone. It is believed that epiacorenone has the same gross structure as acorenone and the asymmetry lies in the position of the carbonyl functional group with respect to the five-membered ring.





The synthesis of the various isomers of 3-(2-isopropyl-5-methylcyclopentyl)glutaric acid from pulegone and from nepetalic acid will give the absolute configuration of both the dibasic acid (33) obtained by Vrkoc and for the one obtained from epiacorenone.

EXPERIMENTAL

The low-boiling, petroleum ether solvent, Skelly-F, used in all column chromatographies was washed with concentrated sulfuric acid intermittently for five days with periodic replacement of the sulfuric acid, distilled, and dried by passing over 1000 g. of neutral alumina. The reagent grade benzene was distilled. Only the middle fractions were used, b.p. 80°C.

The column used for analytical gas chromatographies was a ¼" x 10' column packed with Craig Polyester Succinate on fire brick unless otherwise stated.

The solid phase for column chromatography was Merck acid-washed activity I alumina.

The infrared spectra were taken on a Beckman IR-5A Spectrometer. The n.m.r. were recorded on a Varian A-60 spectrometer with tetramethylsilane as the internal standard (δ=0) and carbon tetrachloride as the solvent. Gas-liquid chromatographic analysis was taken on an Aerograph A-700 Autoprep.

Melting points were taken on a Fisher-Johns apparatus and were uncorrected.

Isolation of Epiacorenone (37).

The range grass was cut, harvested, and dried in the fall of 1962

from the Stillwater, Oklahoma fields of the Department of Agronomy at Oklahoma State University. The coarsely chopped, air-dried plant material (800 g.) was placed into a 12-liter round-bottom flask and steam distilled for three hours to give 5 liters of distillate. The steam distillate was extracted continuously with ether. The ether was dried over magnesium sulfate and evaporated leaving 2 g. (0.25% based on the dry plant weight) of essential oil. The gas-liquid chromatogram (column temperature of 180°C and flow rate of 60 cc. per min.) indicated a complex mixture. However, one major component (40%) with a retention time of 17 min. was obtained.

A 20-g. sample of essential oil was placed on a column of 650 g. of alumina. Fractions of 500 ml. were taken as the solvent was changed stepwise from petroleum ether, to benzene, to ether, to 10% methanol.

The fractions were evaporated and the residues analyzed by infrared spectroscopy and gas-liquid chromatography. The first 500 ml. of petroleum ether contained a mixture of olefins as indicated by the presence of olefinic protons in the n.m.r. at 4.78δ. The next 4 liters of petroleum ether and petroleum ether-benzene fractions contained two ketones, ν_{max} 1674 and 1735 cm^{-1}. The last fractions contained alcohols and ketones, ν_{max} 3500 and 1720 cm^{-1}.

The fractions which contained the ketone carbonyl band at ν_{max} 1674 cm^{-1} was rechromatographed. The material eluted from the column with 50% ether-50% benzene deposited 4 g. of a yellow, α,β-unsaturated ketone. n_D^{20} 1.5039, b.p. 75-80°C (0.1mm.), λ_{max} 240 mμ (EtOH, ε=1200), d_D^{25} 0.9664, $(\alpha)_D^{25}$ -22.6 (C 0.0245%, EtOH), $(\alpha)_D^{25}$ -13 (neat).

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76%; H, 10.98%. Found: C, 82.28%; H, 11.14%.

A 20-mg. sample of the unsaturated ketone was treated at room temperature with an excess of 2,4-dinitrophenylhydrazine in a methanolic hydrochloric acid solution. The 2,4-dinitrophenylhydrazone crystallized as a bright red solid, m.p. 151-152°C after recrystallization from methanol.

Anal. Calcd. for $C_{21}H_{28}N_4O_4$: C, 62.98%; H, 7.05%. Found: C, 62.94%; H, 7.39%.

Preparation of Saturated Ketone Dihydroepiacorenone (38) from Epiacorenone (37).

A 1.63-g. sample of α,β-unsaturated ketone (37) was hydrogenated in 15 ml. of acetic acid with prereduced platinum oxide (Adams catalyst). The hydrogenation proceeded rapidly with the consumption of one equivalent of hydrogen. The catalyst was removed and the solution concentrated under reduced pressure. The product was distilled yielding 1.43 g. (87%) of a colorless oil, b.p. 75°C (0.1mm.), n_D^{25} 1.4860, ν_{max}^{film} 1725, $(\alpha)_D^{25}$ + 13° (neat).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02%; H, 11.78%. Found: C, 81.07%; H, 11.97%.

A 20-mg. sample of the saturated ketone was treated at room temperature with an excess of 2,4-dinitrophenylhydrazine in methanolic hydrochloric acid solution. The 2,4-dinitrophenylhydrazone crystallized as an orange-yellow solid, m.p. 137-138°C after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.66%; H, 7.51%. Found: C, 62.93%; H, 7.92%.

The preparation of a semicarbazone was attempted in the presence

of sodium acetate in dilute ethanol. No crystalline material was isolated.

Preparation of Alcohol 39 From 38.

A 250-mg. sample of dihydroepiacorenone (38) in 25 ml. of dry ether was added to 300 mg. of lithium aluminum hydride suspended in 25 ml. of dry ether. After standing 8 hours at reflux temperature the excess lithium aluminum hydride was destroyed with wet ether. The precipitate of lithium hydroxide was removed by filtration and washed several times with ether. The ether layer was removed, dried over magnesium sulfate, and filtered, the ether removed under vacuum, and the residue distilled under reduced pressures affording 250 mg. of alcohol 39, b.p. 75°C (0.1mm.), n_D^{28} 1.4939, $(\alpha)_D^{CHCl_3}$ + 12.8° (C 0.0609%, 28°C), ν_{max}^{film} 3350 cm^{-1}.

Anal. Calcd. for $C_{15}H_{28}O$: C, 80.29%; H, 12.58%. Found: C, 81.25%; H, 12.62%.

Dehydration of Alcohol 39 to 40.

A 1-g. sample of alcohol 39 was heated at steam bath temperatures with 20 ml. of pyridine and 10 ml. of phosphorus oxychloride for 1 hour. The excess phosphorus oxychloride was destroyed by pouring the reaction mixture over crushed ice. The reaction mixture was extracted with ether. The ether layers were combined, dried over magnesium sulfate and freed of ether under vacuum affording 0.929 g. of a slightly yellow oil. The crude oil was vacuum-distilled yielding 0.766 g. of a colorless oil, b.p. 55-65°C (0.1mm.), and 0.163 g. of a clear viscous oil at 130°C (0.05mm.). Vapor-phase and thin-layer chromatography afforded

two components for the low boiling fraction. Gas-liquid chromatography (column temperature of 140°C and flow rate of 60 cc. per min.) of the low-boiling fraction showed two components with R_f values of 7 and 10.5 min.

Preparation of Hydrocarbon 41 From 40.

A 0.115-g. sample of olefin 40 was hydrogenated in 15 ml. of acetic acid with 20 mg. of prereduced platinum oxide. The hydrogenation proceeded rapidly with the consumption of 1 molar equivalent of hydrogen. Then the catalyst was filtered out and the solvent was removed under vacuum. Ether was added to the residue. The ether layer was neutralized with 10% sodium carbonate, washed with distilled water, dried over magnesium sulfate, and evaporated under vacuum. The residue was vacuum-distilled, b.p. 50-55°C (0.1mm.), yielding 0.114 g. Vapor phase chromatography (column temperature of 150°C and a flow rate of 67 ml. per min.) afforded two peaks of equal height.

Preparation of Thioketal 42 From 38.

A 4-g. (22 mmoles) sample of ketone 38 in 20 ml. of acetic acid was added to 2.13 ml. (23 mmoles) of 1,2-ethanedithiol and 1 g. of p-toluenesulfonic acid monohydrate, sitrred for 48 hours at room temperature, poured onto 50 g. of crushed ice, and taken up in three 50-ml. portions of ether. The ether layers were combined, washed with three 50-ml. portions of a saturated solution of sodium bicarbonate and three 10-ml. portions of distilled water, dried over magnesium sulfate, and evaporated to yield 3.9 g. of a yellow oil. The crude extract was chromatographed on 140 g. of alumina. The petroleum

ether eluent gave 3.8 g. of thioketal 42. N.M.R. (neat): singlets at 3.2δ (4 protons) and 2.15δ (3 protons).

Reduction of Thioketal 42 to Hydrocarbon 41.[29]

A 2.69 g. sample of thioketal 42 was added to 100 g. of anhydrous ethylamine and 1.5 g. (250 mmoles) of lithium. The flask was cooled to -20°C. and shaken for 1 hour. Then water was added dropwise until the dark blue color was dissipated. The ethylamine was allowed to evaporate. Then dry petroleum ether was added and the lithium hydroxide filtered out. The solid lithium hydroxide was washed with three 50-ml. portions of petroleum ether. The petroleum ether fractions were combined, dried over magnesium sulfate, and distilled through a Vigreux column at atmospheric pressures. The yield of hydrocarbon 41 was 1.793 g. (94%) of a clear colorless liquid. The vapor phase chromatogram showed two peaks.

Preparation of Methyl Pulegenate (76).

To a well stirred, ice cold solution of 187.7 g. (1.2 moles) of freshly distilled pulegone in 200 ml. of glacial acetic acid was added dropwise 174 g. (1.1 mole) of bromine. After the addition was complete (1 hr.) the solution was stirred for 30 min., poured onto 200 g. of crushed ice, extracted with three 200-ml. portions of petroleum ether, washed with saturated sodium bicarbonate and dried over magnesium sulfate.

To a refluxing solution of sodium methoxide (43 g. of sodium in 1 liter of methanol) 600 ml. of pulegone dibromide in petroleum ether was added dropwise. The petroleum ether was allowed to distill as the

addition proceeded. After the addition was complete and the petroleum ether had distilled, the solution was refluxed for 3 hours. Then 800 ml. of methanol was distilled. The mixture was poured rapidly into 500 ml. of 10% hydrochloric acid, extracted with ether, dried over magnesium sulfate, evaporated and the residue vacuum distilled affording 133 g. of a yellow oil, b.p. 45°C (0.05mm.). The infrared spectrum indicated the presence of pulegone, ν_{max} 1680 cm^{-1}.

A 133-g. sample of the above mixture was added to 83.5 g. of Girard's "T" reagent, 500 ml. absolute methanol, and 64 ml. of glacial acetic acid. The solution was stirred for two hours, then refluxed for 1 hour, cooled, poured onto 55 g. of sodium bicarbonate in 1 liter of water, and extracted with five 100-ml. portions of ether. The ether extracts were combined, dried over magnesium sulfate, and distilled under reduced pressures affording 80.6 g. (39%) of 93% trans- and 8% cis-methyl pulegenate as determined by vapor-phase chromatography (20% SE 30 on Chromosorb G, flow rate of 60 cc. per min., column temperature of 140°). The n.m.r. spectrum was identical to that of an authentic sample of trans-methyl pulegenate.

Preparation of Dimethyl 2-isopropyl-5-methyl-2-cyclopentene-1,1-dicarboxylate (78).

A 9-g. (50-mmoles) sample of methyl pulegenate was added dropwise under nitrogen to 10 g. (417 mmoles) of sodium hydride and 60 g. (900 mmoles) of dimethyl carbonate in 200 ml. of dioxane at a bath temperature of 80°C. After the addition was complete, the solution was stirred for 24 hours at reflux temperature and then cooled in an ice-bath. The excess sodium hydride was destroyed by carefully adding moist

acetic acid. The reaction mixture was extracted with three 100-ml. portions of ether. The ether extracts were combined, neutralized with saturated sodium bicarbonate, washed with two 50-ml. portions of distilled water, dried over magnesium sulfate, evaporated under reduced pressure, and vacuum distilled yielding two fractions of 5 g. (b.p. 45°C at 10 mm) and 1 g. (b.p. 85°C at 10 mm). The first fraction was epimerized starting material. The second fraction was 78. N.M.R. showed one olefinic proton at 5.7δ, 6 carbomethoxy protons at 3.6δ, 6 methyl protons at 1.1δ (J=1 cps), and 3 methyl protons at .9δ (J=1.5 cps).

Anal. Calcd. for $C_{13}H_{21}O_4$: C, 64.98%; H, 8.39%. Found: C, 65.00%; H, 8.65%.

Preparation of Dimethyl 2-isopropyl-5-methylcyclopentane-1,1-dicarboxylate 70 From 78.

A 1.6 g. sample of 78 was added to 300 mg. of 5% platinum on charcoal in 10 ml. of acetic acid. The mixture was hydrogenated for 20 hours until no further hydrogen was taken up. Only one equivalent of hydrogen was consumed. The catalyst was filtered out and the filtrate extracted with three 100-ml. portions of ether. The ether extracts were combined, neutralized with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and distilled under vacuum yielding 1.4 g. of 70. The n.m.r. showed no trace of olefinic protons at 5.7δ.

Preparation of 1,1-Bis(hydroxymethyl)-2-isopropyl-5-methylcyclopentane 71 From 70.

A 1.4-g. (6.0-mmoles) sample of 70 was added to a stirred solution of 1 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran. The

solution was refluxed for 24 hours. Then wet ether was added to destroy the excess lithium aluminum hydride. The reaction mixture was added to 50 ml. of distilled water, extracted with three 100-ml. portions of ether, dried over magnesium sulfate, and distilled under vacuum affording 0.9 g. (82%) of 71, ν_{max}^{film} 3250 cm^{-1}. The infrared spectrum showed no traces of carbonyl band at 1735 cm^{-1}.

Preparation of Tosylate 72 From 71.

A 0.9-g. (4.85-mmoles) sample of 71 was added to a stirred solution of 3 g. (15.7-mmoles) of p-toluenesulfonyl chloride and 30 ml. of pyridine. The solution was stirred at room temperature for 24 hours, poured onto 10 g. of crushed ice, and extracted with three 25-ml. portions of ether. The ether layers were combined, washed successively with three 25-ml. portions of 5% aqueous hydrochloric acid, 10 ml. distilled water, 10 ml. saturated solution of sodium bicarbonate, and 10 ml. of distilled water, dried over magnesium sulfate, and evaporated yielding 1.6 g. of the p-toluenesulfonate (72), m.p. 98-99°C, ν_{max}^{film} 1200 and 1180 cm^{-1}. No OH bands were observed in the infrared.

Preparation of 1,1-Bis(cyanomethyl)-5-methyl-2-isopropylcyclopentane 73 From 72.

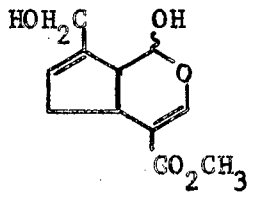
A 0.5-g. sample of sodium cyanide and 0.5 g. of 72 were added to 50 ml. of dimethyl sulfoxide and heated to 135°C for 24 hours. Then 100 ml. of water was added. The reaction mixture was extracted with four 100-ml. portions of ether. The ether extracts were combined, dried over magnesium sulfate, and evaporated under reduced pressure yielding 200 mg. of nitrile 73, ν_{max}^{film} 2500 cm^{-1}. No sulfonic ester bands at 1200 and 1180 cm^{-1} were observed.

PART II

SYNTHESIS AND CONFIGURATIONAL STUDIES OF SUBSTITUTED CYCLOPENTANE-1,2-DICARBOXYLIC ACIDS

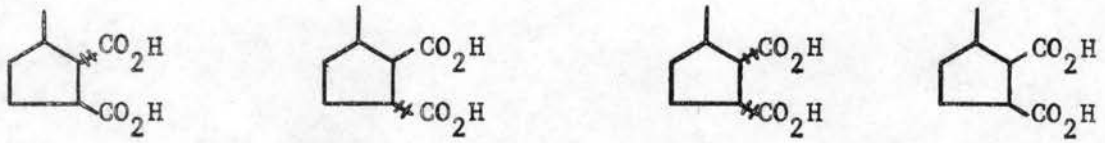
INTRODUCTION

The synthesis of the series of 3-methylcyclopentane-1,2-dicarboxylic acids 81a, 82a, 83a, and 84a shown in Fig. 1 from (+)pulegone (152b) was completed by P. Hanel to verify the absolute configuration of genipin (80) and to compare these optically active 3-methylcyclopentane-1,2-dicarboxylic acids with acids obtained from other natural products.[30]



80 genipin

The proof of the cis configuration at the ring junction of 80[31] was accomplished by its conversion to (-)cis,cis-3-methylcyclopentane-1,2-dicarboxylic acid (84a) (Fig. 1), and isomerization of 84a to 82a and comparison of 82a with 86 of the opposite absolute configuration.[32,33]



81a 82a 83a 84a

Figure 1. 3-Methylcyclopentane-1,2-dicarboxylic Acids Derived from (+)Pulegone (152b)

A recent study by Sister Saint Francis Dilgen has shown that the hydrogenation of 80 and ozonization of the hydrogenation product followed by hydrogen peroxide oxidation provided the 3R-methylcyclopentane-1,2-dicarboxylic acid 84 and the 3S acid 87, (Fig. 2) respectively, in a 2.5 to 1 ratio.[34]

85 86 87 88

Figure 2. Neptic Acids Derived From Nepetalactone

The presence of the isomeric nepetic acid 87 of opposite absolute configuration among the products derived from 80 was established through optical rotation studies and gas chromatography comparison of nepetic acid methyl esters.[34]

The previously mentioned acids 81a, 82a, 83a, and 84a were obtained by a Favorskii-type rearrangement of (+)methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (92) as shown in Fig. 3. P. Hanel[30] showed that if the temperature of the reaction was varied at constant

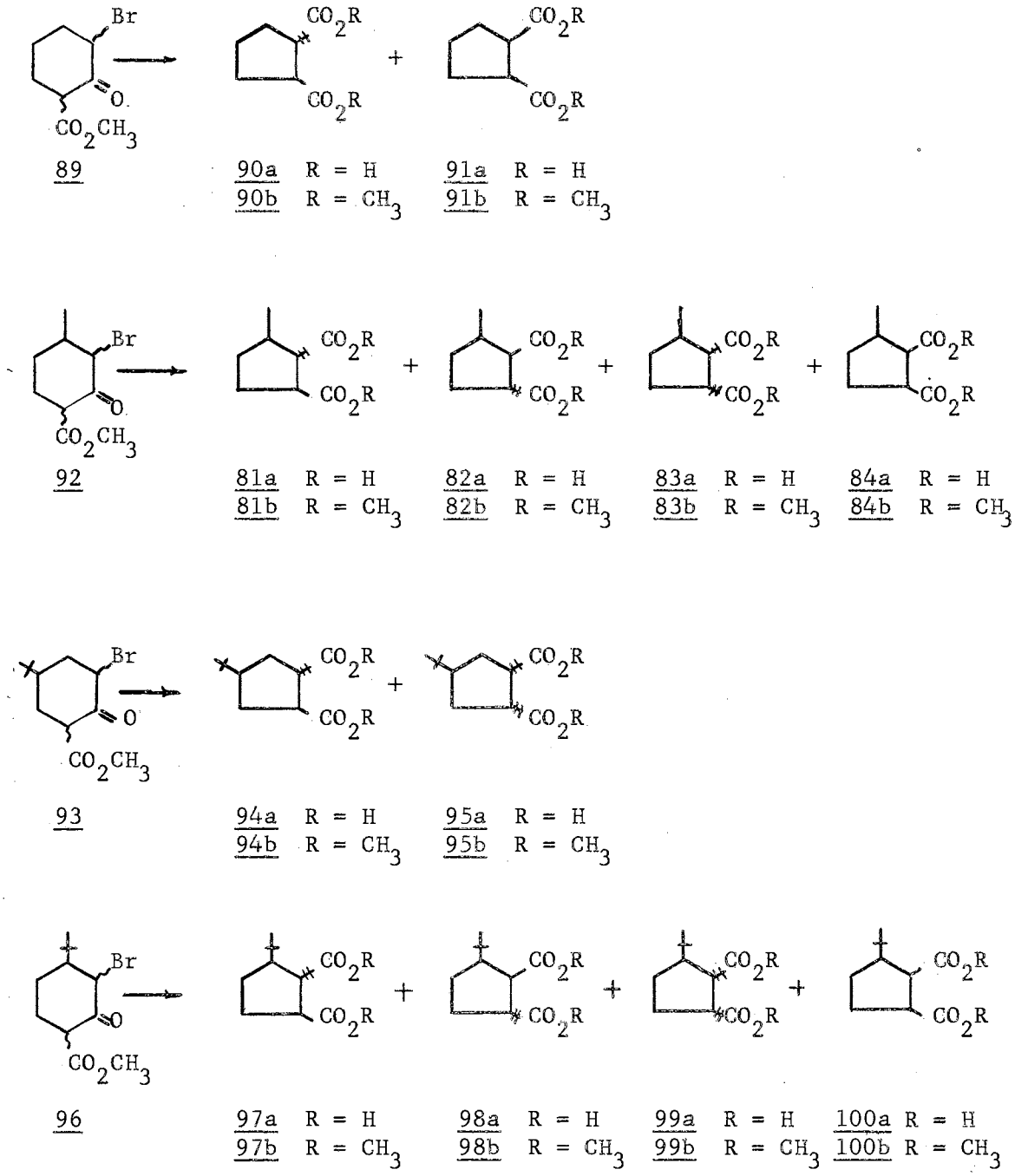


Figure 3. Favorskii-Type Rearrangement of Several Bromo Keto Esters

concentration of the reactants, the composition of dicarboxylic acid products also varied. To account for this it was suggested that the Favorskii rearrangement in this case was temperature-dependent.

These findings indicated that the Favorskii-type rearrangement of several alkyl-substituted bromo keto esters would provide an interesting and fruitful area of study which should result in a novel synthesis of several alkyl-substituted cyclopentane-1,2-dicarboxylic acids. Accordingly, the Favorskii rearrangement of methyl 3-bromo-2-oxocyclohexanecarboxylate (89), methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (92), methyl 3-bromo-5-t-butyl-2-oxocyclohexanecarboxylate (93), and methyl 3-bromo-4-t-butyl-2-oxocyclohexanecarboxylate (96) has now been studied.

HISTORICAL

The Favorskii reaction, a base-promoted rearrangement of α-halo ketones, has been known for many years. Kende wrote an excellent review of this reaction in 1961.[35] During the past five years increased attention has been given to the mechanism of the reaction. The most popular mechanism involves a cyclopropanone intermediate to which two pathways have been proposed as shown in routes I and II of Fig. 4.[36]

Route I (Fig. 4) is an example of an intramolecular S_N2-type rearrangement. A proton α to the carbonyl group is removed and the resulting carbanion 102 is stabilized by pi orbital overlap. A S_N2 intramolecular displacement occurs and the cyclopropanone 103 is formed; this is subsequently cleaved by base to the methyl cyclopentanecarboxylate (104).

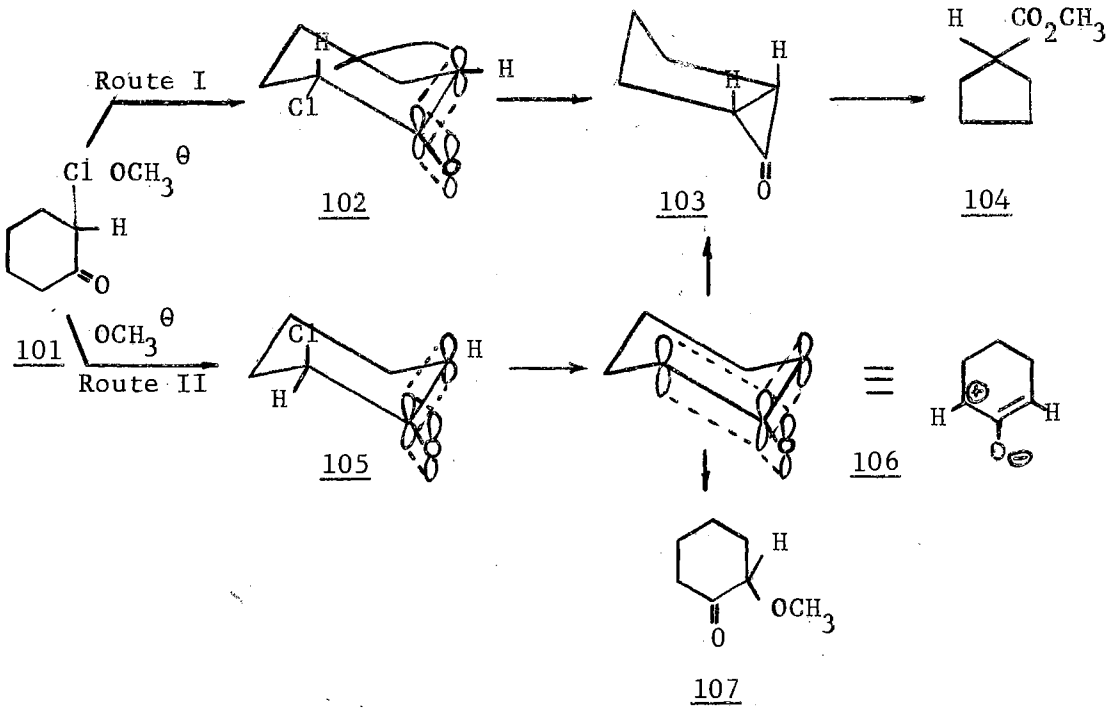


Figure 4. Mechanism for the Favorskii Rearrangement

In route II of Fig. 4, base removes a proton adjacent to the carbonyl group. In the following step, chloride ion is lost so as to leave the zwitterion intermediate 106, which is stabilized through extended pi orbital overlap. The intermediate 106 either collapses to the cyclopropanone intermediate 103 or reacts with methoxide ion to form the methoxy ketone 107. A stereospecific rearrangement occurs by a concerted mechanism in route I, whereas in route II a planar symmetric intermediate forms first. Many factors influence the course of the overall Favorskii rearrangement. For example, an equatorial halogen favors the displacement mechanism of route I, whereas an axial halogen favors the ionization mechanism, route II. The ionization mechanism should be favored by a polar solvent but the concerted mechanism should not.

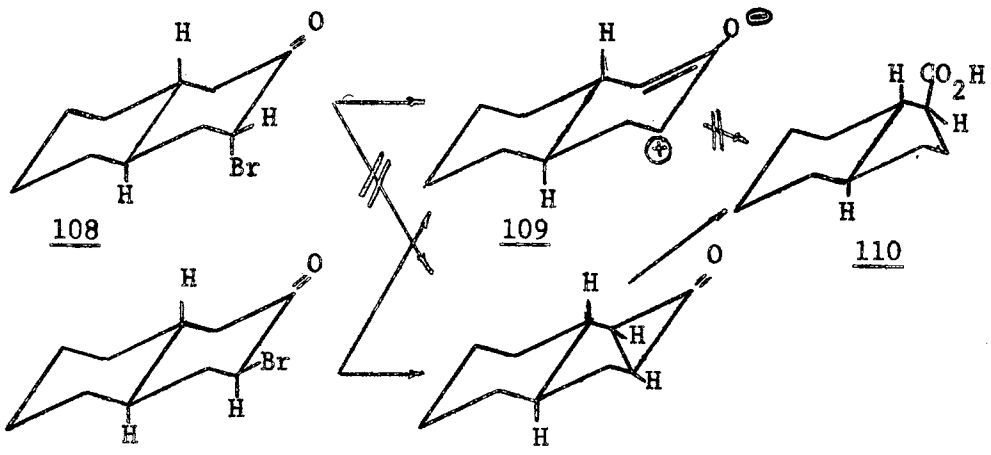
Most authors prefer the mechanism cited in Fig. 4 for the

Favorskii rearrangement. However, several believe that the zwitterionic intermediate does not occur. Smissman and co-workers[37] have shown that the acid 110 expected from the Favorskii rearrangement of cis-3-bromo-trans-2-decalone (108) is not found. They attribute this to the presence of an axial α-halogen. House and Franks[38] claim that the rearrangement of an α-halo ketone having an axial halogen can give the observed acids but the product distribution is not consistent with participation of the zwitterion.[38] Strong support for the cyclopropanone intermediate was cited by Turro and Hammond,[39] who treated cyclopropanones and their hemiketals with base and obtained the expected acids in almost 100 percent yields.

The course of the Favorskii rearrangement is usually studied by examining the products obtained from the reaction. Achmad and Cavill[27] believed that cis- and trans-pulegenic acids obtained from pulegone dibromide were directly formed by the rearrangement. Thus their explanation for the Favorskii rearrangement fits the product distribution. However, Wolinsky and Chan[28] have shown that the product distribution is not a safe indication of the path of the rearrangement. Other factors, such as the relative rates of base-catalyzed epimerization of esters, can determine the product ratio.

Smissman, Lemke, and Kristiansen[37] claimed that the direct formation of the cyclopropanone intermediate requires equatorial departure for halogen and that the solvent polarity has no effect on the rearrangement. They implied that the Favorskii rearrangement would not occur with an axial halogen. The necessity of an equatorial halogen was illustrated by treating cis- (108) and trans-3-bromo-trans-2-decalone (111) with sodium ethoxide in ethanol (polar system) and

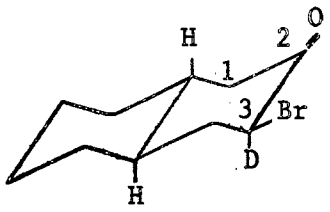
sodium ethoxide in 1,2-dimethoxyethane (nonpolar system).



108 109 110

111 112

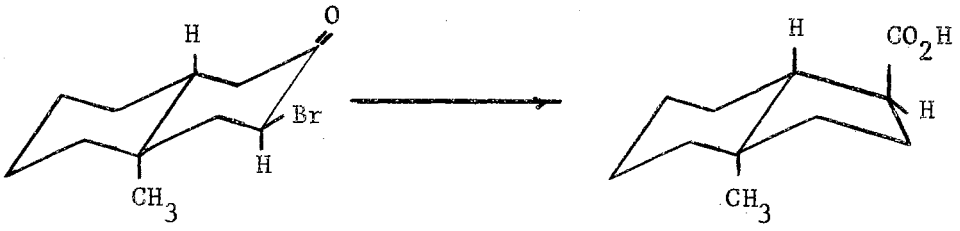
Even if zwitterionic interemediate 109 formed from the axial isomer 108, no 110 was observed as a product in either the polar or nonpolar solvents. Conversely, the isomer 111 with an equatorial bromine atom gave the acid 110 in 13 percent yield in both polar and nonpolar solvents. Since the same yields were obtained in both cases, it appeared that the reaction was not solvent-dependent. A deuterium exchange study was undertaken to determine whether epimerization at the carbon bearing the halogen atom was occurring prior to the rearrangement. The deuterium exchange study showed that the proton at C-3 (113) was highly acidic.



113

Therefore, to show that epimerization was not occurring before the Favorskii rearrangement, 2-bromo-9-methyl-trans-3-decalone (114)

was submitted to conditions to cause this rearrangement.

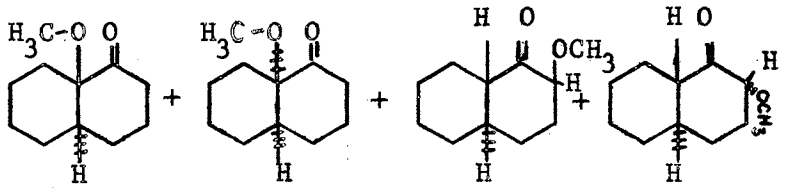


114 115

The isomer 114 was chosen because the equatorial carbon-bromine bond would not epimerize. The large steric interaction between the axial methyl group and the axial bromine group prohibits epimerization of 114 and the equatorial isomer is fixed in one conformation. The Favorskii rearrangement provided 115 in 38 and 44 percent yields respectively when polar and nonpolar solvents were used. Thus Smissman[37] showed that for the 3-bromo-2-decalones the isomer with an equatorial halogen underwent the Favorskii rearrangement and that solvent polarity did not influence the product yield.

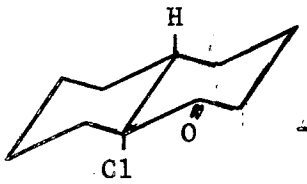
On the other hand, House and Franks,[38] studying the rearrangement of 9-chloro-trans-1-decalone (116), showed that equatorial or axial placement of halogen had no influence on the product composition of the Favorskii rearrangement. No esters were obtained when 116 or 117 were treated with methoxide ion in methanol. The methoxy ketones 118, 119, 120, and 121 were obtained instead, which suggested the presence of the zwitterionic intermediate 112.[38]

Chloro ketones 116 and 117 $\xrightarrow[CH_3OH]{NaOCH_3}$

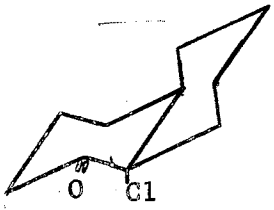


118 119 120 121

PERCENT OF ISOMERS

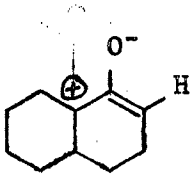


116 → 30 14 17 39



117 → 0 58 2 40

The product distribution from this reaction, however, was not compatible with participation of the zwitterionic intermediate 122, for if 122 were the intermediate, the percentage of different isomers given above should have been the same for both 116 and 117.[38]

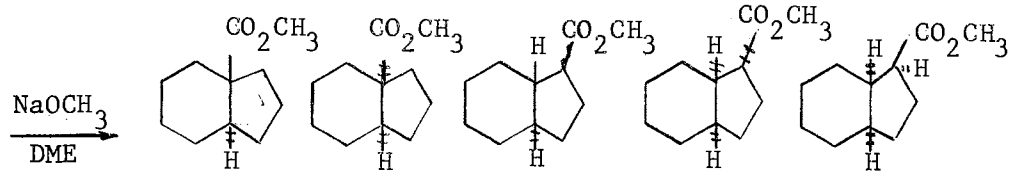


122

House and Frank suggested 123 as a possible intermediate for 118, 119, 120 and 121.

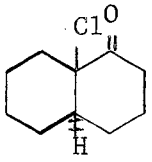
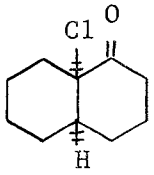
123

When 116 and 117 were treated with sodium methoxide in 1,2-dimethoxyethane (DME), the esters (124-128) were obtained.



124 125 126 127 128

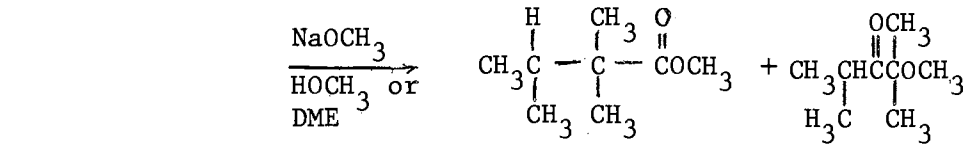
PERCENTAGE OF ISOMERS

	124	125	126	127	128
 116	88	2	5	5	0
 117	0	32	0	57	11

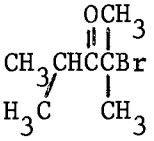
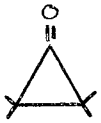
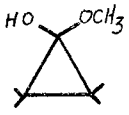
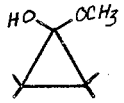
Thus, House and Frank showed that equatorial or axial conformation of the halogen atom did not determine the course of the Favorskii rearrangement.[38]

Evidence has been cited for the cyclopropanone intermediate by

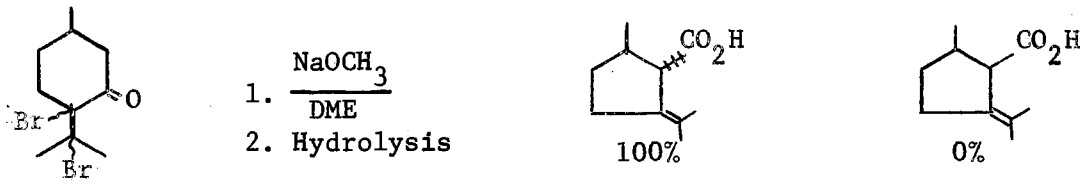
Turro and Hammond.[39] The α-bromo ketone, 2-bromo-2,4-dimethyl-3-hexanone (129), was subjected to Favorskii rearrangement and the expected products 130 and 131 were obtained. The proposed intermediates 132 and 133 were synthesized and treated under similar reaction conditions. The ester 130 was obtained as the major product when 132 and 133 were treated with bases. The base-catalyzed rearrangement of 132 and 133 gives almost 100 percent of the corresponding rearranged product which supports the idea of a cyclopropane intermediate 123.[38]



130 131

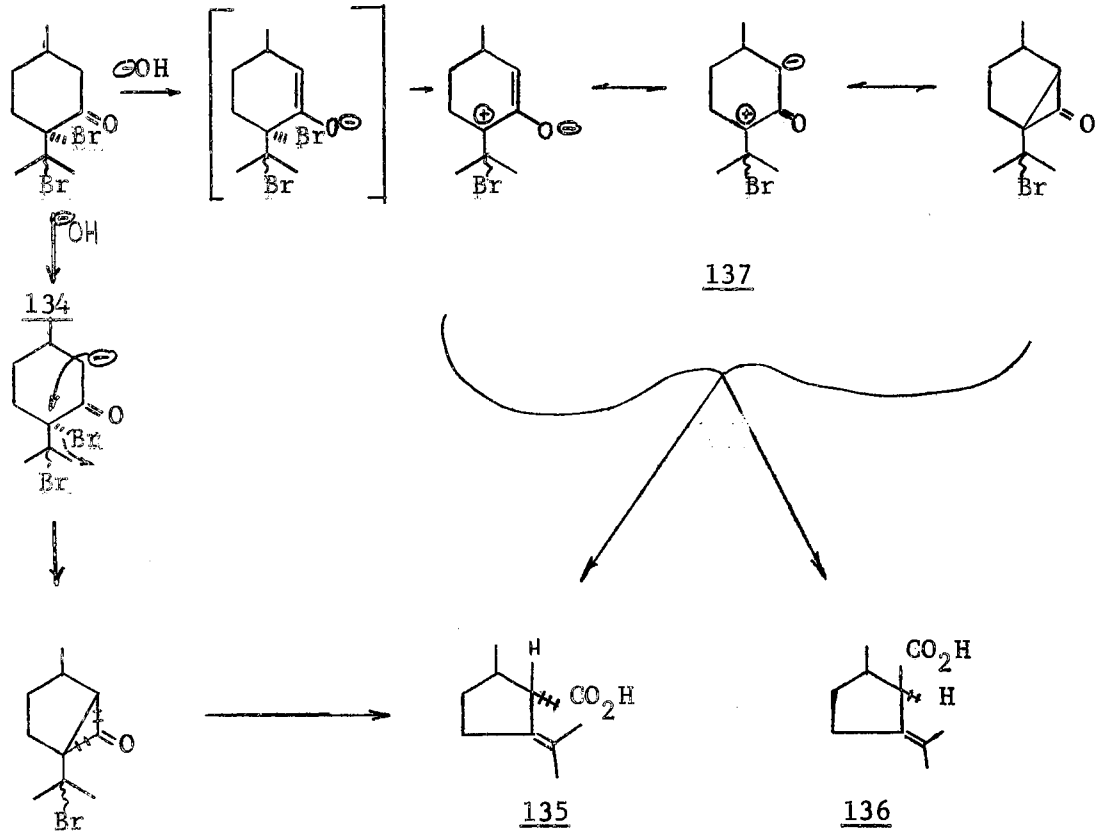
		PERCENTAGE OF ISOMERS		
	"	12	+	88
129				
	"	97	+	3
132				
	"	98	+	1
133				
	$\frac{CH_3OH}{Reflux}$	24	+	76
133				

In 1963 Achmad and Cavill[27] studied the Favorskii rearrangement of pulegone dibromide 134. When 134 was treated with sodium ethoxide in ethanol or sodium methoxide in 1,2-dimethoxyethane and the product hydrolyzed, trans-pulegenic acid (135) was obtained.



134 135 136

However, when sodium hydroxide and water was used, a mixture of 135 and 136 was obtained. The following mechanism, which involves the intermediate 137, was suggested for the reaction.[27]



Achmad and Cavill believed that pulegone dibromide existed as a single isomer to which they assigned structure 134 and that both the

cyclopropanone and the zwitterionic mechanism prevailed in its Favorskii rearrangement.[27]

In the same year Wolinsky, wolf, and Gibson[26] suggested that the products of the Favorskii reaction on pulegone dibromide reflect the possibility that pulegone dibromide actually was present in two isomeric forms.

In 1965 Wolinsky and Chan[28] completed a thorough study of the Favorskii rearrangement of pulegone dibromide. Their findings are summarized in Fig. 5.

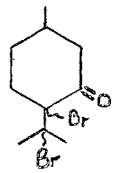
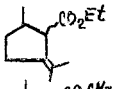
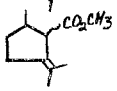
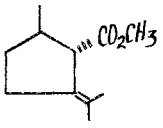
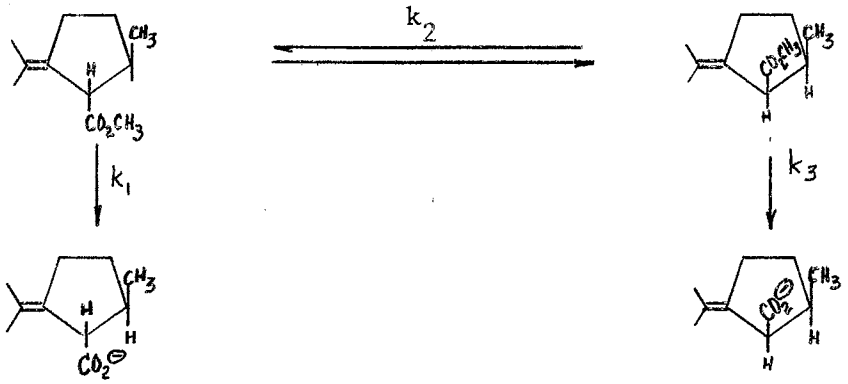
Reactant	Base	Product	% Cis	% Trans
 75	$NaOH-H_2O$		45-60	55-40
	$NaOCH_3-CH_3OH$, H_2O		8	92
	NaOEt-EtOH, H_2O		0	100
	NaOEt-EtOH		26	74
	$NaOCH_3-CH_3OH$		26	74
 135	$NaOCH_3-CH_3OH$		23	77

Figure 5. The Favorskii Rearrangement of Pulegone Dibromide (75) and Equilibration of Methyl Trans-Pulegonate (135)

Wolinsky and Chan[28] showed that the thermodynamic equilibrium position was obtained for 135 and 136 when sodium ethoxide in ethanol or sodium methoxide in methanol was used in the rearrangement. The explanation given for the high percentage of trans-isomer obtained when 75 was treated with alkoxide and then hydrolyzed was that the rate constant k_1 of hydrolysis of the trans-ester is much larger than the rate constant

k_3 of the cis-isomer. Moreover, the rate of epimerization, k_2, is much larger than either k_1 or k_3.

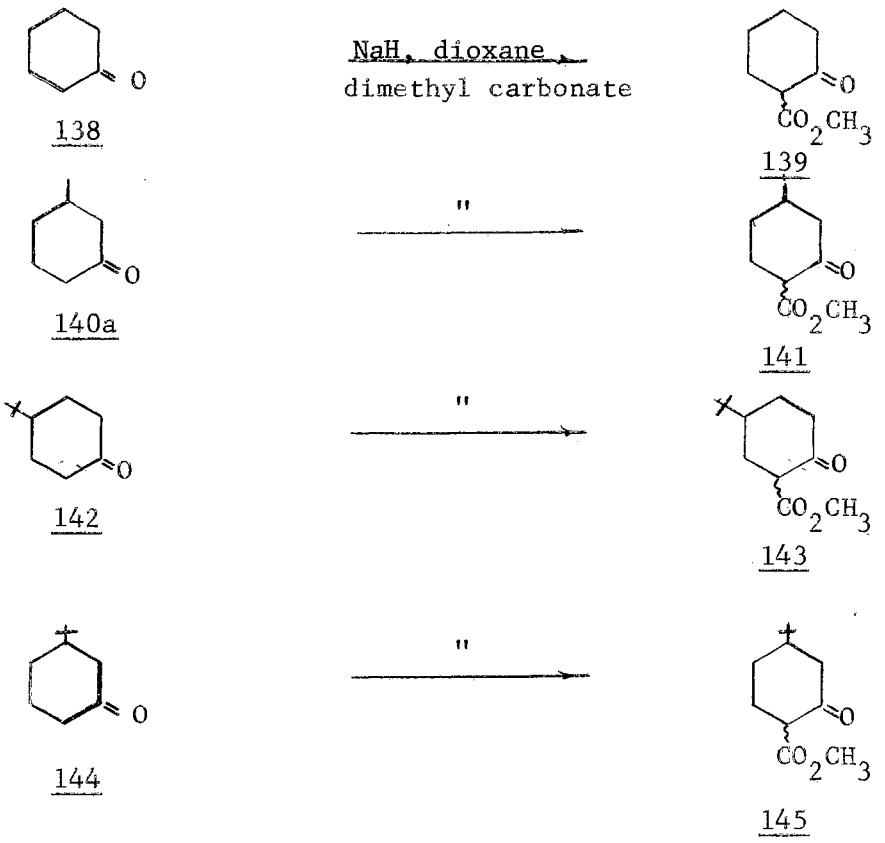


Thus as the saponification of the trans-isomer occurs more trans-isomer is formed by the epimerization of the cis-isomer. Eventually all of the cis-isomer is epimerized to the trans-isomer and then rapidly hydrolyzed to the trans-acid. By using a variety of bases and solvent systems, Wolinsky and Chan showed that other factors unrelated to the initial Favorskii rearrangement determined the final product distribution. They concluded that since the structure of the initial dibromo ketone was not known, nothing conclusive could be said about the mechanism of the reaction.

DISCUSSION AND RESULTS

Several cyclopentane-1,2-dicarboxylic acids were synthesized from the bromo keto esters 89, 92, 93, and 96. The mechanism of formation of these acids via the Favorskii-type rearrangement was studied and the composition of the mixture at equilibrium was determined for each cis and trans pair of the corresponding dimethyl esters. For each example, the β-keto ester was prepared by the addition of dimethyl carbonate to

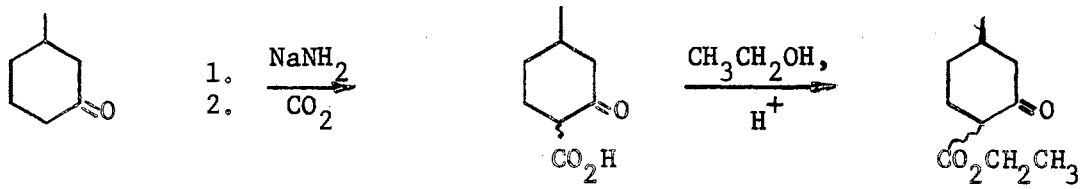
the appropriate ketone -- cyclohexanone (138), (+)3-methylcyclohexanone (140a), 4-t-butylcyclohexanone (142) or 3-t-butylcyclohexanone (144) -- by the method of Corey.[24]



Compounds 139 and 143 were synthesized previously by other routes[40,41,42] from which their configurations were established. Compounds 139 and 141 were synthesized by Hanel[30] using the method of Corey.[24] While the complete structure and the stereochemistry of 141 was not established it was favored over that of 146.

141 146

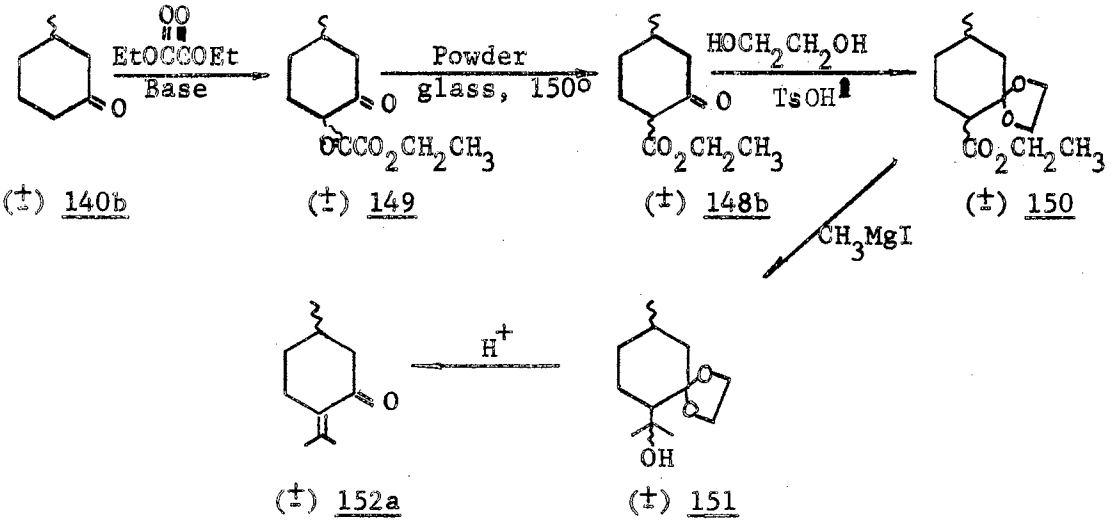
(+)3-Methyl-2-oxocyclohexanecarboxylic acid (147) and the ethyl ester 148a were synthesized in 1910 by Gardner, Perkins, and Watson by combining 140a with sodium amide and then carbon dioxide.[43] The resulting β-keto acid 147 was treated with ethanol and a trace of sulfuric acid to give 148a.[43]



(+) 140a (+) 147 (+) 148a

No conclusive proof of the structure of 148a was given at that time.

The synthesis of (±)pulegone in 1956 by Black, Buchanan, and Jarvie[44] provided evidence, enroute, for the structure of (±)ethyl 4-methyl-2-oxocyclohexanecarboxylate (148b). The synthesis began with (±)3-methylcyclohexanone (140b), which was converted to 149 and this pyrolyzed to the ethyl ester 148b. This ethyl ester was converted to the ketal 150 and then treated with methylmagnesium iodide to give 151. The resulting alcohol was hydrolyzed to (±)pulegone (152a), which established the structure of the β-keto ester 148b.

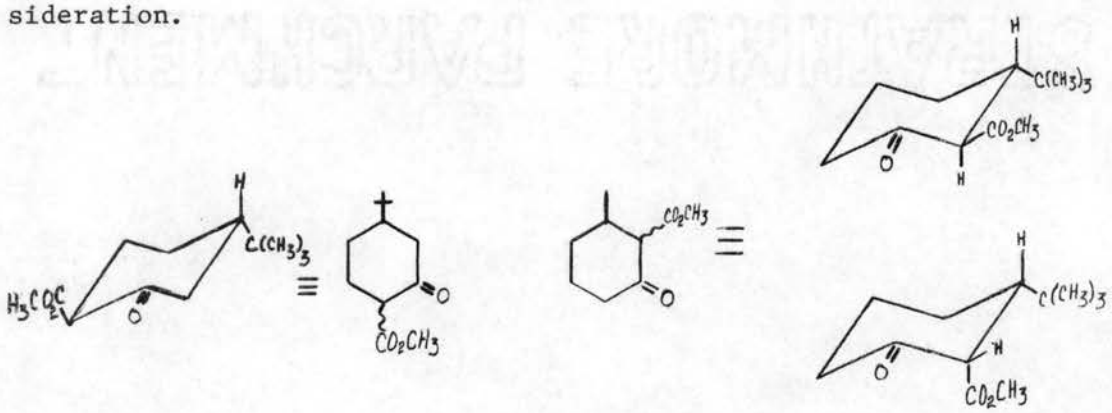


(±) 140b (±) 149 (±) 148b (±) 150

(±) 152a (±) 151

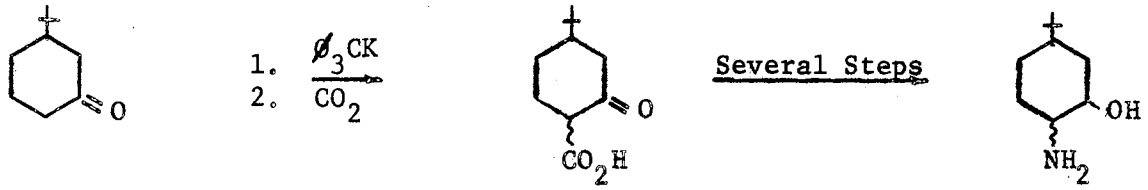
A sample of (+) 148a was obtained from P. Hanel[45] which had been prepared by the method of Black and co-workers[44] from 140a. The infrared spectrum of 148a was identical to that reported by Black and co-workers and also that of commercial sample.[46] The optical rotation, $(\alpha)_D$ 86°, was in good agreement with that reported by Gardner, Perkins, and Watson.[43] We believe that the methyl ester 141 obtained by the Corey[24] method has the same carbon skeleton as the β-keto esters (+) 148a and 148b obtained by the method of Black and co-workers.[44]

The structure 145 is favored over 154 for the reaction product of 3-t-butylcyclohexanone (144) with dimethyl carbonate and sodium hydride because the steric hindrance between the methoxycarbonyl group and the t-butyl group of 154 essentially eliminates this structure from consideration.



153 145 154

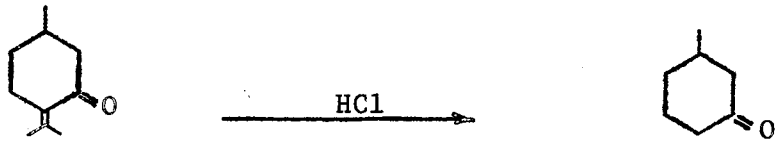
Moreover, 4-t-butyl-2-oxocyclohexanecarboxylic acid (155) was prepared by Tichy and co-workers by treating 144 with triphenylmethylpotassium and then with carbon dioxide.[42] The structure of 155 was proven by converting it through several steps to the amino alcohol 156, for which the structure was known from an independent reaction sequence.[42] The steric hindrance argument and the similarity of synthesis to that of



144 155 156

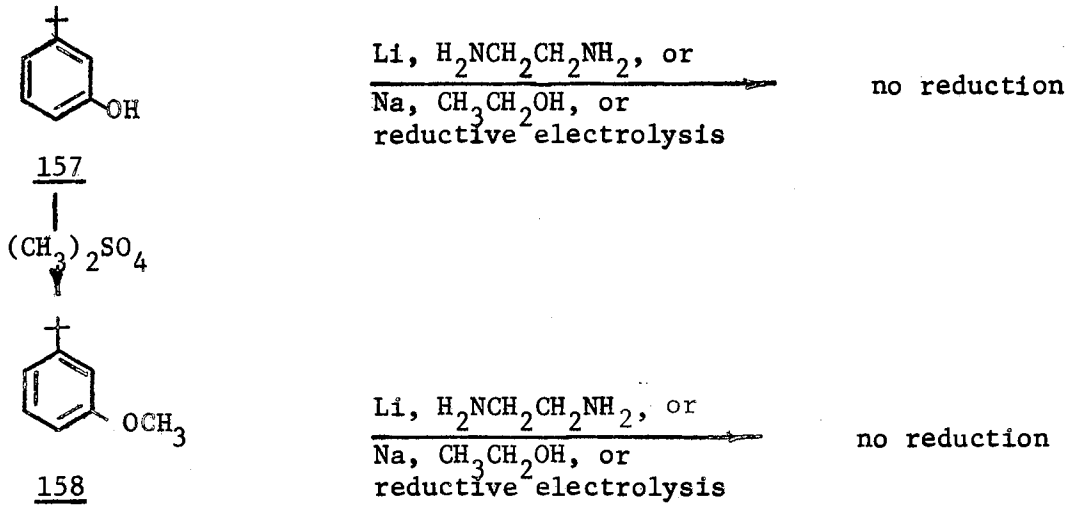
155 are cited as evidence for the structure of 145.

Cyclohexanone (138) and 142 used in synthesis of 139 and 143 are commercially available, but 140a and 144 had to be synthesized. (+)3-Methylcyclohexanone (140a) was obtained by acid hydrolysis of pulegone (152b).[47]

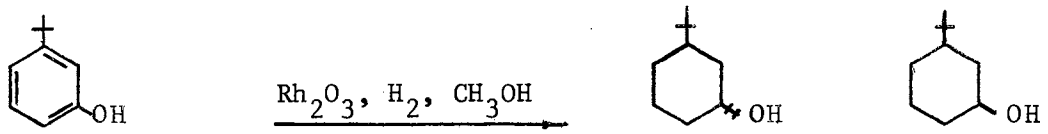


(+)152b (+)140a

Various methods for the preparation of 144 were examined. Attempts to reduce 3-t-butylphenol (157) and 3-t-butylanisole (158) to 144 with lithium in ethylenediamine, sodium in ethanol, and reductive electrolysis[48] failed.

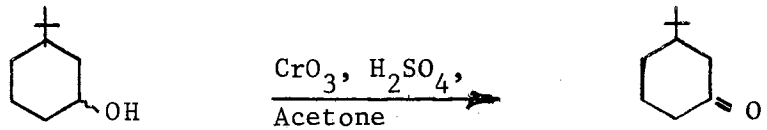


3-t-Butylcyclohexanone (144) was finally prepared by hydrogenation of 157 in the presence of 10% rhodium sesquioxide on carbon.[49] A mixture of 159a and 159b was obtained. This mixture was separated by preparative gas chromatography and physical properties of the products were in agreement with those reported by Winstein.[50] Oxidation of the mixture



157 159a 159b

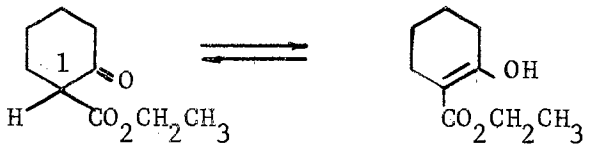
with chromic acid in acetone solution provided 144 which was assumed to be pure since only one gas chromatography peak was observed.[51] This confirms the epimeric relationship of 159a and 159b.



159 a,b 144

The relative configurations of the bromo keto esters 89, 92, 93, and 96 used in the synthesis of alkyl-substituted cyclopentane-1,2-dicarboxylic acids were established by their n.m.r. spectra. Proton signals at 4.8 and 12 δ were assigned to the proton on the carbon bearing the halogen atom and to an enolic proton respectively. If bromination of 139, 141, 143, and 145 occurred at the C-1 position of 160, then a proton at lower fields, 4.8 δ, would not be observed. Thus the appearance of a proton signal at lower fields provides evidence for the assigned structures of the various bromo keto esters.

Evidence for the enolic character of keto esters was obtained through application of n.m.r. by Rhoads,[52] who established the equilibrium position for the keto-enol tautomerization of ethyl 2-oxocyclohexanecarboxylate[52] as shown for structures 160 and 161. She determined the enol content to be 85%.



160 161

Her approach was used to determine the equilibrium content of ketone and enol forms for the ketones and β-keto esters presented in Table II. The percentage of enol form for the ketones 138, 140a, and 142 was determined by scanning the 10 and 13 δ regions in their n.m.r. spectra. No enolic protons could be detected by this method for these three ketones. A value, 0.02%, for the percent of enolic form of cyclohexanone obtained by titration with bromine has been reported.[53] This value is in good agreement with the one here obtained by n.m.r. data. The percentages of enolic form for the keto esters 139, 141, 143, and 145 and the bromo keto esters 89, 92, 93, and 96 were determined by dividing the relative concentration of the methoxycarbonyl group, located at 3.75 δ, into three times the relative concentration of the enolic proton, which is found at approximately 12 δ. The data obtained by this method gives a minimum value for the percentage of enolic form. Comparison of the spectra obtained for the ethyl esters of 139 and 141 with the spectra of 139 and 141 showed the proton attached at C-1 of 160 to be obscured by the methoxycarbonyl protons at 3.75 δ. The

TABLE II

PERCENTAGE OF ENOL-KETONE TAUTOMERIZATION

Compound	% Enol
Cyclohexanone (138)	0
Ethyl 2-oxocyclohexanecarboxylate (160)	84
Methyl 2-oxocyclohexanecarboxylate (139)	71
Methyl 3-bromo-2-oxocyclohexanecarboxylate (89)	66
(+)3-Methylcyclohexanone (140a)	0
(+)Ethyl 4-methyl-2-oxocyclohexanecarboxylate (148a)	75
(+)Methyl 4-methyl-2-oxocyclohexanecarboxylate (141)	73
(+)Methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (92)	100
4-t-Butylcyclohexanone (142)	0
Methyl 5-t-butyl-2-oxocyclohexanecarboxylate (143)	72
Methyl 3-bromo-5-t-butyl-2-oxocyclohexanecarboxylate (93)	75
Methyl 4-t-butyl-2-oxocyclohexanecarboxylate (145)	80

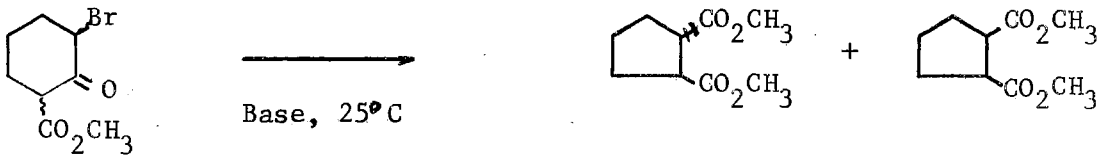
proton at C-1 in the ethyl ester is set apart from the methylene quarter and presents no difficulties.

The rearrangement of the bromo keto esters 89, 92, 93, and 96 was studied in solutions containing methanol, potassium hydroxide in methanol, or potassium hydroxide in water. A typical procedure used for the Favorskii reaction was to add the bromo keto ester to the basic solution and after addition to withdraw 1-ml samples with a syringe. The sample was immediately neutralized with 5% hydrochloric acid and then extracted with ether. The other extracts were analyzed by gas chromatography. If the Favorskii rearrangement yielded acids instead of methyl esters, then esterification with diazomethane was carried out. Otherwise the extracts were directly analyzed by gas chromatography. The results of these analysis are presented in Tables III, IV, and V. The percentages of the various isomers were determined by

TABLE III

THE FAVORSKII REARRANGEMENT OF METHYL 3-BROMO-2-

OXOCYCLOHEXANECARBOXYLATE (89)

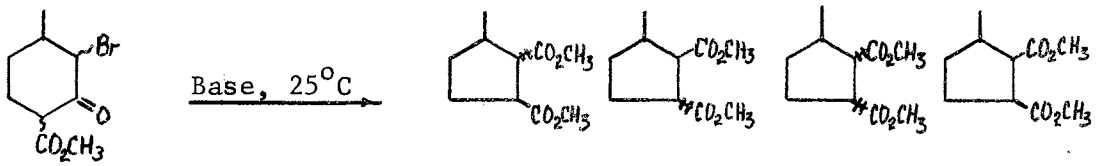


89 90b 91b

Time (min.)	Base/Solvent	% Trans	% Cis
0	$NaOCH_3/CH_3OH$	62	38
1		68	32
5		81	19
10		82	18
60		92	8
24 hours		92	8
0	KOH/CH_3OH	66	34
1		71	29
10		72	28
240		79	21
0	KOH/H_2O	30	70
1		35	65
2		34	66
5		36	64
10		48	52
24 hours		53	47

TABLE IV

THE FAVORSKII REARRANGEMENT OF METHYL 3-BROMO-4-METHYL-2-OXOCYCLOHEXANECARBOXYLATE (92)

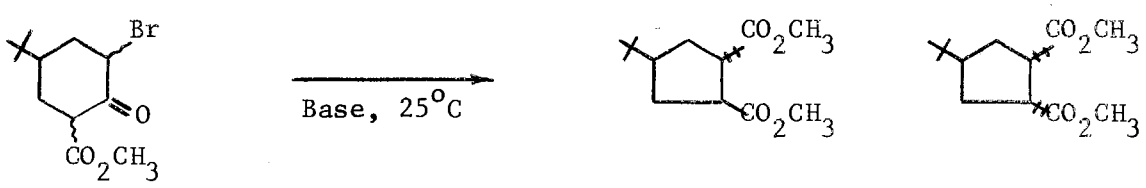


92 81b 82b 83b 84b

Time (min.)	Base/Solvent	% t,t	% t,c	% c,t	% c,c
20	$NaOCH_3/CH_3OH$	73	22	5	0
30		75	22	3	0
45		78	18	4	0
90		79	17	4	0
24 hours		83	12	5	0
0	KOH/CH_3OH	27	12	34	27
1		47	25	16	12
3		53	22	14	11
2.5 hours		52	30	9	9
5 hours		54	32	6	8
0	KOH/H_2O	16	14	24	46
0.5		15	13	26	46
1		16	15	22	47
3		18	15	25	42
5		17	15	23	45
24 hours		21	12	24	43

TABLE V

THE FAVORSKII REARRANGEMENT OF METHYL 3-BROMO-5-*t*-BUTYLCYCLOHEXANECARBOXYLATE (93)



93 94b 95b

Time (min.)	Base/Solvent	% Trans	% Cis
0	$NaOCH_3/CH_3OH$	97	3
1		98	2
5		98	2
10		98	2
20		97	3
24 hours		100	0
0	KOH/CH_3OH	50	50
1		52	48
30		68	32
240		75	25
0	KOH/H_2O	28	72
1		30	70
3		29	71
5		30	70
20		34	66
24		37	63

calculating the areas under the peaks through the peak width at half-height procedure and then comparing the relative areas. The precision of this method was established by mixing known amounts of cis- and trans-4-t-butylcyclopentane-1,2-dicarboxylates and measuring the areas under their respective peaks. This method was found to be accurate to within 1%.

The data shown in Tables III, IV, and V suggest that the cis-isomers, i.e., the thermodynamically less stable products, form first and are the major primary products in the Favorskii rearrangement, and then are equilibrated to the more stable trans-isomers. It was hoped that lowering the temperature of the reaction would decrease the rate of equilibration so that a sample could be obtained which would contain a high percentage of the thermodynamically less stable products. The bromo keto ester 92 was treated with potassium hydroxide in methanol at -50°. The reaction mixture solidified when 92 was added. This solid was promptly added to 5% hydrochloric acid and the reaction product extracted with ether. The ether extract was treated with diazomethane and analyzed by gas chromatography. However, no esters were detected. A second experiment was carried out at 0° using the bromo keto esters 89, 92, and 93. These results are tabulated in Table VI.

It was hoped that a change of solvent polarity would give either a preponderance of the less stable products 83b and 84b for a polar solvent or a preponderance of 81b and 82b for a less polar solvent. Two solvent systems were utilized, the less polar sodium methoxide in dimethoxyethane (DME) and potassium hydroxide in the more polar dimethyl sulfoxide (DMSO) for the Favorskii rearrangement of 92. The results are tabulated in Table VII.

TABLE VI

THE FAVORSKII REARRANGEMENT OF 89, 92, AND 93 AT 0°

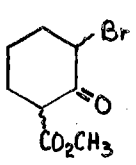
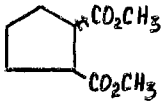
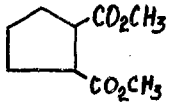
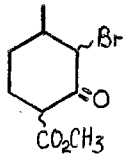
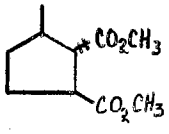
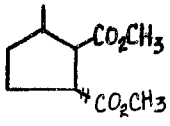
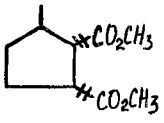
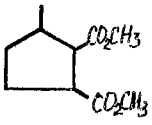
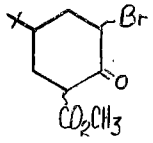
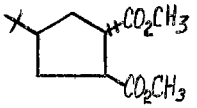
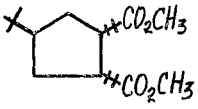
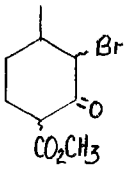
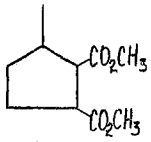
	CH_3OH, KOH				
89		45% 90b	55% 91b		
	CH_3OH, KOH				
92		37% 81b	6% 82b	21% 83b	36% 84b
	CH_3OH, KOH				
93		50% 94b	50% 95b		

TABLE VII

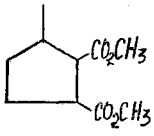
THE FAVORSKII REARRANGEMENT OF 92 UTILIZING TWO SOLVENT SYSTEMS



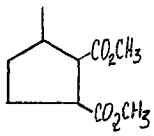
92



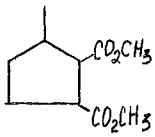
81b



82b



83b



84b

		Time (min.)	Percent Isomers Formed			
92	$NaOCH_3$ / DME	1	75	14	7	4
		5	79	13	5	3
		10	79	11	6	4
		240	81	11	5	3
92	1. KOH, 2 hr., DMSO-10% H_2O 2. $H^{\oplus}$ 3. CH_2N_2		28	29	25	18

Two mechanisms are considered for the Favorskii-type rearrangement of the four bromo keto esters 89, 92, 93, and 96. The first utilizes the cyclopropanone intermediate. The second is a concerted mechanism.

The Favorskii-type rearrangement of 89 involving a cyclopropanone intermediate is given in Fig. 6. If 89 has the configuration shown for structure 162 in Fig. 6, then the products obtained by using various solvent and base systems -- methanol and sodium methoxide, methanol and potassium hydroxide, and water and potassium hydroxide -- are in agreement with the results reported in Table III.

The use of the more polar system, aqueous potassium hydroxide, gives the highest yield of cis-isomer. This polar solvent stabilizes the intermediate dianion 165 and allows time for epimerization to occur at C-2. Thus in structure 168 the negative charge at C-2 is at maximum distance from the negative charge of the carboxylate anion. We have isolated a mixture of half-esters from 166 and 169 by rapidly quenching the reaction mixture with 5% hydrochloric acid. This mixture of half-esters was found to be 36% 166 and 64% 169 by gas chromatography of the respective dimethyl esters. If the reaction was allowed to go to completion, the ratio of cis- to trans-isomers changed to 47% cis- and 53% trans-isomer. A possible explanation for the initial preponderance of cis-isomer is that k_1 is large compared to k_2 and k_3. Thus as 165 is formed an epimerization quickly occurs with equilibration favoring 169. With increased reaction time the hydrolysis of half-esters to the acids occurs. The hydrolysis of 166 is more facile than that of 169, i.e., k_3 is larger than k_2. Thus as 166 is saponified the equilibrium between 169 and 166 shifts so that more trans-isomer is obtained. When a less polar solvent is used k_3 is larger and more trans-isomer is obtained

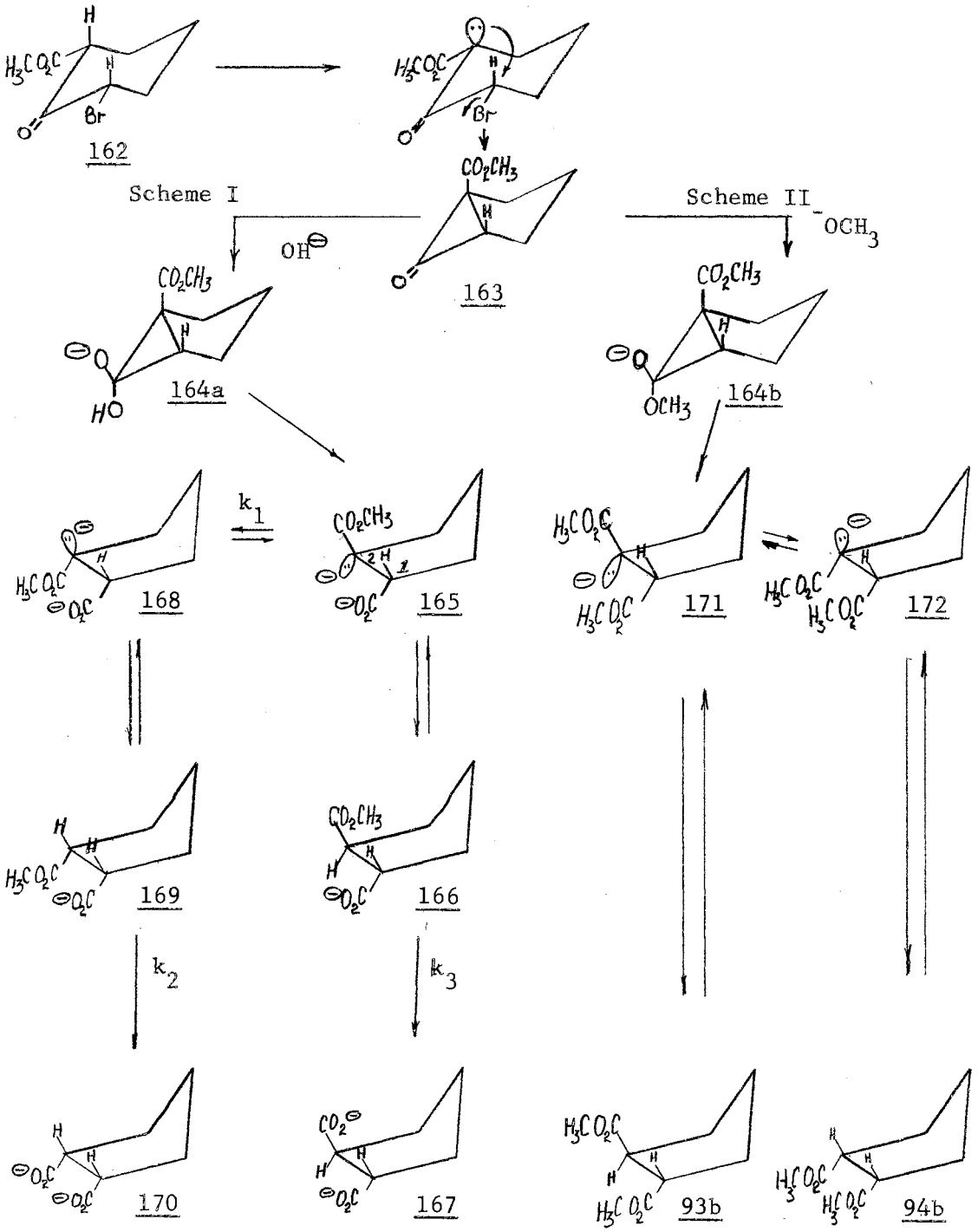


Figure 6. The Mechanism of the Favorskii-type Rearrangement of Methyl 3-Bromo-2-oxocyclohexanecarboxylate Involving Cyclopropanone Intermediate

initially. The reaction mechanism for sodium methoxide in methanol is described by scheme II, Fig. 6. This mechanism does not explain why the cis-isomer in this instance occurs in relatively large amounts during the initial phase of the reaction, for if the more stable isomer is produced first then at most only 10% cis-isomer is to be expected thereafter.

The concerted mechanism shown in Fig. 7, in which bond formation and bond breaking occur in one step during the rearrangement of methyl 3-bromo-2-oxocyclohexanecarboxylate, fits the data in Table III better than the mechanism described in Fig. 6. The relative configuration of 89 is not known. It is known, however, that the enolic form predominates as shown in Table II. Assuming that the keto form and not the enol form participates in the rearrangement, there could be several conformers of 89. However, those structures with equatorial halogen are favored and structure 162 is probably the most stable conformer. A concerted mechanism for the Favorskii-type rearrangement of 162 leads to the least stable half-ester 169 which either hydrolyzes to 170 or epimerizes to 166. The latter may finally hydrolyze to 167. Support for this may be found in the work of Wolinsky and Chan,[28] who showed that methyl trans-pulegenate (135) hydrolyzes much faster than the cis-isomer and that epimerization between the cis- and the trans-isomer is facile. In our case the hydrolysis of 166 is expected to be faster than the hydrolysis of 169. Thus if epimerization is occurring, the shift from predominately cis- to trans-isomer is in agreement with Table III. The small amounts of trans-isomer found initially may be explained by assuming that some of the bromo keto ester 173 or 174 exists and that the rearrangement of 173 or 174 yields the trans

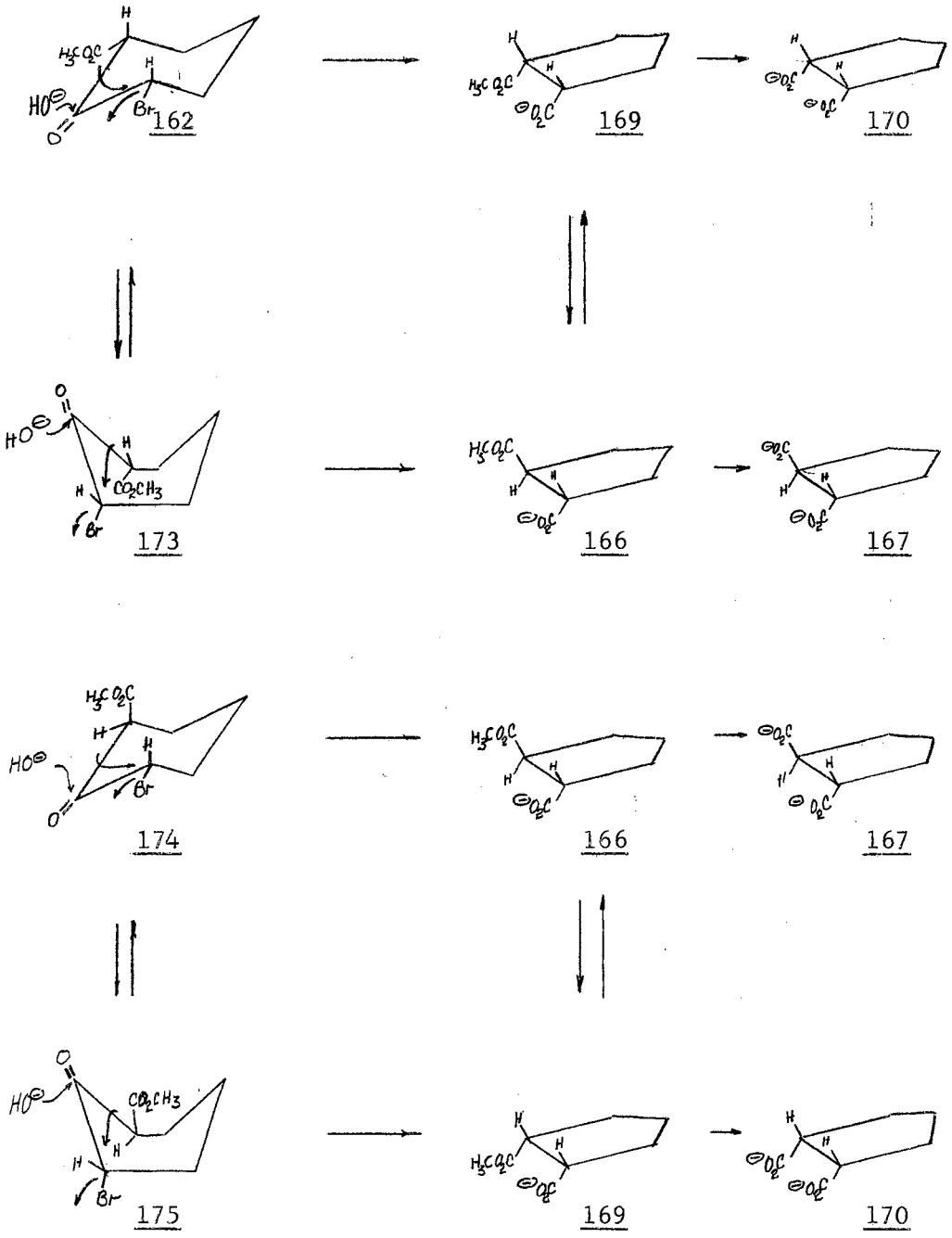


Figure 7. The Favorskii-type Rearrangement of Methyl 3-Bromo-2-oxocyclohexanecarboxylate Involving a Concerted Mechanism

half-ester directly or that the epimerization of 169 to 166 occurs so rapidly that the pure cis half-ester is not detected.

A mechanism involving a cyclopropanone intermediate for the rearrangement of methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate (92) in potassium hydroxide and methanol or potassium hydroxide in water is given in Fig. 8. If k_1 is larger than k_2 and k_3 larger than k_4, then the products obtained in Table IV can be rationalized by the mechanism described in Fig. 8. The most stable conformers of 92 are 176 and 182. The conformer 176 is assumed to form intermediate 177 which rearranges to the half-ester 178 and this either hydrolyzes to 179 or epimerizes to 180, which in turn can hydrolyze to anion 181. On the other hand, the conformer 182 could be expected to form the cyclopropanone intermediate 183 which in turn would rearrange to 184 and then either hydrolyze to 185 or epimerize to 186. If the latter is formed, there is the possibility of hydrolysis to 187. The rates of hydrolysis k_1, k_2, k_3, and k_4 are small as compared to the rate of epimerization for if the reaction mixture is quenched with 5% hydrochloric acid immediately after the bromo keto ester 92 is added to base, then the half-esters obtained from 178, 180, 184, and 186 are isolated. The structures of the half-esters were established through n.m.r. spectroscopy. The n.m.r. spectra showed the presence of methoxycarbonyl protons and carboxylic acid protons in a ratio of 3:1. The (+)methyl 3-bromo-4-methyl-2-oxocyclohexanecarboxylate was also treated with base and the reaction mixture was quenched immediately with 5% hydrochloric acid. The four racemic half-esters were obtained. Schemes I and II of Fig. 8 suggest that the most stable isomers trans,trans-178 and trans,cis-184 should be formed first, which is in disagreement with the data in

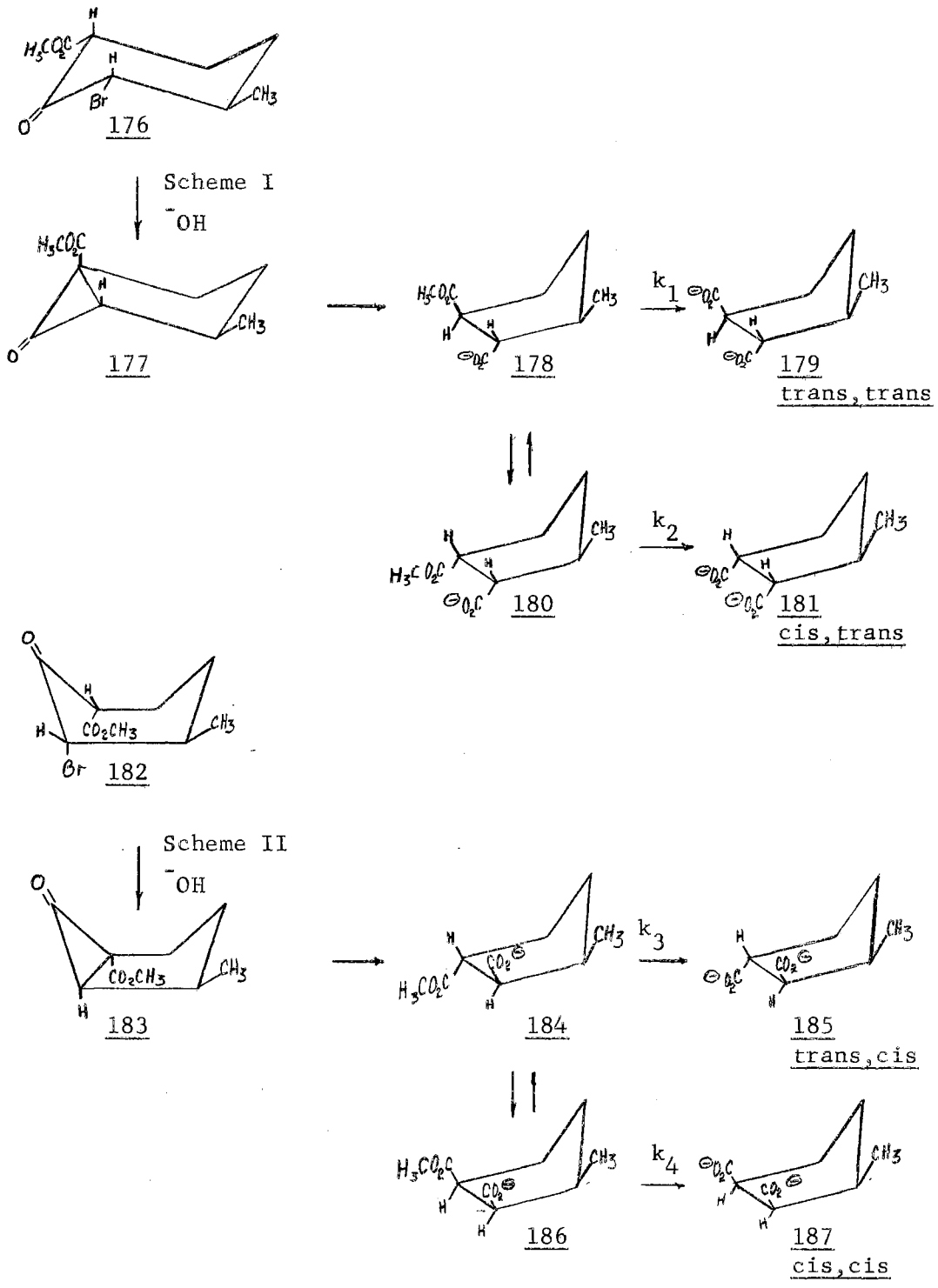


Figure 8. The Favorskii Rearrangement of Methyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (92) Involving the Cyclopropanone Intermediate

Table IV.

The concerted mechanism in Fig. 9 fits the data of Table IV better than the cyclopropanone mechanism, Fig. 8. The most stable conformers of 92 are 176 and 188 as shown in Fig. 9 and these give the less stable isomers. The rearrangement of the boat conformer 188 gives the less stable half-ester 186 which can epimerize to the more stable isomer 184 or hydrolyze to the dianion 187; whereas, the rearrangement of 176 gives the less stable half-ester 180 which in turn may epimerize to the more stable isomer 178 or hydrolyze to 181. When aqueous potassium hydroxide is used as the base and solvent in the rearrangement, a yield of 46% cis,cis-isomer 186 is obtained as the major product. Since 186 is the less stable product it must be formed first during the rearrangement; otherwise it would have been epimerized to a more stable isomer. If we assume that conformer 176 is the precursor to the trans,trans-dianion 179 and the cis,trans-dianion 181 whereas the conformer 188 leads to the trans,cis-dianion 185 and the cis,cis-dianion 187 and there is no intersystem crossing, the total percentage yield of 179 and 181 should remain constant during the course of the reaction even though the relative amount of either isomer may become altered by epimerization. The same argument should hold for the other two dianions 185 and 187 derived from 188. The data in Table IV support this argument and provide strong evidence for the concerted mechanism shown in Fig. 9. The data in Table II shows that the bromo keto ester 92 is mostly in the enolic form. However, a mixture of keto forms may be obtained on ketonization. In a more polar solvent the boat conformer 188 shown in Fig. 9 may predominate, which would explain the increase in the percentage of cis,cis-isomer 186 which forms initially. On the

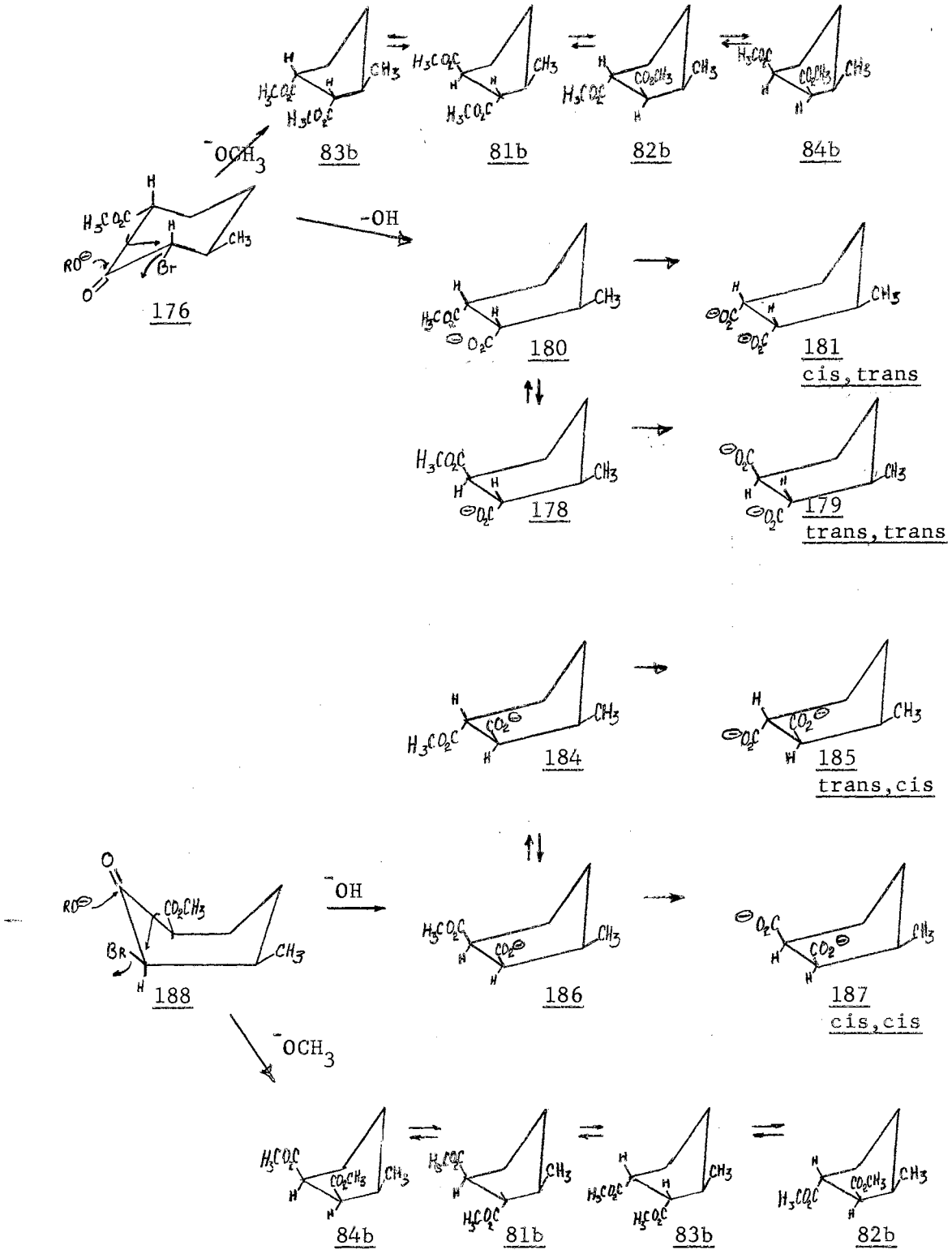


Figure 9. The Favorskii-type Rearrangement of Methyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (92) Involving the Concerted Mechanism

other hand, it is difficult to explain the formation of this less stable cis,cis-isomer 186 by way of the cyclopropanone intermediate.

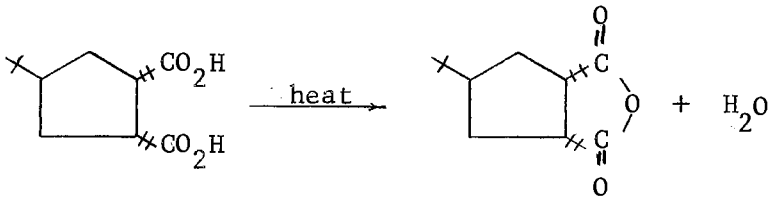
The data given in Table IV for the rearrangement of methyl 3-bromo-5-t-butyl-2-oxocyclohexanecarboxylate (93) is similar to that for 89 (Table III). Thus the mechanisms proposed for the rearrangement of 89 are applicable to 93 as well except for the effects imposed by the stereochemical requirements of the t-butyl group.

The Favorskii-type rearrangement of methyl 3-bromo-4-t-butyl-2-oxocyclohexanecarboxylate (96) has been carried out and 97b has been isolated. However, the separation and determination of structure of the other products has not been completed. When 96 was treated with sodium methoxide in methanol, only one dimethyl ester was detected by gas chromatography. The n.m.r. spectrum of this ester showed 6 protons at δ = 3.75 and 9 protons at δ = 0.85. These data suggest dimethyl 3-t-butylcyclopentane-1,2-dicarboxylate for its structure. Since it was directly obtained from the basic reaction medium as the dimethyl ester it is undoubtedly 97b.

Authentic samples of dimethyl esters 81b, 82b, 83b, 84b, 90b, and 91b used as standards for gas chromatography studies of the dimethyl esters obtained from the rearrangement of the bromo keto ester 89 and 92 were acquired from P. Hanel.[45] The dimethyl esters 94b, 95b, and 97b were obtained from the Favorskii-type rearrangement of the corresponding bromo keto esters 93 and 96.

A mixture of trans,trans- and cis-trans-4-t-butylcyclopentane-1,2-dicarboxylic acid (94a, 95a) was obtained from the Favorskii-type rearrangement of 93 with potassium hydroxide in methanol. The cis,trans-isomer 95a was separated from the trans,trans-acid 94a by

partial recrystallization from ether. The latter was found to be more soluble in ether than the former. A pure sample of cis,trans-4-t-butylcyclopentane-1,2-dicarboxylic acid (95a) was obtained by several recrystallizations from ether. The methyl ester was prepared by esterification of 95a with diazomethane. The hydrolysis of the dimethyl ester 94b from the base-catalyzed rearrangement of 93 gave 94a. The cis assignment to carboxyl groups of 95a is based on the ease of conversion to the corresponding anhydride (189).[32]



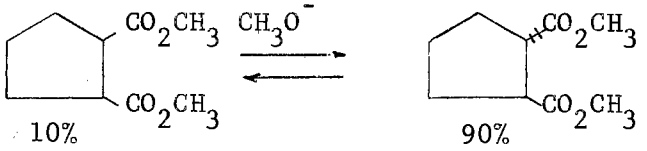
95a 189

Differential thermal analysis of several cis- and trans- cyclopentane- and cyclohexane-1,2-dicarboxylic acids has shown the utility of differentiating cis- and trans-isomers. In all of the cases investigated, the cis-isomer decomposed at a lower temperature than the trans-isomer because of the ease of formation of the cis-anhydride. Moreover, the cis-isomer was distinguished from the trans-isomer by adding sodium methoxide in methanol to the dimethyl ester and observing the change in isomer ratio through gas chromatography analysis. Usually an equilibrium ratio of cis- and trans-dimethyl esters results. In the case of 95b complete epimerization to 94b was observed.

Dimethyl trans,trans-3-t-butylcyclopentane-1,2-dicarboxylate (97b) was obtained in pure form from the Favorskii-type rearrangement of 96 with sodium methoxide in methanol as the base-solvent system since gas chromatography analysis showed only one isomer. When potassium

hydroxide in methanol was used, other isomers were detected. These isomers have not been isolated. However, it is believed that the procedure outlined by Hanel[30] for the separation of the four isomers of 3R-methylcyclopentane-1,2-dicarboxylic acids could be used for the separation of the various 3-t-butylcyclopentane-1,2-dicarboxylic acid isomers.

A study of equilibration of 90b and 91b; 81b, 82b, 83b and 84b; 94b and 95b; and 97b, 98b, 99b, and 100b was undertaken to show that when sodium methoxide in methanol is used as the base in the Favorskii-type rearrangement the thermodynamically predicted products of equilibration are obtained. Fonken[54] had established the equilibrium mixture for the dimethyl cis- and trans-cyclopentane-1,2-dicarboxylates to contain 10% cis- and 90% trans-isomers.



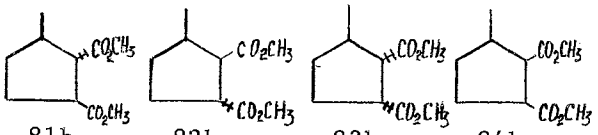
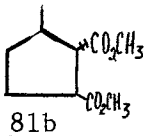
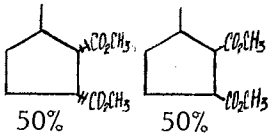
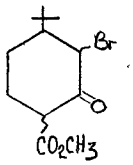
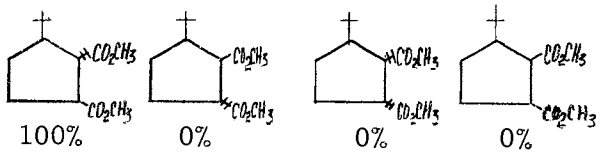
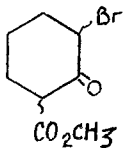
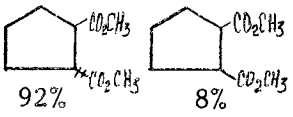
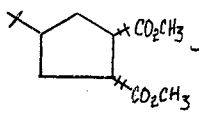
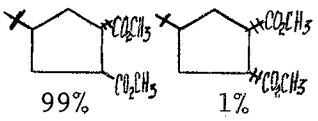
91b 90b

We have established the ratio of isomers at equilibrium for the dimethyl esters 81b, 82b, 83b and 84b; 90b and 91b; 94b and 95b; 97b, 98b, 99b, and 100b. The equilibrium ratios of isomers for the dimethyl 3-methylcyclopentane-1,2-dicarboxylates (81b, 82b, 83b, 84b) and dimethyl 4-t-butylcyclopentane-1,2-dicarboxylates (94b, 95b) were obtained by stirring a pure isomer or a known mixture of two isomers in methanol solution containing methoxide ion at room temperature for twenty-four hours. The equilibrium ratio for the dimethyl

TABLE VIII

THE EQUILIBRIUM RATIO OF SUBSTITUTED DIMETHYL

CYCLOPENTANE-1,2-DICARBOXYLATES

Reactant	Base/Solvent	Percent Products
	$NaOCH_3$, CH_3OH, 24 hours, 25°	 81b 82b 83b 84b
 81b	"	83% 11% 6% 0%
 50% 50% 83b 84b	"	82% 11% 7% 0%
 96	"	 100% 0% 0% 0% 97b 98b 99b 100b
	"	 92% 8% 90b 91b
89  95b	"	 99% 1% 94b 95b

cyclopentane-1,2-dicarboxylates (90b and 91b) was obtained by vapor-phase chromatography analysis of the reaction product from the base-catalyzed rearrangement of bromo keto ester 89. The ratio obtained was in good agreement with that reported by Fonken.[54] In a similar manner, the composition of the equilibrium mixture for the dimethyl 3-t-butylcyclopentane-1,2-dicarboxylates was obtained. The results are shown in Table VIII.

CONCLUSIONS

The synthesis of the four keto esters 139, 141, 143, and 145 and the corresponding bromo keto esters 89, 92, 93, and 96 was accomplished. The minimum percent of enolic form for these esters and some ketones was established by n.m.r. analysis.

A novel method for the preparation of substituted cyclopentane-1,2-dicarboxylic acids by the Favorskii-type rearrangement of substituted methyl 3-bromo-2-oxocyclohexanecarboxylates was investigated. The usefulness of this preparation has been shown by its extension to the synthesis of pure cis,trans- and trans,trans-3-t-butylcyclopentane-1,2-dicarboxylic acids and trans,trans-3-t-butylcyclopentane-1,2-dicarboxylic acid and their respective methyl esters. It was shown that if sodium methoxide is used as the base in the Favorskii-type rearrangement the equilibrium between the isomeric dimethyl ester products is established. However, if potassium hydroxide in water or methanol is used the half-esters of the less stable isomers may be obtained as the major initial product.

The Favorskii-type rearrangement of the four bromo keto esters 89, 92, 93, and 96 was examined under a variety of conditions. A concerted

mechanism provides the best fit for the observed reaction products and is preferred over the cyclopropanone intermediate since the latter mechanism does not explain why the less stable isomer should occur as the major product in the initial phase of the rearrangement.

EXPERIMENTAL

An Aerograph A-700 Autoprep unit was used for gas chromatography. Unless otherwise stated the 10' x ¼" column used for analytical gas chromatography was packed with acid-washed Chromosorb W (60-80 mesh) coated with LAC 886. The column temperature was usually 180°. Infrared spectra were obtained with a Beckman IR-5A spectrometer; the nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal standard (δ=0) and carbon tetrachloride as the solvent. Melting points were obtained in capillary tubes and are uncorrected. Thin layer chromatograms (TLC) were made on glass plated coated with a 5μ layer of silica gel.

Preparation of Methyl 2-Oxocyclohexanecarboxylate (139).

A solution of 49g. (0.5 moles) of cyclohexanone in 100 ml. of anhydrous dioxane was added dropwise to a well stirred mixture of 25 g. (1 mole) of sodium hydride (obtained from an oil dispersion which contained 54% sodium hydride) in 400 ml. of anhydrous dioxane. The reaction temperature was kept at 80 to 85°. After about half of the ketone had been added the solution became very viscous and developed a yellow color. The total addition time was 2 hours and the viscous solution was stirred for an additional hour. The reaction mixture was cooled with an ice bath, and concentrated acetic acid was added slowly and

cautiously. The reaction temperature was not allowed to raise above 50°. An emulsion formed during the addition of acetic acid which disappeared when most of the sodium hydride was decomposed. After sodium hydride had been destroyed, the excess acetic acid was neutralized with a saturated solution of sodium carbonate, washed with distilled water until neutral to litmus paper and extracted five times with 100-ml. portions of ether. The ether layers were combined, dried over anhydrous magnesium sulfate, filtered, evaporated under vacuum, and distilled to yield 55 g. (70%) of a colorless oil, b.p. 55°/0.12 mm. The n.m.r. spectrum in benzene showed a singlet at 3.5δ (3 protons), multiplet at 2.15δ (4 protons), multiplet at 1.4δ (5 protons). Its infrared and ultraviolet spectra showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1750, 1725, 1665, 1630, 1440, 1360, 1325, 1300, 1260, 1195, 1175, 1085, 1065, 980 cm^{-1} and $\nu_{max}^{CH_3OH}$ 255 mμ ($\log \varepsilon = 3.94$). The compound was recrystallized three times from chilled n-hexane and once from methanol to give colorless crystals melting at 12°.

Preparation of Methyl (+)3-Methyl-2-oxocyclohexanecarboxylate (141).

The procedure described for the preparation of methyl 2-oxocyclohexanecarboxylate was used. The yield of 141, b.p. 75°/2 mm., after distillation was 75%. The melting point after three recrystallizations from n-hexane at 0° and two recrystallizations from methanol was 40.5-41.5°; lit. value 22°.[30] $\lambda_{max}^{CH_3OH}$ 255 mμ ($\log \varepsilon = 3.8$); $(\alpha)_D^{23°}$ 101.5° (c 0.5%, $CHCl_3$). The n.m.r. spectrum in CCl_4 showed a singlet at 3.75δ (3 protons) and a doublet at 0.95δ (J = 6 c.p.s., 3 protons). Its infrared spectrum showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1745, 1725, 1670, 1620, 1440, 1360, 1280, 1220, 1160, 1090, 1040 cm^{-1}.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51%; H, 8.29%. Found: C, 63.93%; H, 8.11%.

Preparation of Methyl 5-t-Butyl-2-oxocyclohexanecarboxylate (143).

The procedure used in the preparation of 141 was followed. A yield of 47% was obtained for 143 boiling at 95-105°/1 mm.; $\lambda_{max}^{CH_3OH}$ 255 mμ ($\log\varepsilon = 4.03$). The n.m.r. spectrum of a neat sample of 143 showed a singlet at 3.5 δ (3 protons) and a singlet at 0.8δ (9 protons). Its infrared spectrum showed ν_{max}^{film} 2950, 2900, 1725, 1650, 1610, 1440, 1360, 1280, 1220, 1100, 1090, 1065, 830 cm^{-1}. Attempts to crystallize the compound failed.

Preparation of Methyl 4-t-Butyl-2-oxocyclohexanecarboxylate (145).

The procedure described for 141 was followed. The keto ester 145 boiling at 100°/1 mm. was obtained in 54% yield with a melting point of 59° after recrystallization from methanol. The n.m.r. spectrum in CCl_4 showed a singlet at 3.75δ (3 protons) and a singlet at 0.95δ (9 protons). $\lambda_{max}^{CH_3OH}$ 260μ ($\log\varepsilon = 4.2$). Its infrared spectrum showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1670, 1625, 1440, 1365, 1335, 1280, 1250, 1220, 1110, 1085, 1065, 1015, 890 cm^{-1}.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89%; H, 9.50%. Found: C, 67.66%; H, 9.52%.

Hydrogenation of 3-t-Butylphenol (157) to cis- and trans-3-t-Butylcyclohexanol (159a, 159b).

A 10-g. (0.06 moles) sample of 3-t-butylphenol was added to a 100-ml. thick-walled centrifuge tube, 75 ml. of methanol, and 2.3 g. of

rhodium sesquioxide. The mixture was placed in a Parr apparatus, flushed several times with hydrogen and shaken with added hydrogen at 50 lbs/sq. in. The hydrogen uptake stopped after two hours but shaking was continued for an additional 18 hours at which time the centrifuge tube was removed and spun at 1000 r.p.m., the supernatant decanted, and the catalyst washed with methanol. The methanol extracts were combined and concentrated under vacuum yielding 8 g. (80%) of a colorless oil. This oil was analyzed by gas chromatography, which showed three peaks. The first peak was characterized as starting material by mixed injection with an authentic sample. The other peaks were separated on a 45' x 3/8" LAC 886 column (column temperature of 150° and a flow rate of 80 lbs./sq in.). Two solid compounds were isolated, m.p. 60° and 40°. These were identified through their melting points as trans- and cis-3-t-butylcyclohexanol (159a, 159b).[50] The trans-isomer 159a appeared on the gas chromatogram first and the ratio of 159a:159b was 71:29.

Preparation of 3-t-Butylcyclohexanone (144) from 3-t-Butylcyclohexanol (159a, 159b).[51]

A solution of oxidizing reagent prepared by the addition of 133 g. of chromic oxide to 115 ml. of concentrated sulfuric acid and 385 ml. of water was added dropwise to 4.5 g. (0.03 moles) of the epimeric alcohols 159a and 159b. The reaction temperature was not allowed to rise above 40°. The chromic acid solution was added until a brown coloration persisted for more than 20 minutes. The solution was stirred an additional 0.5 hours. Isopropyl alcohol was added to destroy the excess oxidizing agent. A 1-ml. sample was removed and extracted with ether, dried over anhydrous magnesium sulfate, filtered, and evaporated

for gas chromatographic analysis. No starting alcohols were found. Only one peak was observed, which was attributed to the ketone 144. The main reaction mixture was processed by adding an excess of solid sodium bicarbonate, extracting with three 100-ml. portions of ether which were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to give 4.5 g. (95%) yield of the ketone 144, b.p. 60-65°/0.3 mm. The n.m.r. spectrum of a neat sample showed a singlet at 0.95δ (9 protons). The infrared spectrum showed ν_{max}^{film} 2950, 2900, 1720, 1480, 1425, 1375, 1240, 1175 cm^{-1}.

Preparation of Methyl 3-Bromo-2-oxocyclohexanecarboxylate (89) from Methyl 2-Oxocyclohexanecarboxylate (139).

To a well stirred solution containing 25 g. (0.15 moles) of methyl 2-oxocyclohexanecarboxylate (139) in 50 ml. of anhydrous ether at ice bath temperatures was added dropwise over a period of 1 hour 24 g. (0.15 moles) of liquid bromine. The solution was allowed to stir for an additional hour, and then neutralized by pouring into a saturated solution of sodium bicarbonate. The solution was extracted with ether and the combined extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 25 g. (67%) of methyl 3-bromo-2-oxocyclohexanecarboxylate (89). Only one spot was observed when 89 was tested for purity with thin layer chromatography with benzene as the moving phase. The n.m.r. spectrum of a neat sample showed a singlet at 12.1δ (1 proton), multiplet at 4.75δ (1 proton), singlet at 3.8δ (3 protons). Its infrared and ultraviolet spectra showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1750, 1670, 1620, 1440, 1360, 1330, 1290, 1260, 1210, 1190, 1180, 1400, 1100, 1065, 1045, 985, 960, 900 cm^{-1}, and ν_{max}^{film} 875, 860,

800, 710 cm^{-1} and $\lambda_{max}^{CHCl_3}$ 267μ (log ε = 4.026).

Preparation of Methyl 3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (92) from Methyl 4-Methyl-2-oxocyclohexanecarboxylate (141).

By the above procedure, 141 (25 g., 0.15 moles) was brominated to yield 92 (36 g., 99%). The n.m.r. spectrum in CCl_4 showed a singlet at 12.0 δ (0.6 protons), singlet at 12.2 δ (0.4 protons), doublet at 4.6 δ (0.5 protons), doublet at 4.32δ (0.5 protons), singlet at 3.75δ (3 protons), doublet at 1.09δ (3 protons). Its infrared spectrum showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1735, 1665, 1625, 1440, 1380, 1360, 1320, 1280, 1230, 1190, 1160, 1110 cm^{-1}. The doublet at 4.6δ and 4.32δ and the singlet at 12.0δ and 12.2δ indicate that 92 is a mixture of two isomers with axial and equatorial halogen.

Preparation of Methyl 3-Bromo-5-t-butyl-2-oxocyclohexanecarboxylate (93) from Methyl 5-t-Butyl-2-oxocyclohexanecarboxylate (143).

The above procedure was used for the bromination of 143 (10 g., 0.05 moles) to give 12.7 g. (94%) of 93 which melted at 54.5-55° after recrystallization from n-hexane. The n.m.r. spectrum of 93 in CCl_4 showed a singlet at 12δ (1 proton), doublet at 4.8δ (1 proton, J = 3 c.p.s.), singlet at 3.8δ (3 protons), singlet at 0.95δ (9 protons). Its infrared and ultraviolet spectra showed $\nu_{max}^{CCl_4}$ 2950, 2900, 1670, 1620, 1440, 1380, 1340, 1320, 1275, 1240, 1220, 1200, 1115, 1040, 1010, 945 cm^{-1}; ν_{max}^{film} 870, 800, 705 cm^{-1} and $\lambda_{max}^{CHCl_3}$ 268μ (log ε = 4.21).

Anal. Calcd. for $C_{12}H_{19}BrO_3$: C, 49.5%; H, 6.5%. Found: C, 49.44%; H, 6.66%.

Preparation of Methyl 3-Bromo-4-t-butyl-2-oxocyclohexanecarboxylate (96) from Methyl 4-t-Butyl-2-oxocyclohexanecarboxylate (145).

The above procedure was applied to 145 to give a 95% yield of 96. The n.m.r. spectrum of 96 in CCl_4 showed a doublet at 4.5δ, singlet at 3.8δ, singlet at 1.0δ, doublet at 0.95δ. Its infrared spectrum showed ν_{max}^{film} 2950, 2900, 1670, 1620, 1430, 1325, 1280, 1220, 1190, 1130, 1080, 1030, 980, 950, 900, 870, 805 (Strong), 765, 725 cm^{-1}.

The Favorskii-type Rearrangement of Methyl 3-Bromo-2-oxocyclohexanecarboxylate (89) to trans- and cis-Cyclopentane-1,2-dicarboxylic Acid (90a, 91a) at Room Temperature.

A. With Aqueous Potassium Hydroxide. To a well stirred solution of 10 g. (0.18 moles) of potassium hydroxide in 50 ml. of distilled water was added 10 g. (0.045 moles) of 89. The temperature of the reaction rose sharply and a deep yellow, sirupy solution was obtained. Immediately after 89 was added to the basic solution a 1-ml. sample was removed with a syringe. This was considered to be zero time and other samples were removed periodically. The samples were neutralized immediately with 10 ml. of a 5% solution of hydrochloric acid and extracted several times with ether, and the ether extracts were dried over anhydrous magnesium sulfate, filtered and then added to an ethereal solution of diazomethane. The excess diazomethane was allowed to evaporate in the hood. The remaining solution was dried with magnesium sulfate, filtered, and each sample was analyzed by gas chromatography for the ratio of dimethyl cis- and trans-cyclopentane-1,2-dicarboxylate (90b, 91b). Authentic samples of dimethyl cis- and trans-cyclopentane-1,2-dicarboxylates[45] were used to identify the cis- and trans-isomers

in the gas chromatogram. The order of elution from the gas chromatography column was the trans-isomer followed by the cis-isomer. A third unidentified component with longer retention time than the cis-isomer has been observed. A sample of this unknown compound has been obtained by preparative gas chromatography and its infrared spectrum showed ν_{max}^{film} 2950, 2900, 1730, 1650, 1430, 1340, 1270, 1200, 1150, 1090, 1020, 950, 770, 745 cm^{-1}. The ratio of trans- to cis-isomer with respect to time is tabulated in Table II. The total yield of trans- and cis-acids 90a and 91a was 8.35 g. (57%).

B. With Methanolic Potassium Hydroxide. To a well stirred solution of 50 ml. of methanol and 5 g. (0.09 moles) of potassium hydroxide was added 5 g. (0.023 moles) of 89. The temperature rose sharply and a deep yellow color was observed as in part A. Samples were taken as in part A. The ratio of trans- to cis-isomers with respect to time is tabulated in Table II. The total overall yield was 2.5 g. (70%).

C. With Sodium Methoxide in Methanol. To a well stirred solution of 23 g. (1.0 moles) of sodium in 150 ml. of methanol was added in one portion 70.8 g. (0.3 moles) of 89. Samples (1-ml.) were removed periodically and neutralized with 10 ml. of a 5% solution of hydrochloric acid. The samples were extracted with ether, dried over anhydrous magnesium sulfate and analyzed by gas chromatography for the ratio of trans- to cis-isomers as in part A. The results are tabulated in Table II. The total yield of methyl trans- and cis-cyclopentane-1,2-dicarboxylate (90b, 91b) was 27 g. (48%).

The Preparation of trans,trans-; trans,cis-; cis,trans; and cis,cis-3-methylcyclopentane-1,2-dicarboxylic Acid and Methyl Esters via the Favorskii-type Rearrangement of 92.

By procedures A, B, and C, 92 was rearranged to the acids 81a, 82a, 83a, 84a, or the esters 81b, 82b, 83b, 84b. The acids were converted to methyl esters and analyzed by gas chromatography. The order of elution from the gas chromatography column was 81b, 82b, 83b, and 84b. The results are tabulated in Table III. The average total yield was 44%. Authentic samples of the four methyl esters 81b, 82b, 83b, and 84b were used to identify the various isomers in the gas chromatogram.[45]

Preparation of trans,trans- and cis,trans-4-t-Butylcyclopentane-1,2-dicarboxylic Acids (94a, 95a) and their Methyl Esters 94b and 95b via the Favorskii-type Rearrangement of 93.

Procedures A, B, and C were used to rearrange 93 to the acids 94a and 95a or the esters 94b and 95b. The acids were analyzed as their methyl esters as described above. The results are tabulated in Table IV. Authentic samples of 94b and 95b obtained by a synthetic route described below were used to identify these isomers in the gas chromatogram. The order of elution from the gas chromatography column was trans,trans- followed by cis,trans-isomers. A third component was also observed and is under investigation.

Preparation of trans,trans-3-t-Butylcyclopentane-1,2-dicarboxylic Acid (97a) and its Methyl Ester 97b via the Favorskii-type Rearrangement of 96.

Procedures A, B, and C for the Favorskii-type rearrangement of 89 were used to rearrange 96 to 97a or its methyl ester 97b. Only trace quantities of other isomers were detected. The n.m.r. spectrum of 97a in CCl_4 showed a singlet at 11δ, a doublet at 3.7δ (J = 1 c.p.s.), doublet at 0.85δ (J = 2 c.p.s.). The n.m.r. spectrum of 97b in CCl_4 showed a singlet at 3.7δ (6 protons) and a singlet at 0.85δ (9 protons). The boiling point of 97b was 95°/0.45 mm. The infrared spectrum of 97a showed ν_{max}^{film} 3300 (broad), 2950, 2900, 1710 cm^{-1}. The infrared spectrum of 97b showed ν_{max}^{film} 2950, 2900, 1735, 1450, 1380, 1215, 1070 cm^{-1}.

Preparation of cis,trans-4-t-Butylcyclopentane-1,2-dicarboxylic Acid (95a) and Its Methyl Ester 95b From Methyl 3-Bromo-5-t-butylcyclohexanecarboxylate (93).

To a well stirred mixture of 20 g. (0.35 moles) of potassium hydroxide in 100 ml. of 95% ethanol was added dropwise 34.5 g. (0.12 moles) of 93. After all of 93 was added the solution was refluxed for 2 hours, cooled, acidified with dilute hydrochloric acid, and extracted with five 100-ml. portions of ether which were combined, dried over anhydrous magnesium sulfate, filtered, and allowed to stand for several hours. A solid precipitated out of the ethereal solution. It was filtered to yield a 1-g. sample of 95a, m.p. 164° after recrystallization from a mixture of benzene and ether. Decomposition of 95a with evolution of gas was observed on melting. This was attributed to the formation of the cis-anhydride. The infrared spectrum of 95a showed ν_{max}^{KBr} 2950, 2900, 1700, 1410, 1220 cm^{-1}.

The purity of the cis,trans-isomer 95a was determined by gas

chromatographic analysis of the corresponding methyl ester 95b prepared by the addition of an ethereal solution of diazomethane to 95a. The boiling point of 95b was 110°/0.5 mm. The n.m.r. spectrum of a neat sample showed a singlet at 3.68δ (6 protons), multiplet at 2.95δ (2 protons), singlet at 0.85δ (9 protons). Its infrared spectrum showed ν_{max}^{film} 2950, 2900, 1730, 1440, 1370, 1220, 1175, 1090, 1030 cm^{-1}.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44%; H, 9.15%. Found: C, 64.14%; H, 9.27%.

Removal of the ether from the initial reaction mixture yielded 23 g. (82%) of a mixture of cis,trans- and trans,trans-isomers 95a and 94a and another unknown compound which is being studied.

Preparation of Methyl trans,trans-4-t-Butylcyclopentane-1,2-dicarboxylate (94b) and the Corresponding Acid 94a.

The dimethyl ester 94b can be obtained directly from the Favorskii-type rearrangement of 93 with sodium methoxide as base. The boiling point of 94b was 130°/2 mm. The n.m.r. spectrum of a neat sample showed a singlet at 3.6δ (6 protons), multiplet at 3.1δ (2 protons), multiplet at 1.85δ (4 protons), and a singlet at 0.85δ (9 protons). Its infrared spectrum showed ν_{max}^{film} 2950, 2900, 1730, 1430, 1475, 1200, 1170 cm^{-1}.

Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44%; H, 9.15%. Found: C, 64.17%; H, 9.08.

A 5-g. sample of methyl trans,trans-4-t-butylcyclopentane-1,2-dicarboxylate (94b) was added to 5 g. (0.09 moles) of potassium hydroxide in 50 ml. of water. The solution was refluxed for 2 hours, cooled,

neutralized with dilute hydrochloric acid, and extracted with three 100-ml. portions of ether, which were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum to yield 3.5 g. (80%) of 94a, m.p. 192°. Its infrared spectrum showed ν_{max}^{KBr} 2950, 2900, 1700, 1410, 1300, 1225, 1200, 930 cm^{-1}.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66%; H, 8.47%. Found: C, 61.38%; H, 8.35%.

Preparation of Methyl Hydrogen cis- and trans-Cyclopentane-1,2-dicarboxylate Acids From Methyl 3-Bromo-2-oxocyclohexanecarboxylate (89).

A 14-g. (0.056 moles) sample of 89 was added at room temperature in one portion to a well stirred solution of 5 g. (0.09 moles) of potassium hydroxide in 50 ml. of distilled water. The solution was shaken vigorously for 0.5 minutes. A sharp rise in temperature was observed. The solution was then neutralized with dilute hydrochloric acid, extracted with three 100-ml. portions of ether, which were combined and extracted with a saturated solution of sodium bicarbonate. The sodium bicarbonate solution was extracted with ether, then neutralized with dilute hydrochloric acid and extracted with ether. The final ether extract was dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 3 g. (31%) of methyl hydrogen cis- and trans-cyclopentane-1,2-dicarboxylate. The n.m.r. spectrum in CCl_4 showed a singlet at 10.3δ (1 proton), singlet at 3.75δ (0.31 protons), singlet at 3.7δ (0.69 protons), multiplet at 3.15δ (2 protons), multiplet at 2δ (6 protons). The infrared spectrum showed ν_{max}^{film} 2950 (broad), 1700 (broad), 1425, 1200 cm^{-1}. The half-ester mixture was

added to an ethereal solution of diazomethane and the resulting dimethyl esters were compared by gas chromatography with authentic samples of dimethyl trans- and cis-cyclopentane-1,2-dicarboxylate (90b, 91b). The dimethyl esters were found to be a mixture of 36% trans- and 64% cis-isomer which is in agreement with the n.m.r. analysis. The methoxy carbonyl signals at 3.7 for the cis-half ester and 3.75 for the trans-half ester are in a ratio of 31:69 which is in good agreement with the ratio derived by gas chromatography.

Preparation of 1-Methyl Hydrogen 3-Methylcyclopentane-1,2-dicarboxylate From Methyl (+)3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (92).

A 5-g. (0.02 moles) sample of 92 was added to 50 ml. of a 10% solution of aqueous potassium hydroxide. The solution was shaken for 0.5 minutes, then quenched with 5% hydrochloric acid. The solution was basified with a saturated solution of sodium bicarbonate and extracted with ether. The ether solution was set aside and designated as the neutral fraction. The basic fraction was neutralized with 5% hydrochloric acid and extracted with five 50-ml. portions of ether which were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to yield 2 g. (54%) of four isomers of 1-methyl hydrogen 3-methylcyclopentane-1,2-dicarboxylate. The n.m.r. spectrum in CCl_4 showed a singlet at 11.5δ (1 proton), singlets at 3.65δ and 3.6δ (3 protons), multiplet at 1.1δ (3 protons). Its infrared spectrum showed ν_{max}^{film} 2950 (broad), 1730, 1700, 1445, 1200 cm^{-1}.

The half-ester mixture was added to an ethereal solution of diazomethane and the resulting dimethyl esters were compared by gas chromatography with authentic samples of 81b, 82b, 83b, 84b.[45] The ratio

of isomers 81b, 82b, 83b, 84b from the half-esters was found to be 16:6:29:49 respectively.

A 1.9-g. sample of neutral material was obtained. The infrared spectrum showed the presence of a β-keto ester. The infrared spectrum showed ν_{max}^{film} 2950, 2900, 1725, 1650, 1620, 1440, 1275, 1220 cm^{-1}. However, the n.m.r. spectrum did not show the presence of an enolic proton which was present in the starting material. The n.m.r. spectrum in CCl_4 showed a multiplet at 3.88 and a multiplet at 1.18. The neutral fraction was steam distilled yielding 0.8 g. of steam distillate and 0.3 g. of residue. The spectra of the product obtained from the steam distillate was the same as that of the neutral fraction above.

Preparation of (±)1-Ethyl Hydrogen 3-Methylcyclopentane-1,2-dicarboxylate From Ethyl (±)3-Bromo-4-methyl-2-oxocyclohexanecarboxylate (148b).

By the above procedure 14.3 g. (0.054 moles) of 148a was rearranged to (±)ethyl hydrogen trans,trans-, trans,cis-, cis,trans-, cis,cis-3-methylcyclopentane-1,2-dicarboxylate (5 g., 46%). The n.m.r. spectrum in CCl_4 showed a singlet at 10.58 (1 proton), quartet at 4.18 (0.5 protons, J = 7 c.p.s.), quarter at 3.458 (0.5 protons, J = 7 c.p.s.), multiplet at 1.28 (6 protons). Its infrared spectrum showed ν_{max}^{film} 2950 (broad), 1725, 1700, 1445, 1365, 1300, 1200 cm^{-1}.

The half-ester was added to an ethereal solution of diazomethane. The resulting methyl ethyl esters were analyzed by gas phase chromatography. The chromatogram showed 5 peaks in the ratio 10:6:29:50:5 which were due to the (±)1-ethyl methyl trans,trans-, trans,cis-, cis,trans-, cis,cis-3-methylcyclopentane-1,2-dicarboxylate and an unknown substance which is being investigated. The ratio of (±)1-ethyl

methyl trans,trans-, trans,cis-, cis,trans-, and cis,cis-3-methylcyclopentane-1,2-dicarboxylates is 11:6:30:53, which is the same within experimental error as the ratio of isomers obtained from methyl (+)3-bromo-4-methyl-2-oxocyclohexanecarboxylate given above.

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