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A Study Of The Dual Mechanism Of The Favorskii Rearrangement

Richard Donald Mortimer

A STUDY OF THE DUAL MECHANISM OF THE FAVORSKII REARRANGEMENT

by

Richard Donald Mortimer

Department of Chemistry

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Abstract

The rearrangement of α-haloketones to carboxylic acid derivatives can occur by either of two different mechanisms: the cyclopropanone mechanism or the semibenzilic mechanism. In at least one system, 1-bromobicyclo [5.3.1] undecan-11-one, both mechanisms can be observed together. This study was concerned with the search for other systems with α′-protons which might rearrange by the semibenzilic pathway in order to show that it is more general than previously thought. Three systems were examined: α-chlorocyclopentanone, α-chlorodicyclohexyl ketone and α-bromocyclopropyl alkyl (aryl) ketones.

The rearrangement of α-chlorocyclopentanone has been attempted in the past. Then, as now, it proved to be unsuccessful. Side reactions are much faster than the rearrangement. With dilute methoxide ion, α-methoxycyclopentanone is cleanly produced. As an extension of this system, the ethylene ketal of α-bromocyclopentanone was observed to react with silver ion by a 1,2-oxygen shift rather than ring contraction.

Rearrangement of α-chlorodicyclohexyl ketone to cyclohexyl cyclohexane carboxylate is a known reaction. By synthesizing this chloroketone with deuterium label on the ring bearing the chlorine atom, it was shown that the reaction occurs entirely by the cyclopropanone mechanism.

A general synthesis of bromocyclopropyl ketones was developed. When α-bromocyclopropyl methyl ketone was treated with concentrated base, a single Favorskii acid was isolated. Since the α′-protons are completely exchanged in a deuterated medium, a semibenzilic mechanism is proposed. When a cyclopropyl or benzene ring replaced the methyl

group, products were isolated which indicate that an oxirane intermediate is formed. No Favorskii acids were isolated from these two systems and an explanation is offered.

Acknowledgement

I would like to acknowledge the guidance and support of Dr. E. W. Warnhoff throughout my graduate and undergraduate years. His patience is phenomenal.

A special thank you to Anne King for her proof-reading and typing. Finally, to my many friends and colleagues, already scattered around the world, many thanks for some fine years.

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CHAPTER 1

GENERAL REVIEW

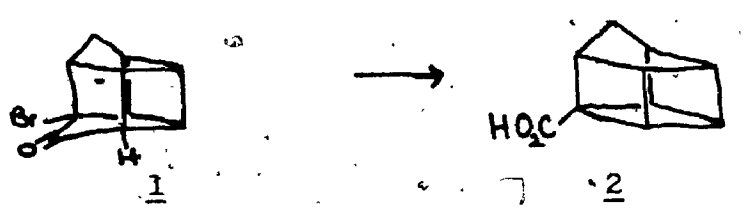
Introduction

The Favorskii rearrangement refers to that reaction in which an α-halo ketone undergoes a change in the carbon skeleton to yield a carboxylic acid or a carboxylic acid derivative. Although this rearrangement is generally induced by base, it is known to occur in several cases by reaction with strong, neutral nucleophiles or silver ion.

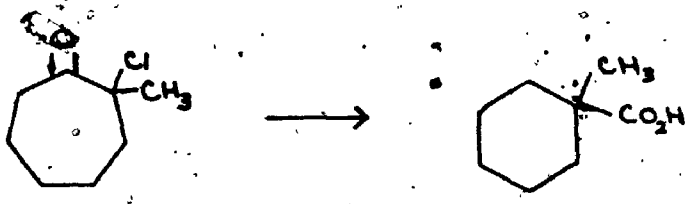
The overall change is the migration of the α'-carbon atom from the carbonyl function to the α-carbon atom with loss of the halide and modification of the ketone group. In this respect, the Favorskii reaction is related to those base-induced migrations observed in halohydrins, α-diketones and α-ketols. Although the reaction is usually observed with halo ketones, because they are more easily prepared, the rearrangement has been observed with other leaving groups. A tosyl group or an epoxide ring at the α-position are two which have been used successfully.

Since its discovery as a general reaction in the late nineteenth century,[1] the Favorskii rearrangement has proven to be a useful synthetic reaction and there are several reviews which testify to this.[2,3,4,5]

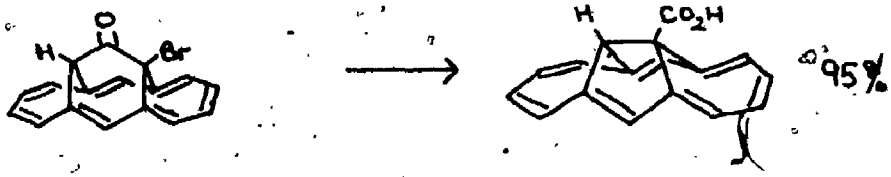
The following are a few examples which illustrate its utility:



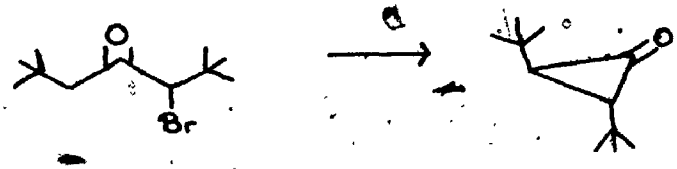
1 → 2 100% Ref. 6



3 → 4 41% Ref. 7



5 → 6 95% Ref. 8

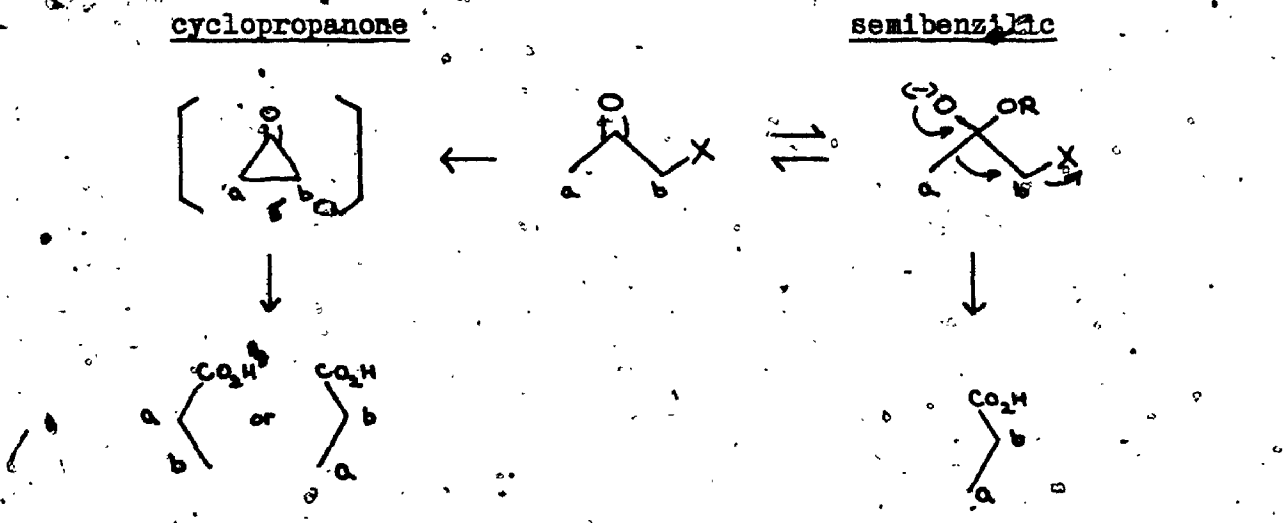


7 → 8 20-40% Ref. 9

The last example is of interest because it is not the expected Favorskii product. The trans-1,2-di-t-butylcyclopropanone 8 is a remarkably stable representative of a group of compounds which are thought to be intermediates in the Favorskii reaction. In fact, it is the only such intermediate which has been isolated under the basic conditions of the rearrangement. If only one intermediate has ever been isolated, what evidence is there that this is a general feature

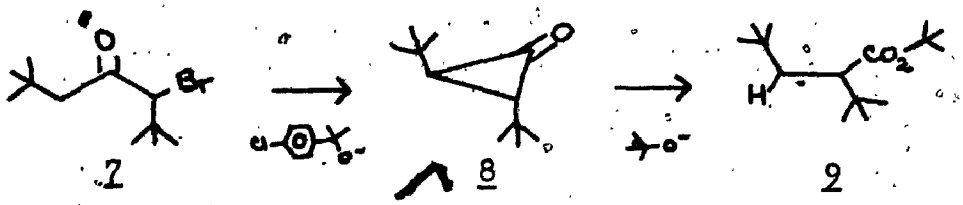
rather than an exceptional one? This leads to the long-studied question of how the reaction occurs.

The evidence gathered since Favorskii's time and especially in the last twenty-five years has substantiated two distinct mechanisms: the "symmetrical" or "cyclopropanone" mechanism and the "unsymmetrical" or "semibenzilic" mechanism. Schematically, they are as follows:



The Cyclopropanone Mechanism

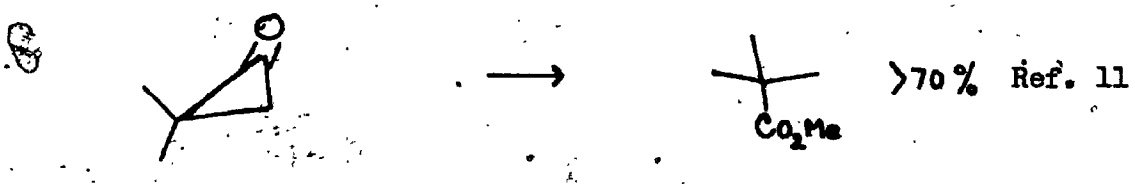
When α-bromodineopentyl ketone 7 was treated with one equivalent of potassium t-butoxide or an excess of the more hindered alkoxide of p-chlorophenyldimethyl carbinol, the cyclopropanone 8 was isolated. However, even a slight excess of t-butoxide produced the expected Favorskii ester.[9] At the same time, the growth and decline of a band in the ir spectrum (1822cm^{-1}) was observed and attributed to the carbonyl function of the cyclopropanone intermediate. Furthermore, when



7 8 9

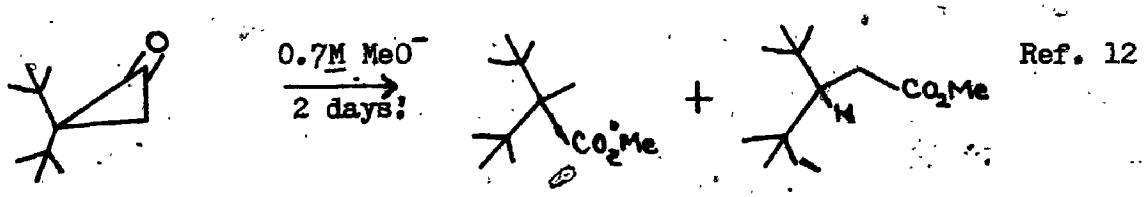
Ref. 10

the isolated cyclopropanone was treated with potassium t-butoxide, the same Favorskii ester was produced.[10] That a cyclopropanone will cleave in this manner was demonstrated earlier by Turro and Hammond who successfully prepared 2,2-dimethylcyclopropanone 10 by the addition of diazomethane to dimethylketene.[11] On treatment with methoxide in methanol this cyclopropanone was cleaved to give a single ester 11. Crandall



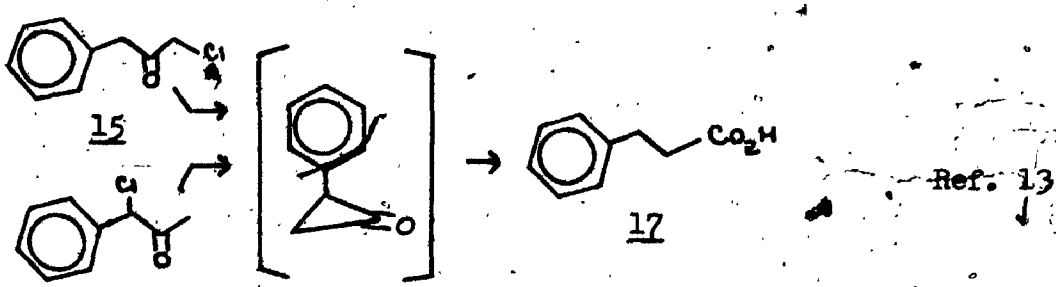
10 11

and Machleder demonstrated the cleavage of a cyclopropanone by base to give a carboxylic acid derivative.[12] They treated 1,1-di-t-butylcyclopropanone 12 with methoxide in refluxing methanol and obtained a mixture of two esters.



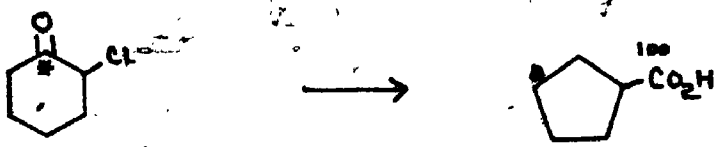
12 13 14

The results of these experiments, then, provide strong support for the cyclopropanone mechanism which had been suggested as early as 1894[2] but not supported experimentally until fifty years later. In 1944 McPhee and Klingsberg observed the same Favorskii product from both



15 16 17

isomeric chlorides of benzyl methyl ketone.[13] Then, Loftfield found that 2-chlorocyclohexanone 18, labelled with carbon-14 at the 1- and 2-positions, reacted with base to give cyclopentane carboxylic acid 19 with the carbon isotope distributed between the α- and β-positions.[14]



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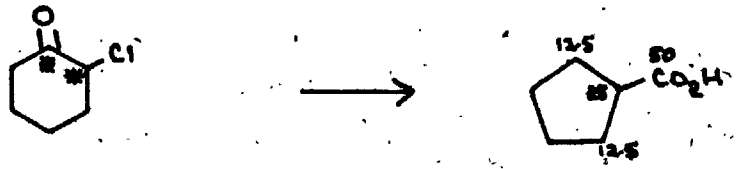
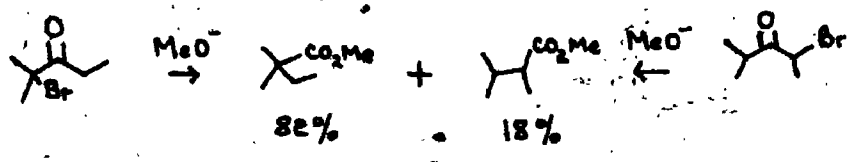


1:2 = 50:50

18 19

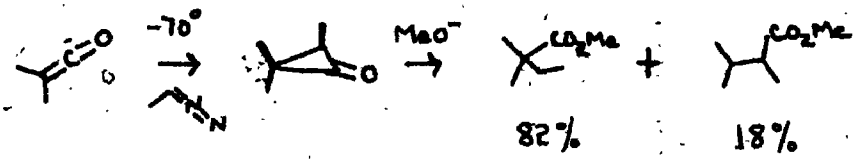
When the reaction was done with less than one equivalent of base, the recovered chloroketone showed no change in the labelling distribution, thereby excluding the possibility of halogen migration from one α-position to the other prior to rearrangement. Loftfield concluded that the α- and α'-positions must have become equivalent in some other manner, thus providing experimental proof for a symmetrical stage in the reaction consistent with a cyclopropanone intermediate.

Recently, Turro and Rappe observed that both the isomeric bromides of isopropyl ethyl ketone not only gave the same esters but also the same ratio of esters. Furthermore, they found that the same ratio was produced with 1,1,2-trimethylcyclopropanone 24, the postulated intermediate, under the same conditions.[15]



Ref. 15

20 22 23 21



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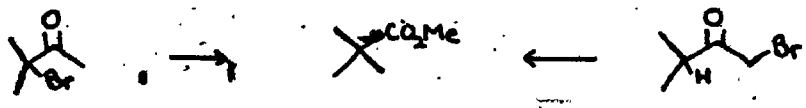
24 22 23

Similarly, the isomeric bromides of isopropyl methyl ketone gave a Favorskii product, which was the same as the cleavage product of 1,1-dimethylcyclopropanone.[16]



25 11 26

Ref. 16

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The mode of cleavage of the cyclopropanones, with the exception of 1,1-di-t-butylcyclopropanone 12*, appears to be determined by the

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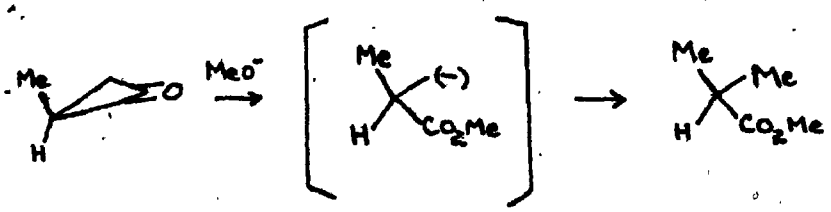
* Although further work is needed in this area, there is evidence that steric factors play a part in the cleavage.[17] It has been suggested that steric compression can lead to cleavage at the most substituted carbon; hence the result with 1,1-di-t-butylcyclopropanone 12[18]. However, opening of 1,1,2-trimethylcyclopropanone 24 with t-butoxide gives > 99% cleavage at the less substituted site, in contrast with methoxide which gives a ratio of 82:18 for 2° vs. 3° cleavage.

stability of the resulting carbanion. A choice between a 1^{o} and a 2^{o} carbanion or a 1^{o} and a 3^{o} carbanion gives a single product due to formation of the primary anion, whereas a choice between a 2^{o} and a 3^{o} carbanion leads to a mixture. For example, cleavage of methylcyclopropanone with methoxide gives only methyl isobutyrate.[19] Formation

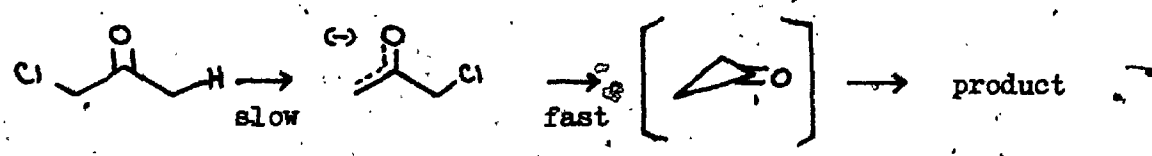


Ref. 19

27 28

of a carbanion as a result of cleavage of a cyclopropanone is an important feature of the cyclopropanone mechanism since cleavage in a deuterated medium would result in incorporation of an atom of deuterium in the final product. This is a distinguishing feature of this pathway since the semibenzilic mechanism involves no carbanion and therefore no deuterium incorporation.*

If a cyclopropanone is involved and the evidence certainly demands it, the question remains as to how this intermediate is formed. Loftfield formulated the process in the following manner:



Subsequent studies have shown that either step may be rate-determining.

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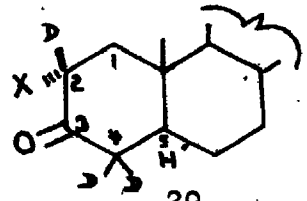
* Excluding deuterium incorporated in the ketone due to reversible enolization prior to reaction.

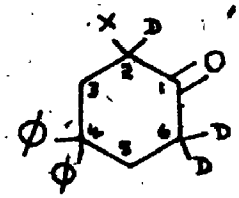
Nace and Olsen studied the reaction of 2α-bromocholestan-3-one-2,4,4-d_3 29 and its chloro-homolog with sodium ethoxide in ethanol. After one half-life of the Favorskii reaction, the recovered bromoketone showed no loss of deuterium at the 4-position and the recovered chloroketone, which has more acidic α'-protons due to the slightly stronger inductive effect of the chlorine atom, showed only slight exchange at the 4-position.[20] On the other hand, Bordwell, et.al., found partial



29

Ref. 20

loss of deuterium in the 6-position of recovered 4,4-diphenyl-2-bromocyclohexanone-2,6,6-d_3 30 after one half-life of the Favorskii reaction in a solution of sodium methoxide in methanol but complete exchange

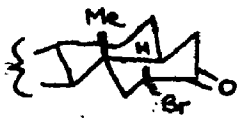


30

Ref. 21

with the chloro-homolog.[21] Furthermore, Nace's observed rate ratio, k_{Br}/k_{Cl}, for ketone 29, was only 6, whereas Bordwell found a rate ratio of 116 for ketone 30. Part of this difference is due to the choice of solvent-base systems, since with ethoxide in ethanol the rate ratio of 116 for ketone 30 fell to 79. Likewise the rate ratio of the 3-halocholestanone 29 system rose to 36 with methoxide in methanol. For 2-bromo- and 2-chloro-4-methyl-cis-4-phenyl cyclohexanone 31, which is sterically analogous to the 3-halocholestanone 30 system, Bordwell found a rate ratio of 52 using methoxide in methanol. In methanol-O-d_1,

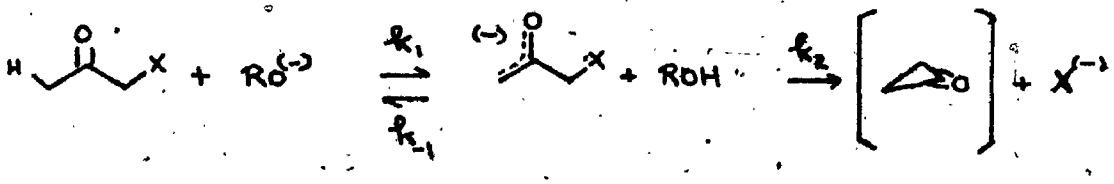
the chloroketone 31 exchanged at least 50% of its α'-protons, whereas the bromoketones showed no exchange. These results show that although



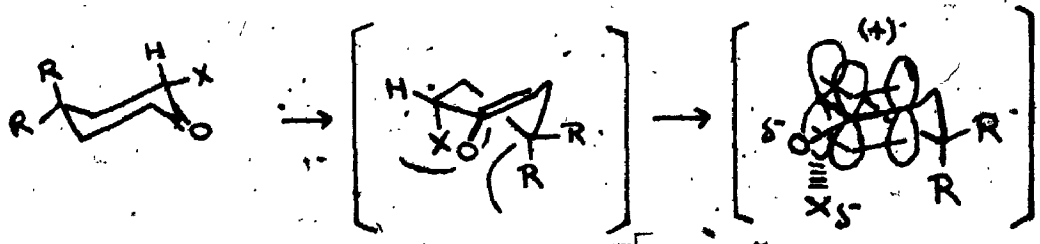
29

31

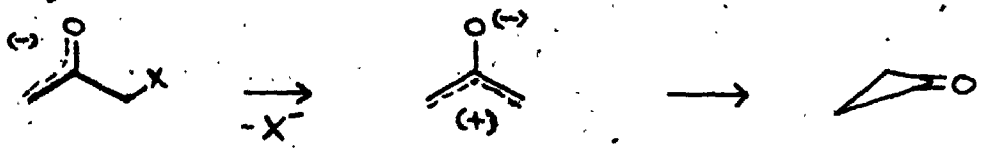
proton removal may be rate determining, it need not be so. A pre-equilibration may occur which depends on the acidity of the solvent, the leaving group and the nature of the substrate.



Bordwell, et al., also noticed a considerable rate reduction (40x) between 2-chlorocyclohexanone 18 and 4,4-diphenylchlorocyclohexanone 30 which was not observed between 2-chlorocyclohexanone 18 and 4-mono-substituted chlorocyclohexanones. Using deuterium exchange rates as a probe, he found no significant differences among any of the three systems.[22] It appeared that only k_2, the rate of loss of halide, was reduced by the axial substituent. Is this because the leaving group must assume an axial position in the transition state in order that the rupturing carbon-halogen bond be parallel with the axes of the π-orbitals of the enolate system?



Loftfield's conception of the ring closure was an S_N2 displacement of the halide by the enolate carbanion; however, Dewar and Burr argued that there was little interaction between the α- and α'-carbons because of the perpendicular orientation of the enolate orbitals relative to the carbon-halogen bond and that considerable driving force would be needed for ring closure.[23] They calculated that the necessary energy would arise from the increase in conjugation energy if the halide was released prior to ring formation to give an oxyallyl species A. The collapse of the oxyallyl species to the cyclopropanone would be sufficiently exothermic to provide its driving force.*



A

On the other hand, Stork and Borowitz[7] felt the chloroenolate could collapse directly to the cyclopropanone and in order to test their hypothesis they prepared the cis and trans forms of 1-acetyl-1-chloro-2-methyl-cyclohexane.[32] If the oxyallyl species were formed, the epimeric chloroketones would give the same acidic product(s). If cyclopropanone formation were conderted, each epimer would give a single acid which would be distinct from the other. In fact, they observed single acids from each epimer with inversion at the halogen position as expected from direct cyclopropanone formation. However, the

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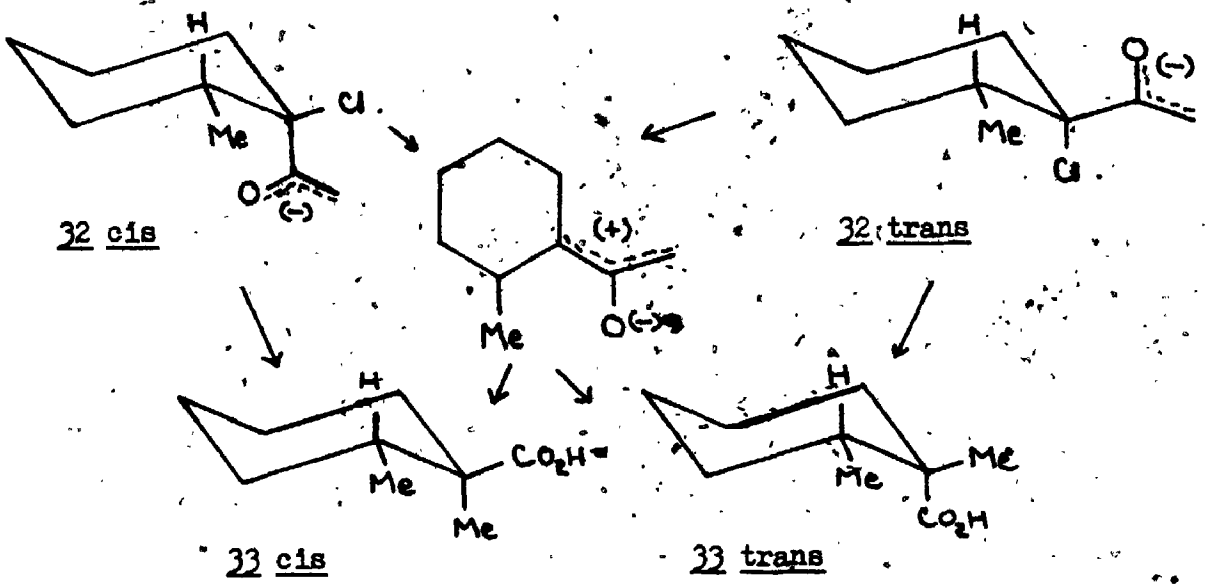
* Recent calculations by INDO and "ab initio" SCF calculations show singlet oxyallyl to be 83 Kcal/mole less stable than cyclopropanone.[24]



solvent system used was benzyloxide in ether. When House and Gilmore repeated the reaction of the cis isomer using methoxide in methanol instead, they found approximately equal amounts of both acids.[25] Only in the aprotic solvent, dimethoxyethane, could they observe formation of the single acid product (95%) due to inversion.* Since there was no evidence for epimerization of the chloroketone or for formation of the isomeric chloroketone due to halogen migration, it was concluded that direct formation of a cyclopropanone occurred in the aprotic medium and oxyallyl formation occurred in the protic medium.

Tchoubar's group also studied the effect of the solvent system on the stereospecificity of this reaction and obtained results similar to those of House and Gilmore.[26,27] With methoxide in t-butanol or dimethylsulfoxide, they found predominantly inversion, 84% and 76% respectively, whereas with methoxide in methanol they obtained only 55% inversion. Moreover, increasing the methoxide concentration from 0.2M

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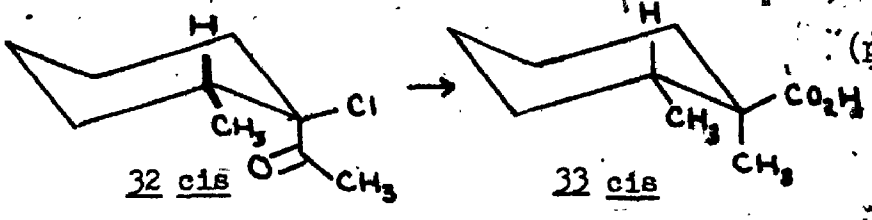
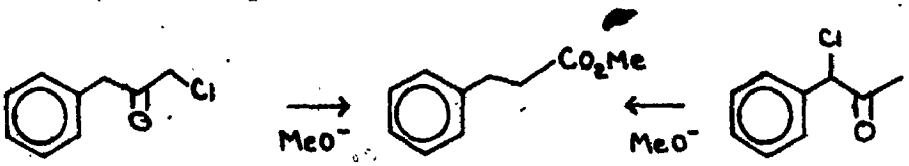
* Methoxide in dimethoxyethane is a heterogeneous system but, when sufficient methanol was added to give homogeneity, the selectivity dropped only slightly (84%).



32 cis → 33 cis (product of inversion)

to 5.0M caused the ratio of inversion to retention to rise from 0.55 to 5.8. The same preference for inversion was observed if the methoxide concentration was maintained at 0.2M and an inert salt (NaI) added instead. The use of a less polar solvent or a high concentration of salt in a polar solvent has the same effect, namely, a preference for the product of inversion. Does this indicate a preference for an S_N2 displacement for cyclopropanone formation? Tchoubar decided that the results in either medium reflected the reduced solvation of the anion. Since in a protic solvent a smaller anion is solvated preferentially to a larger, more delocalized anion because the strength of the hydrogen bond is inversely proportional to the size of the anion, addition of further salt would reduce the solvation of the enolate anion. It seems logical that a less solvated anion would be more reactive and the result of this might be direct formation of a single cyclopropanone in preference to an oxyallyl species.

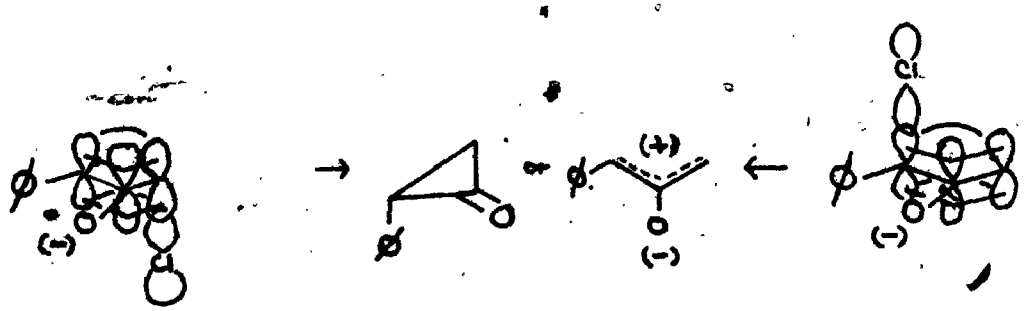
Tchoubar also observed that with 1-chloro-1-acetylcyclohexane 34, an increased salt concentration in methanol produced an increased yield of Favorskii ester (15-75%). Likewise, Bordwell and Scamehorn noted that the addition of $LiClO_4$ (2M) to a 0.05M solution of methoxide in methanol gave an increased yield of Favorskii product (63% from 37%) with the α-chloro-isomers of benzyl methyl ketone.[28,29]



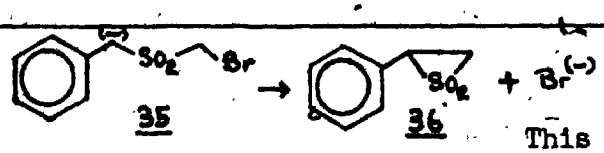
Ref. 28

15 17 16

Since they observed negative rho values (-5)* and almost 80% deuterium incorporation at the α'-position, they concluded that halide loss was the rate determining step and, therefore, interpreted the salt effect as an increase in the ionizing power of the medium. These data suggest that there is a high degree of ionic character in the carbon-halogen bond in the transition state. They do not indicate whether there is an oxyallyl species produced or whether the transition state leads directly to a cyclopropanone. Bordwell suggests π-participation in the following manner:

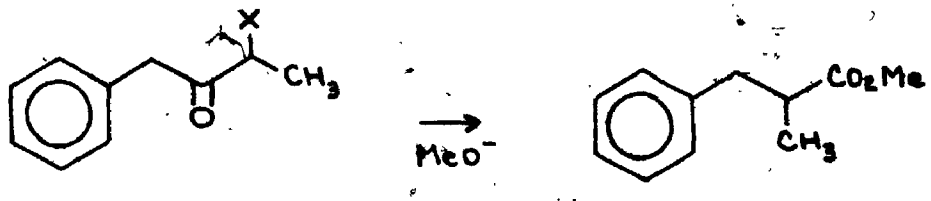


Since they expected a substituent at the α-carbon to have a strong effect on the ionization of the carbon-halogen bond, they examined the 1-haloethyl benzyl ketone 37 system and observed a dramatic change.[30]



35 36

* This reaction also has a negative rho value (-3). Since "it is unlikely that any of the positive charge on carbon released by ionization of the C-Br bond can be delocalized to the aryl group, the high sensitivity of the reaction to substituent effects must then reflect a sensitivity to changes in the nucleophilicity of C-α."[28,29]

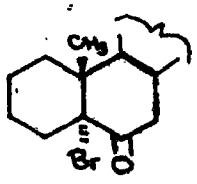


Ref. 30

37 38

The rate increased 250 fold, negligible deuterium was incorporated at the α'-carbon, the rate ratio (k_{Br}/k_{Cl}) was approximately unity, a small positive rho value was measured and no salt effect could be found. The loss of halide was now so fast that enolate formation had become the rate determining step. The methyl group's ability to enhance halide loss again suggests ionic character in the breaking C-X bond.

This leads to the final point of interest in the cyclopropanone mechanism. Does the carbon-halogen bond need a parallel arrangement with the axes of the π-enolate system during its solvolytic step? Bordwell's concept of π-participation most definitely requires a parallel arrangement of orbitals and his explanation for the rate retardation with 4-axial substituents in the cyclohexanone systems also requires an axial halogen such that the carbon-halogen bond is parallel with the axes of the enolate p-orbitals.[29,22] Known systems, illustrated below, in which the halogen is fixed in the axial position suffer



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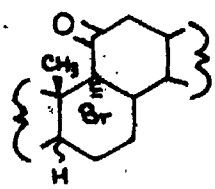
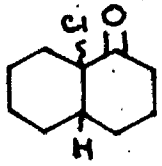
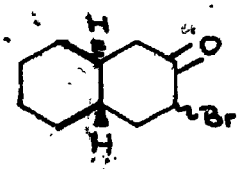


40 cis or trans



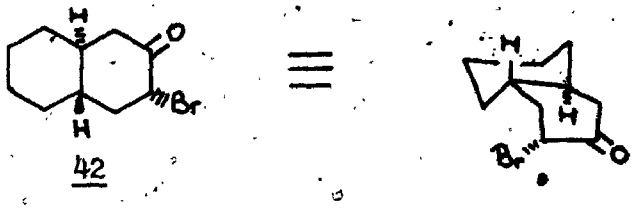
41 cis or trans



42 cis or trans

from a competitive side reaction, methoxy ketone formation, which

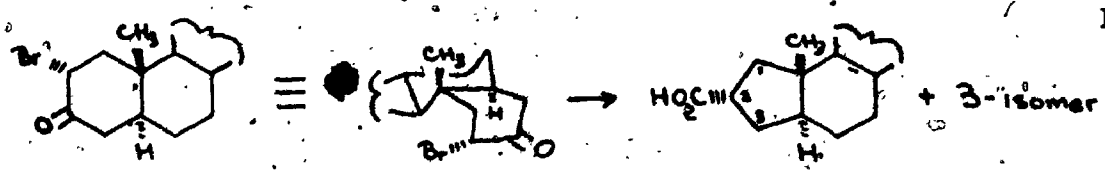
Bordwell has shown to be due to solvolysis of the enol halide. House and Frank noticed that Favorskii acids are formed from both trans- and cis-9-chloro-1-decalones 41 but only in heterogeneous systems where either the solvolysis of enol halide is reduced or the enol concentration is small.[32] In protic media, Smissman, et al., found that only the cis-3-bromo-2-decalone 42 (equatorial Br) gave Favorskii product.[31] The trans-isomer 42 was completely converted to side products. These workers concluded that the axial orientation which would have the parallel arrangement of orbitals was unnecessary. Bordwell disputes this conclusion; instead, he thinks the cis isomer reacts via a boat form which would have a parallel arrangement of orbitals. He argues that preferential loss from the equatorial position cannot explain the



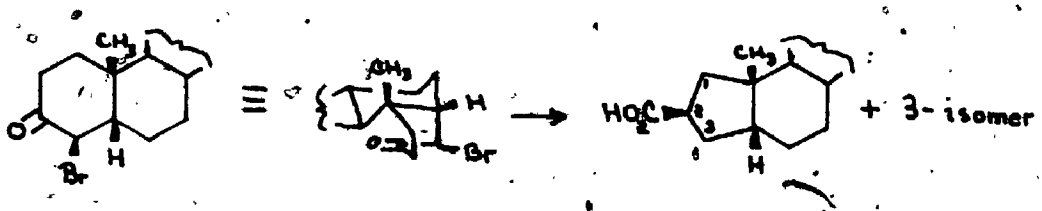
42

rate retardation by a 4-axial substituent in other cyclohexyl systems.[22] Shoppee's group has successfully rearranged bromoketones in a steroid system where the halogen was equatorial.[33] Do they react via boat forms or is the parallel arrangement of orbitals unnecessary? The problem remains unsolved.

Ref. 33



43 45

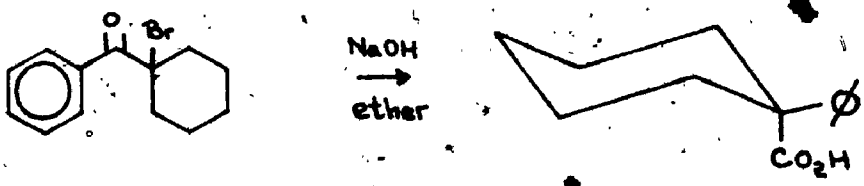


Ref. 33

44 46

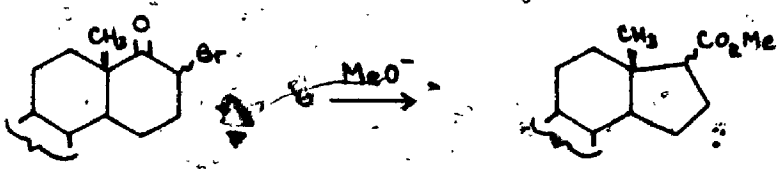
The Semibenzilic Mechanism

The experimental evidence for a cyclopropanone intermediate was not always as strong as it is today. Indeed, haloketones were discovered which gave Favorskii products but which could not possibly pass through a cyclopropanone because they lacked the necessary α'-proton.



Ref. 34

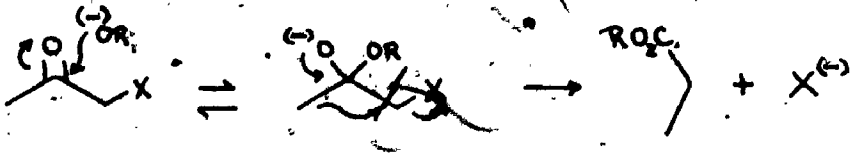
47a 48a



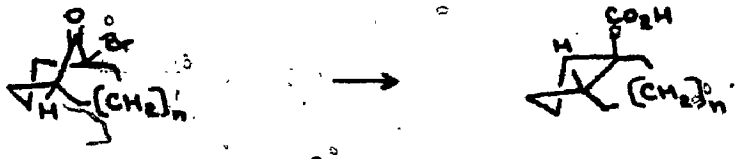
Ref. 35

49 50 (low yield)

These compounds were thought to react by an unsymmetrical 1,2-shift mechanism analogous to that of the benzilic acid rearrangement;[36] hence, it was named the semibenzilic mechanism[34] although the term quasi-Favorskii has also been used. Schematically, it is presented as follows:



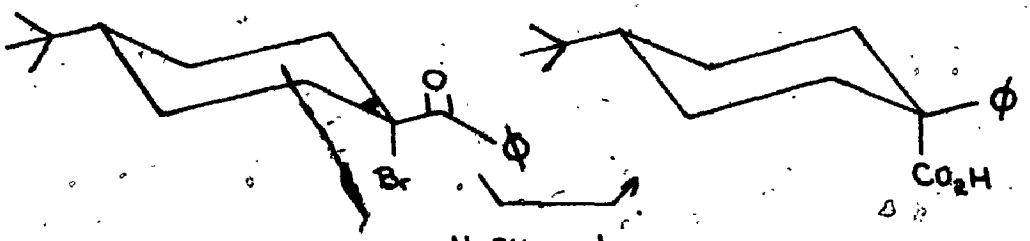
This scheme requires that only one Favorskii product be formed and in such a manner that inversion would occur at the α-carbon since it is an intramolecular S_N2 displacement. This has been clearly demonstrated in the following cases:[37,38]



n = 1, 2 & 3

Ref. 37

51 52



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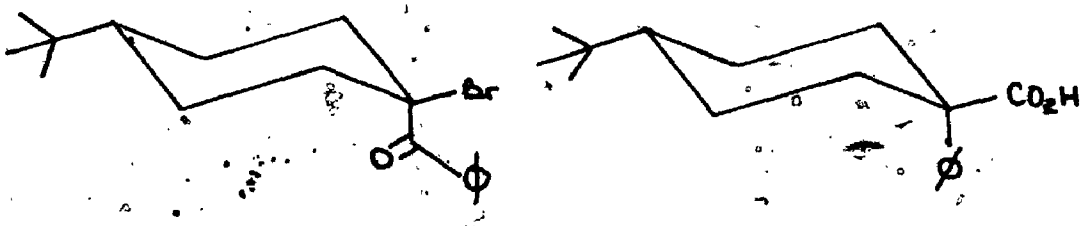
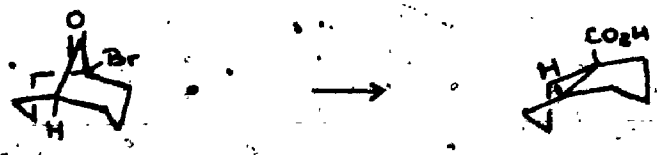
53 54



Ref. 38

55 56

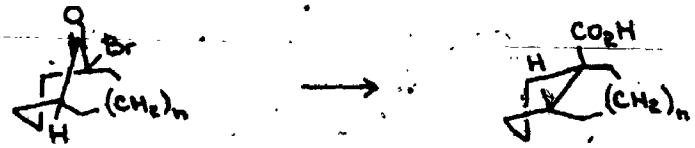
However, the semibenzilic mechanism is not restricted to haloketones lacking an α-proton. In 1951, Cope and Graham published their results with 1-bromobicyclo[3.3.1] nonan-9-one 51.[39] They found that this bromoketone readily rearranged to the Favorskii acid 52 on treatment with silver ion or potassium hydroxide. Since formation of the



Ref. 39

51a 52a

enolate ion with bases of moderate strength is prohibited according to Bredt's rule, this reaction was assumed to proceed by the semibenzilic pathway. Warnhoff and co-workers have demonstrated that this is the case for the [3.3.1] system, but that for larger ring homologs either mechanism is possible depending on the reaction conditions.[37]



Ref. 37

n = 1, 2 & 3

51 52 cis only

Since a semibenzilic pathway proceeds without incorporation of deuterium (unless prior to rearrangement), without a symmetrical intermediate, and with inversion at the halogen-bearing carbon atom, optical activity and deuterium incorporation can be useful mechanistic probes. Whereas bromoketone 51a (n=1) gives the Favorskii acid through the semibenzilic pathway (no deuterium incorporated) with both hydroxide and t-butoxide, the n=2 homolog 51b reacts by a semibenzilic pathway with hydroxide but by a cyclopropanone mechanism with t-butoxide. In the latter case, the α'-proton has only limited acidity and only the strongest base, t-butoxide, can effect its removal. With the n=3 homolog 51c the α'-proton is of sufficient acidity to be removed even by hydroxide and this system is seen to react via the cyclopropanone mechanism with hydroxide, methoxide or t-butoxide. It is interesting to note that the n=3 homolog gave Favorskii product without either deuterium incorporation or loss of optical activity when reacted with silver ion.

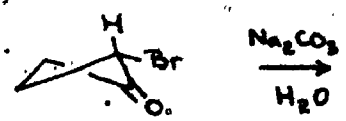
Later work by Warnhoff and Toong examined the role of solvent and

base more closely.[40] In the n=3 system (bromoketone 51c) which had been observed to rearrange by a symmetrical mechanism even with hydroxide, the semibenzilic mechanism was found to be competitive when the strength of the base was decreased and its carbonyl nucleophilicity

Reagent	Solvent	Semibenzilic (%)	Cyclopropanone (%)
HOO^-	H_2O-EtOH	100	—
HS^-	H_2O-MeOH	34	66
CN^-	MeOH	43	57
HCO_3^-	MeOH	12	88
phenoxide	dioxane	--	100

increased. Furthermore, they observed an interesting Br/Cl effect. The mechanism became at least 80% cyclopropanone with hydroperoxide ion when chloride was the leaving group instead of bromide. This is possibly due to a further increase in the acidicity of the α'-proton due to the slightly greater inductive effect of a chloro group. A final factor which favours the cyclopropanone mechanism as "n" increases is the reduced equilibrium constant for the carbonyl addition by nucleophiles. This is reflected in a rate decrease for the semibenzilic pathway as "n" increases.

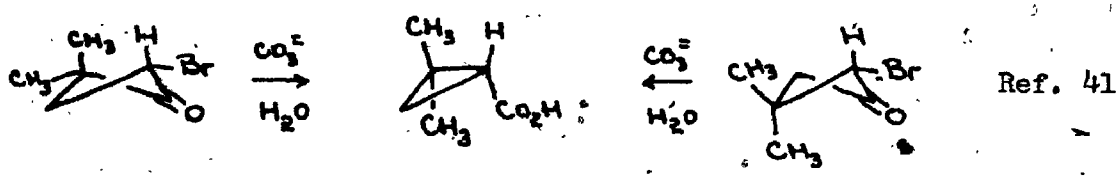
A second system which has been demonstrated to rearrange by the semibenzilic pathway although it has a relatively acidic α'-proton is the bromocyclobutanone 57 system. Although Conia and Salaun[41] first



Ref. 41

57 58

observed the ring contraction of this system and suggested an unsymmetrical mechanism, credit for providing solid evidence that required a semibenzilic pathway must go to Rappe and Knutson.[42] Conia and Salaun found that 2-bromocyclobutanone 57 was converted rapidly and quantitatively to cyclopropane carboxylic acid under a variety of basic conditions. Their argument for an unsymmetrical mechanism rested on the similarity of the PMR spectrum of the acid isolated from a deuterated medium with that of a non-deuterated sample and on an analogy to two related systems. They found that 4,4-dimethyl-2-bromocyclobutanone 59 and 3,3-dimethyl-2-bromocyclobutanone 60 gave the same acid 61 under identical conditions. Since the former system demanded a



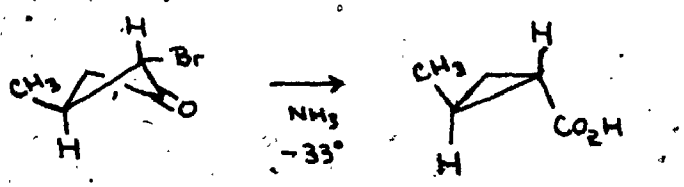
Ref. 41

59 61 60

semibenzilic mechanism, by analogy, the other systems could too. On closer examination, Rappe and Knutson found that some deuterium was incorporated in the cyclopropane carboxylic acid. However, the high ratio of β-hydrogen to α-hydrogen in the cyclopropane ring of the Favorskii acid could not be explained by a cyclopropanone mechanism alone when only 0.85 to 1.25 deuterium atoms were incorporated. They concluded that a semibenzilic mechanism was in effect although their results do not exclude some competition from a cyclopropanone pathway. As expected, no deuterium was incorporated in the acid when 2-bromocyclobutanone 57 was rearranged with silver ion in D_2O.

Conia and Salaun also demonstrated that the ring contraction occurred with inversion of configuration at the α-position since trans-

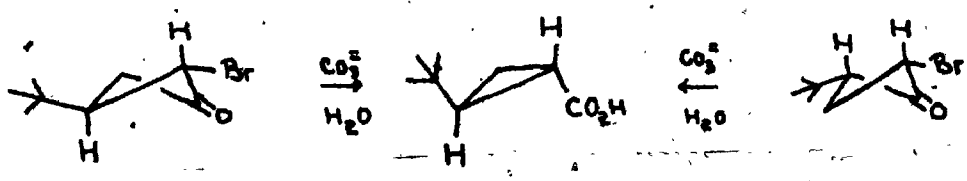
3-methyl-2-bromocyclobutanone gave only trans-2-methylcyclopropane-1-carboxylic acid.



Ref. 41

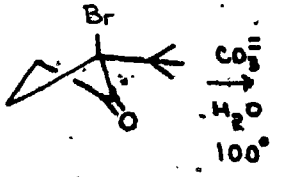
62 63

In substituted 2-bromocyclobutanone systems in which the bromine atom is fixed in a pseudo-axial position, no Favorskii rearrangement is observed with either silver ion or base.[43] This evidence supports the contention that the leaving group must be equatorial in order that the migrating carbon may achieve greatest overlap with the back lobe of the carbon-bromine bond.



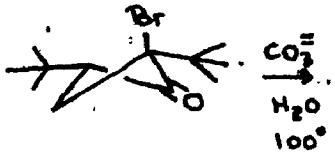
Ref. 43

64 66 65



no Favorskii acid Ref. 43

67



no Favorskii acid Ref. 43

68

In summary, the evidence available today strongly favours a cyclopropanone as the normal intermediate prior to formation of the Favorskii product except in those systems which for any one of a number of reasons cannot form it or form it at a relatively slow rate.

If the energy needed to form the cyclopropanone is too high, a second mechanism, the semibenzilic pathway, may be observed instead. The second mechanism is favoured by highly nucleophilic, weak bases since it involves initial nucleophilic attack at the carbonyl function, but even then the symmetrical mechanism may be preferred if the α'-proton is sufficiently acidic.

The nature of the transition state for cyclopropanone formation is not as clear. When proton removal is the rate determining step, one observes little or no deuterium exchange, a low k_{Br}/k_{Cl} ratio and no salt effect, whereas when loss of halide is the rate determining step complete proton exchange may occur, a high k_{Br}/k_{Cl} ratio is observed and a positive salt effect is found. The latter results suggest that the nature of the carbon-halogen bond at the transition state is highly ionic, but this does not prove that an oxyallyl species is formed. The only evidence for an oxyallyl species is the loss of stereochemistry in some systems in protic solvents. Furthermore, when the loss of halogen is rate determining, a 4-axial substituent causes a rate decrease. Whether this is due to a demand for a parallel arrangement of π-orbitals in the transition state is not certain. Bordwell's work suggests that there is π-participation in the transition state at least in the benzyl methyl ketone system. With the semibenzilic mechanism an anti-parallel, co-planar arrangement of migrating carbon and leaving group appears necessary.

The predominant effect of changing bromine to chlorine in the semibenzilic mechanism is to make the α'-proton more acidic and thereby to improve the likelihood of a cyclopropanone mechanism.

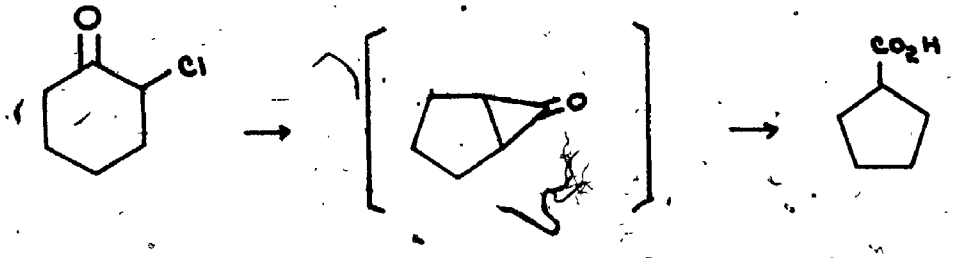
Incorporation of at least one deuterium atom, loss of optical

activity in symmetrical systems and a possibility of two acidic products are characteristic of the cyclopropanone mechanism, whereas lack of deuterium incorporation, no loss of optical activity and a single, stereoisomeric acid are marks of the semibenzilic pathway.

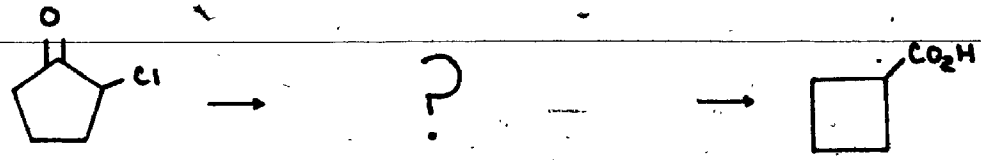
Objectives

There is no a priori reason for excluding the semibenzilic mechanism in the Favorskii rearrangement of haloketones which have an α'-proton. In at least one system, 1-bromobicyclo[5.3.1]undecan-11-one 51c, the balance between the two mechanisms is very delicate and both mechanisms can be observed together. As a result, our research was directed towards examining other systems with α'-protons in which the semibenzilic pathway might be operative to determine whether it might be more general than previously thought. A case in point is the study of cis-1-acetyl-1-chloro-2-methylcyclohexane 32 by Tchoubar's group[26,27] mentioned earlier (p. 11). It is interesting that the product of inversion which can be produced preferentially in non-polar or aprotic solvents is the one expected from the semibenzilic pathway. Are there two competing mechanisms in this system? The possibility cannot be disregarded. One wonders how many other cases exist in which the cyclopropanone and semibenzilic mechanisms occur together.

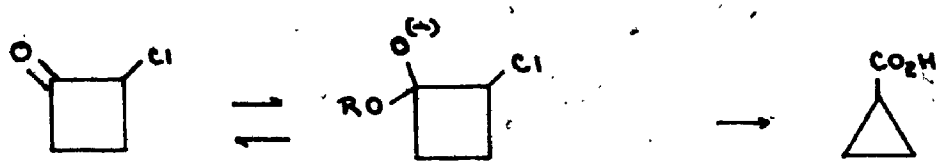
The first project was the examination of the reaction of 2-chlorocyclopentanone 69 with base. Since 2-chlorocyclohexanone 18 reacts by a symmetrical mechanism and 2-bromocyclobutanone 57 by an unsymmetrical mechanism, it follows that the five membered ring might react by either mechanism under the right conditions. Unfortunately, past attempts to rearrange 2-chlorocyclopentanone 57 had failed to induce ring contraction,



18 19



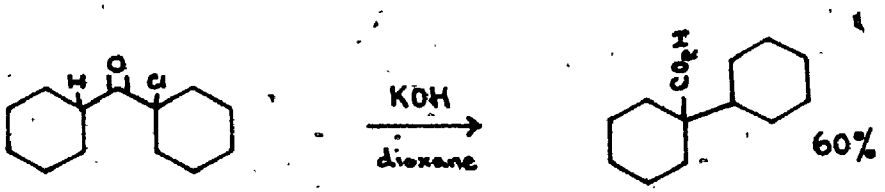
69 70



57 58

instead giving polymeric tars.[44,45] Our first task, then, was to find conditions which would effect the rearrangement.

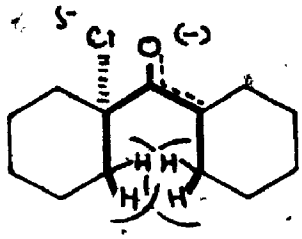
A second system, α-chlorodicyclohexyl ketone 167, which is known to give a Favorskii product under heterogeneous conditions was examined



Ref. 46

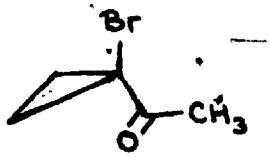
167 168

to uncover its mode of reaction.[46] Because of the proximity of the two rings, there is probably considerable steric interaction between opposing methylene hydrogens. This interaction would reach a maximum when a co-planar arrangement of atoms about the carbonyl function was adopted. It has been suggested that a parallel arrangement of the carbon-halogen bond and the axes of the enolate π-orbitals is necessary



at one stage during cyclopropanone formation. If this is true and if the steric interaction between the two rings is sufficiently large to prevent it, then, the Favorskii acid must be produced by a semibenzilic mechanism.

A third project undertaken was a study of the reaction of α-bromocyclopropyl alkyl (aryl) ketones with base. Since they were new compounds, it was not known whether they would give Favorskii acids. To



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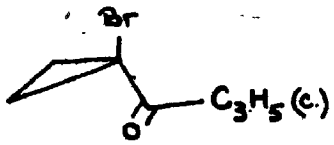

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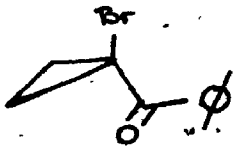

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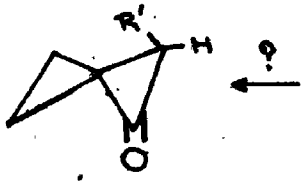
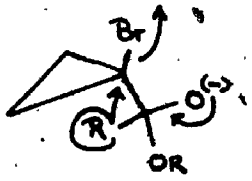
do so by a cyclopropanone mechanism would require a novel, highly strained spiro-intermediate. This strain might prevent a symmetrical mechanism. On the other hand, the semibenzilic mechanism would require





an S_N2 displacement at a cyclopropyl carbon atom. Admittedly, this would be an intramolecular displacement, but only one example of such a displacement was available at the beginning of this project.[47]

Generally, the investigation involved the synthesis of substrates and the search for optimum reaction conditions. This required varying the solvent, the nature and concentration of the base and the tem-

perature and either identifying the major product(s) or comparing the crude product with known standards. Deuterium incorporation and deuterium labelled substrates were used to elucidate the reaction mechanism.

CHAPTER II

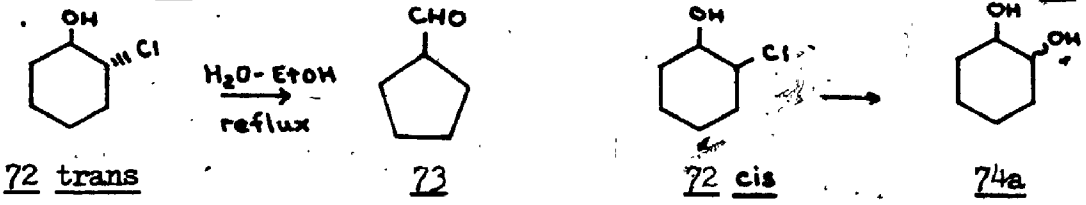
ATTEMPTED FAVORSKII REARRANGEMENT OF α-HALOCYCLOPENTANONE DERIVATIVES

Introduction

Earlier attempts to rearrange chlorocyclopentanone 69 to cyclobutane carboxylic acid 70 have all met with the same result: polymeric tars and no Favorskii product. In 1913, Kotz, et al., treated chlorocyclopentanone 69 with refluxing aqueous KOH, refluxing aqueous $NaHCO_3$ and silver acetate in ether, respectively, to produce only resin.[48] Later, Favorskii and Bojovsky added alcoholic KOH to an alcoholic solution of chlorocyclopentanone 69.[49] The first few drops produced a bright, cherry red colour, but by the end of the addition of base the colour had become black. They reported that no volatile acids were isolable. Godchot, et al., produced cyclopentenone 71 by treating chlorocyclopentanone 69 with diethylamine or by distilling it at atmospheric pressure.[50] Mousseron, et al., also reported a 25% yield of cyclopentenone 71 when chlorocyclopentanone 69 in methanol was added dropwise to a solution of sodium methoxide in methanol at 0° or sodium methoxide in ether.[51] Beside the cyclopentenone 71 they also observed a large amount of polymeric material and an unidentified acid. Treatment of chlorocyclopentanone 69 with either phenoxide or the alkoxide of cyclohexanol gave in their hands only α-substituted cyclopentanones and polymer. Since chlorocyclohexanone 18 had been rearranged

to cyclopentanone carboxylic acid 19 in good yield, it appeared that the energy requirements for the ring contraction of the five-membered homolog were either much greater or the competing side reactions were much faster.[52]

When Conia and Salaun showed that bromocyclobutanone 57 rearranged with ease to cyclopropane carboxylic acid 58, the five-membered system was left in a familiar situation as seen below.[41] There are examples in the literature which illustrate ring contractions in the six- and four-membered systems under conditions which do not induce ring contraction in the five-membered homolog. Mousseron, et al., found that the trans isomer of 2-chlorocyclohexanol 72 gave cyclopentane carboxaldehyde 73 and that the cis isomer 72 gave 1,2-cyclohexanediol 74 but that neither isomer of 2-chlorocyclopentanol 75



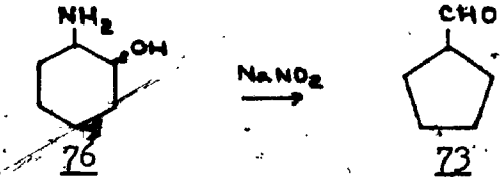
72 trans 73 72 cis 74a

Ref. 53

no ring contraction

75 cis or trans 74b

gave ring contractions.[53] A similar result had been observed with the

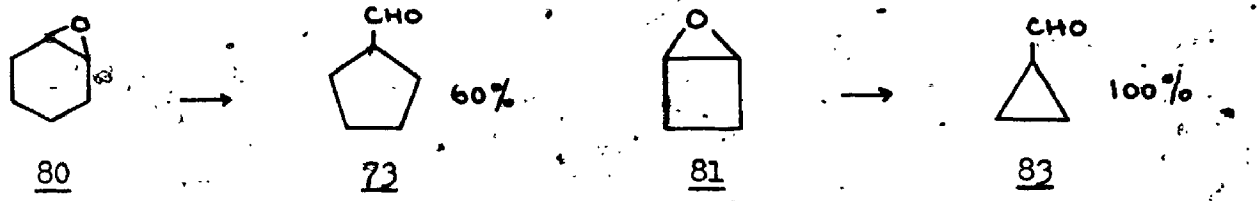


76 73

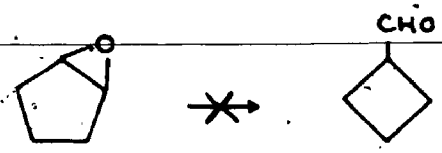
Ref. 54

77 78 79

homologous 1,2-aminoalcohols 76 and 77.[54] Likewise, the epoxides of cyclohexene 80 and cyclobutene 81 produce ring-contracted aldehydes in the presence of mineral or Lewis acids, but epoxyclopentane 82 does not.[55]



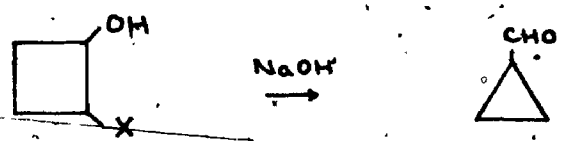
80 → 73 81 → 83



82 ✗ 84

Ref. 55

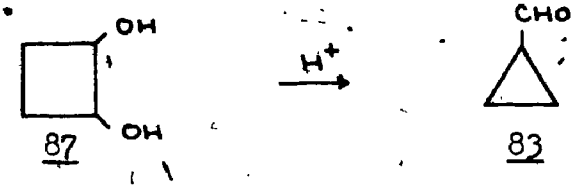
Conia's group has observed the facile ring contraction of 2-bromocyclobutanol 85 and 2-tosyloxycyclobutanol 86 in base and the ring



85 X = Br → 83

86 X = OTs → 83

Ref. 43



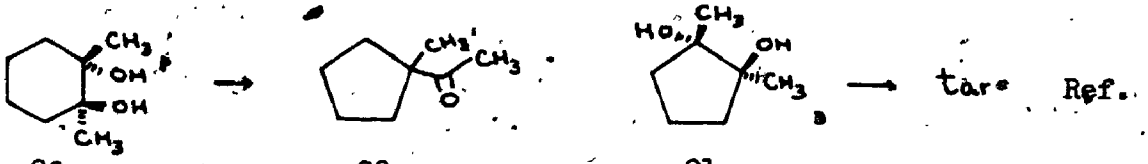
87 → 83

$k_{trans} > k_{cis}$

contraction of both isomers of cyclobutanediol 87 with acid.[43]

Bartlett observed ring contraction of the six-membered diol 89 but not of the five-membered ones 90 and 91.[56]

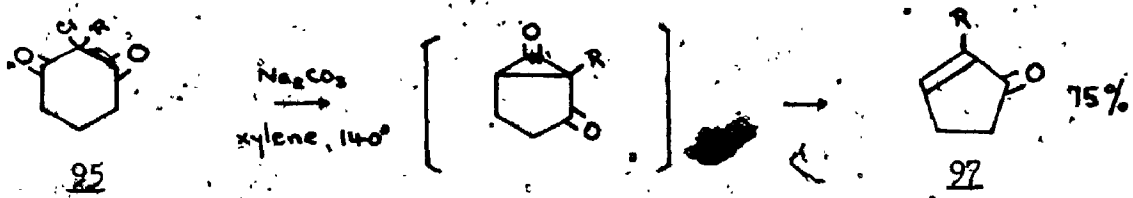
88 → 92 90 → 94



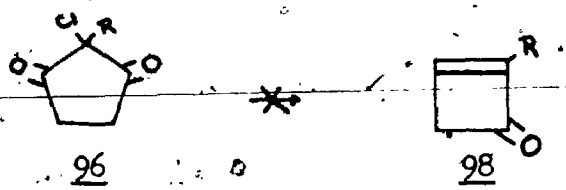
89 → 93 91 → tars

Ref. 56

Buchi observed cyclopropanone decarbonylation in the six-membered system 95 but not the five-membered homolog 96.[57] Similarly, Wiberg



95 97

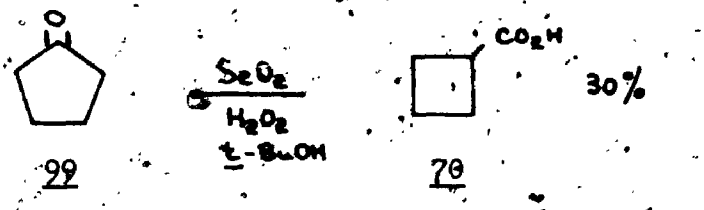


96 98

Ref. 57

and Koch isolated a 75% yield of cyclopentane carboxylic acid 19 after treating cyclohexanone with thallic ion in aqueous $HClO_4$, but produced an unidentified complex mixture with cyclopentanone.[58,59] Unfortunately, the comparison with cyclobutanone was not made.

On the other hand, Payne and Smith observed ring contraction in both cyclopentanone and c[illegible]xanone with H_2O_2 in the presence of a catalytic amount of S[illegible] suggested that the H_2O_2 served to



99 70

Ref. 60

oxidize the selenous acid to selenic acid, but offered no mechanism.*

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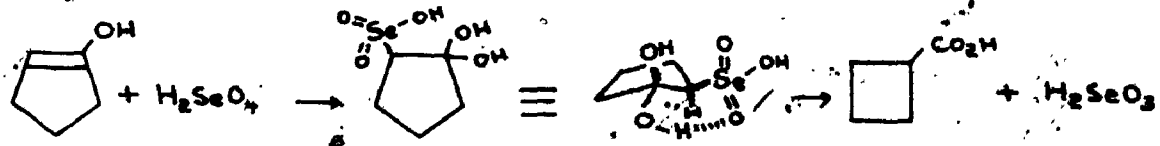
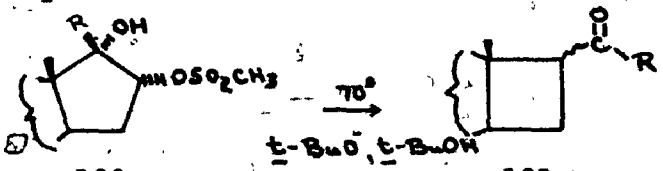
* Present author's suggestion:



Perhaps the chair is adopted due to intramolecular hydrogen-bonding. This favours an anti-parallel, co-planar 1,2-shift as in semibenzilic mechanism.

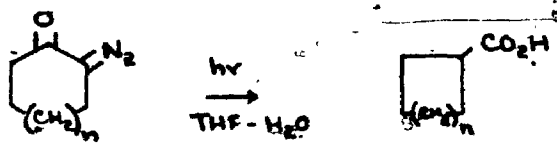
This reaction is of interest, however, since it shows that the five-membered system will ring-contract if the conditions are right. An interesting example of this in the steroid series was observed by



100 101 Ref. 61

Ghera's group.[61] It emphasizes the co-planar, anti-parallel arrangement of leaving group and migrating carbon needed for the semi-benzilic-like step.

Regitz and Ruter have found that the Wolff rearrangement of diazoketones 102 generally produces the ring contracted products in good to excellent yield.[62] It is interesting that the five-membered



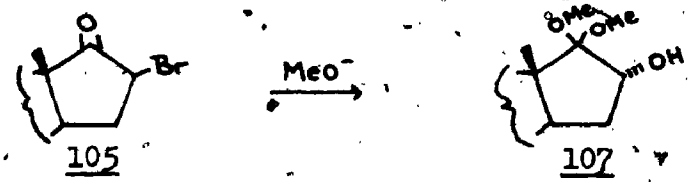
102 103

n=0, 68%
1, 95
2, 91
3, 85
4, 81
5, 62
6, 35
7, 25

Ref. 62

system gives the worst yield of the common rings. Hassner observed this type of rearrangement in a steroid system in which the normal Favorskii rearrangement had failed.[63,64]

104 106

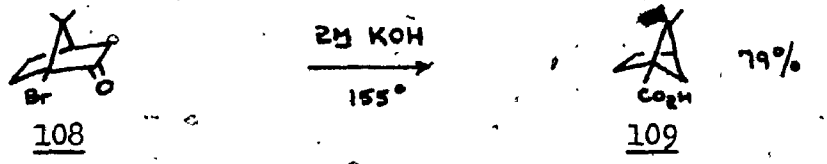


105 107

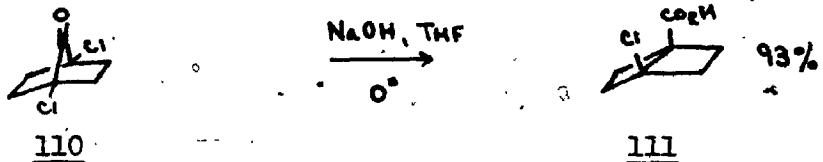
Ref. 64

Another five-membered ring system which generally undergoes ring

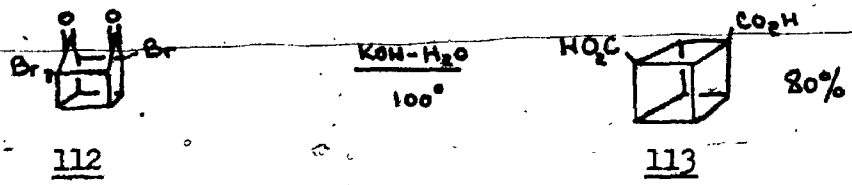
contraction in good to excellent yield is the bridged system. With the Wolff rearrangement there is sufficient driving force for ring contraction that side reactions are not competitive, whereas in the bridged systems side reactions such as S_N2 substitution, elimination and condensation, are minimized by the nature of the substrate. For example:



108 109 Ref. 65



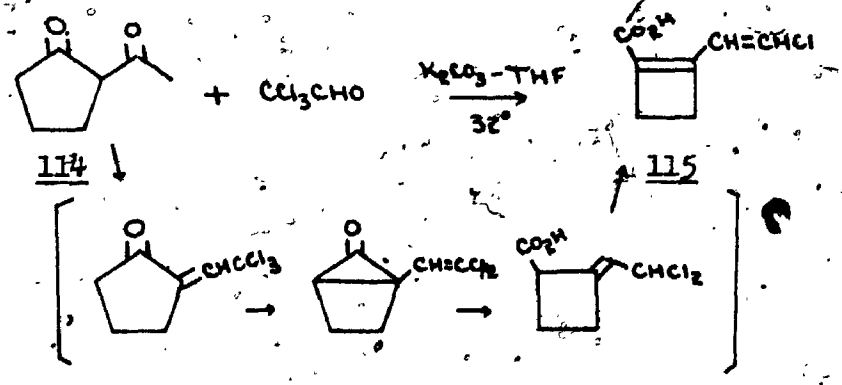
110 111 Ref. 65



112 113 Ref. 66

In the first case, there are enolizable hydrogen atoms, but it is highly unlikely that a cyclopropanone could form; so a semi-benzilic pathway is probably operating as in the last two examples. In fact, all the successful ring contractions of five- to four-membered systems have occurred by a 1,2-shift mechanism.

One exception may be the recently published condensation of α-acetylcyclopentanone 114 with chloral and subsequent ring contraction

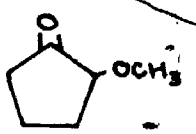


114 115 Ref. 67

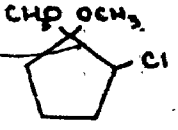
to form a cyclobutene carboxylic acid 115.[67] If this is a vinylogous Favorskii reaction, it occurs under surprisingly mild conditions.

Reaction of 2-Chlorocyclopentanone 69 with Methoxide Ion

The work was begun by repeating Mousseron's experiment.[51] Chlorocyclopentanone 69 in an equal volume of methanol was added dropwise to a 3M solution of sodium methoxide in methanol at 0°. As noticed by Favorskii, a cherry red colour formed initially, gradually giving way to amber and finally turning dark brown.[45] Aqueous workup gave besides a tarry mass which was insoluble in both ether and water, a small amount of complex acidic material and a neutral fraction (40%) consisting of two major compounds, 2-methoxycyclopentanone 116 and 1,1-dimethoxy-2-chlorocyclopentane 117 in approximately equal amounts. There was no methyl cyclobutanecarboxylate 118 present by comparison with an authentic sample on GLPC.



116

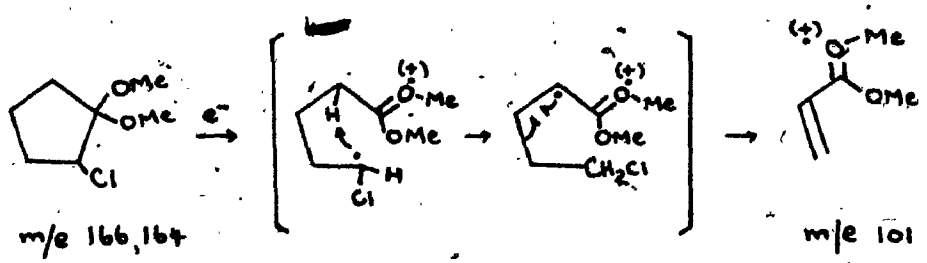


117

In an attempt to minimize condensation the reaction at 0° was repeated, but the substrate was added at one quarter of the previous rate. This effectively eliminated the tar but gave the same complex acidic mixture as before. However, the neutral fraction (41%) was now predominantly (85%) the less polar (GLPC) ketal 117. Again no evidence of Favorskii ester was found. By doing this reaction at -20°, not only was the tar eliminated but the acidic fraction was greatly reduced. The quantity of neutral fraction (65%) increased and the ratio of ketal 117 to ketone 116 now favoured the ketone slightly, but there was no

ester 118 produced. A control experiment showed that methyl cyclobutanecarboxylate 118 was stable under the reaction conditions as expected. The low temperature-slow addition experiment was repeated, but the methanol solutions were diluted by a factor of ten. This effectively eliminated the acidic fraction and gave a slightly larger neutral fraction (75%) which was ~65% ketone 116 but contained no Favorskii ester 118

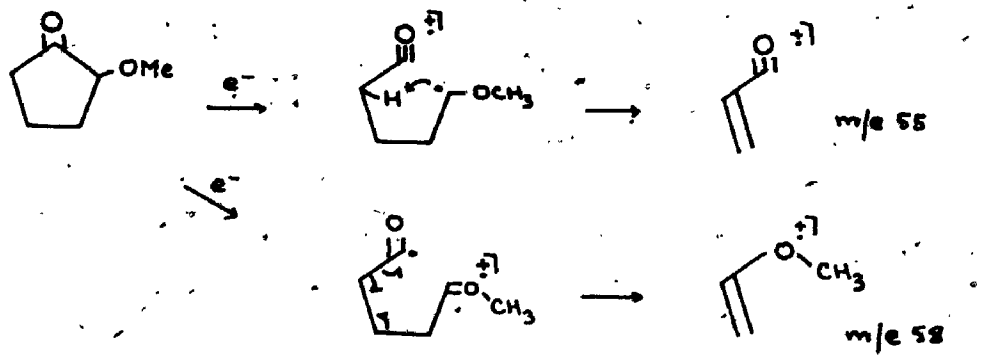
Since these conditions had failed to give any Favorskii product, it was thought that a higher temperature might provide the necessary activation energy. When the first reaction above was repeated at reflux temperature, the result was a large amount of insoluble polymeric material and a small amount of neutral material which contained only ketal 117 as shown by GLPC and the presence of only two of the usual three singlets (CH_3O-, 3.18 and 3.25 δ in carbon tetrachloride) in the PMR spectrum. The structure of the ketal 117 was assigned by PMR spectroscopy which showed two sharp methoxy singlets and a broad doublet at 4.08 δ for the proton geminal with the chlorine atom; by ir spectroscopy which showed only weak hydroxyl and carbonyl absorption in the crude material and strong absorption at 2835, 1050, 1085 and 1120 cm^{-1} characteristic of a methoxy ether and by mass spectroscopy which showed parent peaks at m/e 164 and 166 indicating a



m/e 166, 164 m/e 101 (100%)

mono-chloro compound and a base peak at m/e 101 due to alpha-cleavage characteristic of a ketal. Furthermore, acid catalyzed hydrolysis gave chlorocyclopentanone 69 identified by comparison of its ir spectrum with that of the authentic material.

The structure of the ketone was assigned by examination of its spectra and by analysis of its 2,4-dinitrophenyl hydrazone. The PMR spectrum showed a single methoxy peak at 3.53 δ ($CDCl_3$) and an overlapping multiplet resembling a broad doublet of doublets at 3.7 δ ($CDCl_3$) due to the proton alpha to the methoxy group. The ir spectrum exhibited strong carbonyl absorption (1745 cm^{-1}, $CHCl_3$) and peaks indicating a methoxy ether (2830, 1123 cm^{-1}; $CHCl_3$). The mass spectrum gave a small parent ion at m/e 114 and a fragmentation pattern which indicated that oxonium ion formation occurred at both the carbonyl and ether



sites as expected of an α-keto ether.[68] The 2,4-dinitrophenyl hydrazone 119, a bright yellow solid of m.p. 165-179°, was a nearly equal mixture of syn- and anti-isomers and gave a correct analysis for $C_{12}H_{14}N_4O_5$. Its PMR spectrum ($CDCl_3$) showed two sharp methoxy singlets (3.57 and 3.48 δ) and a phenyl proton pattern similar to that of Fig. 9, p. 196.

At this point an aprotic medium was tried. Chlorocyclopentanone 69 was added to a suspension of sodium methoxide in ether. Besides a

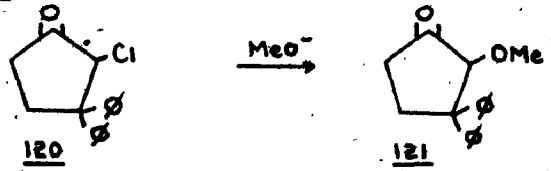
large amount of polymeric tar and a viscous acidic fraction, a neutral fraction was obtained with a single peak on GLPC which corresponded to the methoxyketone 116. Although Mousseron reported a 25% yield of cyclopentenone 71 by treating chlorocyclopentanone 69 with sodium methoxide in ether or in methanol at 0°,[51] none of the characteristic bands of cyclopentenone 71 (3055, 1590, 1440, 1345, 1178, 915 cm^{-1}) were ever observed in the ir spectra of the neutral fractions. Since it was originally identified by its 2,4-dinitrophenyl hydrazone, m.p. 214-215°, it is probable that Mousseron actually had 2-methoxycyclopentanone 116 which underwent acid-catalyzed loss of methanol from the dinitrophenyl hydrazone, a known reaction.[69,70] When chlorocyclopentanone 69 was added to a dilute, refluxing suspension of sodium methoxide in dimethoxyethane, methoxyketone 116 appeared to be the major, volatile product but neither Favorskii ester nor acid were observed by GLPC.

Attempts to separate the two major neutral products from the previous reactions by preparative GLPC were unsatisfactory due to decomposition of ketal 117 on the column. Although they could be partially separated by distillation on the spinning band unit, column chromatography gave the best separation. During column chromatography a small amount of chlorocyclopentanone was isolated. This was puzzling since the starting mixture contained none. However, when the structure of the ketal 117 was determined, it became obvious that partial hydrolysis had occurred on the silica gel column.

Although it seemed likely that the ketal 117 was formed in the methanol solution prior to reaction rather than in the basic reaction mixture, the first control experiment which simply involved adding a

drop of chlorocyclopentanone 69 to methanol and leaving at room temperature showed no peak on GLPC corresponding to ketal 117 after 2-3 hours. The difficulty was apparently that the first control was far too dilute and, when it was repeated at the same concentration as used in the reactions with base, ketal 117 was gradually formed. When a freshly prepared methanolic solution of chlorocyclopentanone 69 was added rapidly (5 sec) to a dilute solution of sodium methoxide in methanol, the reaction was complete within 10 seconds and showed only methoxyketone 116 in the neutral fraction. The trace of acid which catalyzes the ketal formation is presumably in the chlorocyclopentanone 69. It either distills over with the chloroketone 69 during purification or is formed during distillation. It was noticed that bromocyclopentanone 69b immediately turned brown on contact with the metallic thread of the exit valve in the stillhead. Possibly the chlorocyclopentanone 69 also decomposed at this point but to a much less noticeable extent.

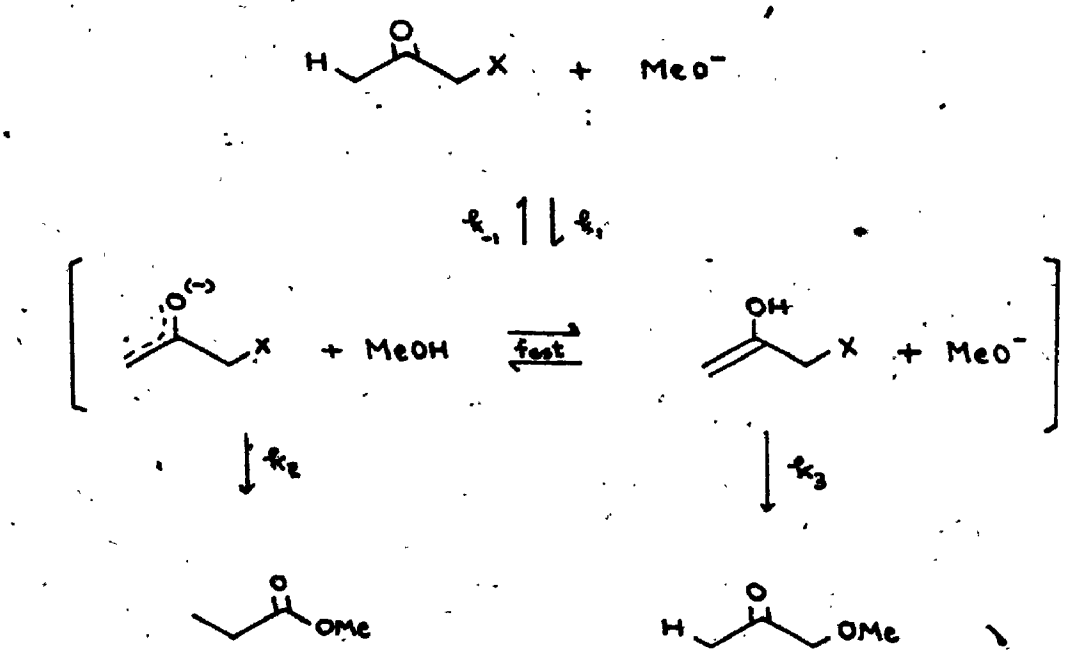
It appears that α-methoxycyclopentanone 116 is the only volatile product formed when α-chlorocyclopentanone 69 reacts with methoxide ion. When 2-chloro-3,3-diphenyl cyclopentanone 120 is treated with 0.1M sodium methoxide in methanol, the only product is 2-methoxy-3,3-diphenyl cyclopentanone 121.[71] Bordwell has presented strong evidence that some methoxyketones are formed by solvolysis of the enol halides which are in equilibrium with the enolate halides. At low base



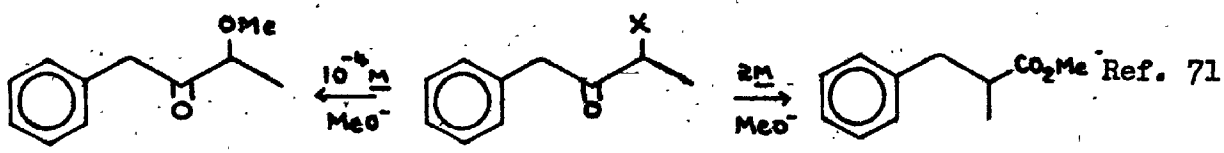
120 121 Ref. 71

concentrations the enol is favoured and methoxyketone predominates, but at higher concentrations of base the enolate is favoured and

the Favorskii product is formed. Schematically, this is presented below and one can see that not only does it depend on the equilibrium constant but also on the relative values of k_2 and k_3:



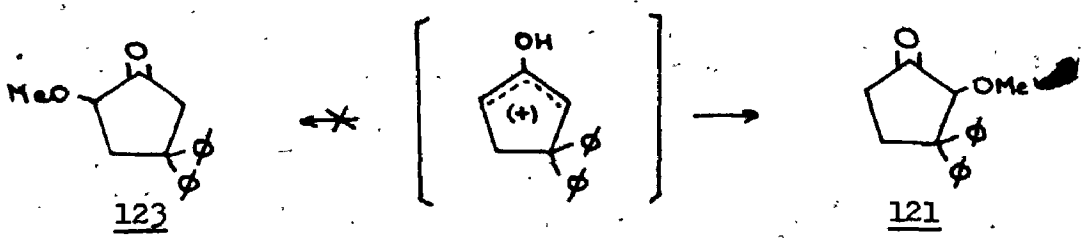
Bordwell found that haloketone 37 gave 100% methoxyketone 122 at 0.0001M methoxide ion but 100% Favorskii ester 38 at 2M methoxide ion. This is a particularly favourable system because of its ease of enolization and of solvolysis due to conjugation with the aromatic system.



122 37 38

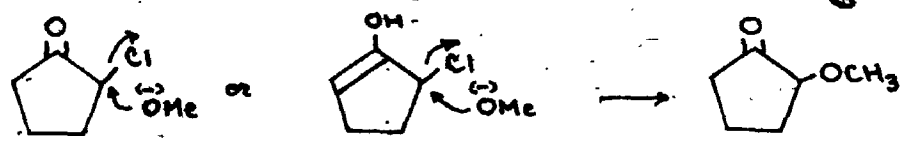
With chlorocyclopentanone 69, base concentrations from 0.1M to 3M gave only α-methoxycyclopentanone 116. Either the relationship

$k_3 \gg k_2$, is in effect or another pathway exists for methoxyketone formation. Since 2-chloro-3,3-diphenylcyclopentanone 120 gives a methoxyketone with substitution at the most hindered position, the second alternative seems the most realistic for the cyclopentanone



123 121

system. The methoxyketone could either form by direct S_N2 attack at the alpha carbon or via an epoxyether. Since epoxyethers



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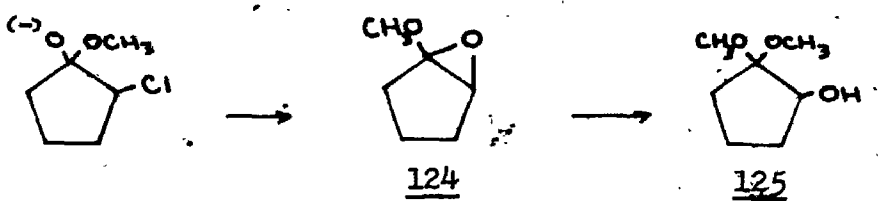
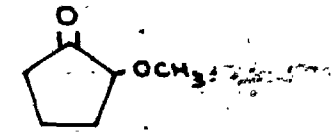
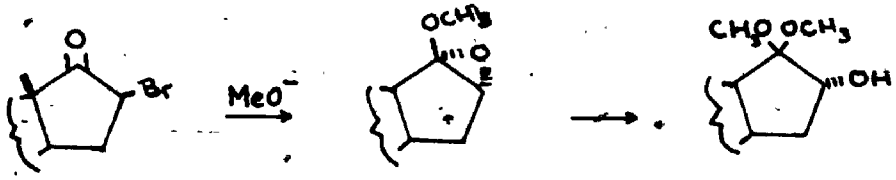


124 125



116

generally give hydroxy ketals with sodium methoxide in methanol and since no 2-hydroxy-1,1-dimethoxycyclopentane 125 was observed, the pathway for methoxycyclopentanone formation is perhaps best formulated as an S_N2 substitution at the α-carbon.

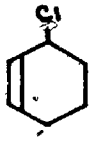


Ref. 64

105 107

The rate determining step for the Favorskii rearrangement of 2-chlorocyclohexanone 18 is loss of chloride.[21] Goering, et al.,[73] measured the relative rates of solvolysis of 1-chlorocyclopent-2-ene 126 and 1-chlorocyclohex-2-ene 127 in ethanol at 30° and found the five-membered ring to solvolyze nearly six hundred times faster than the six-membered ring. Since, under basic catalysis, cyclo-

126



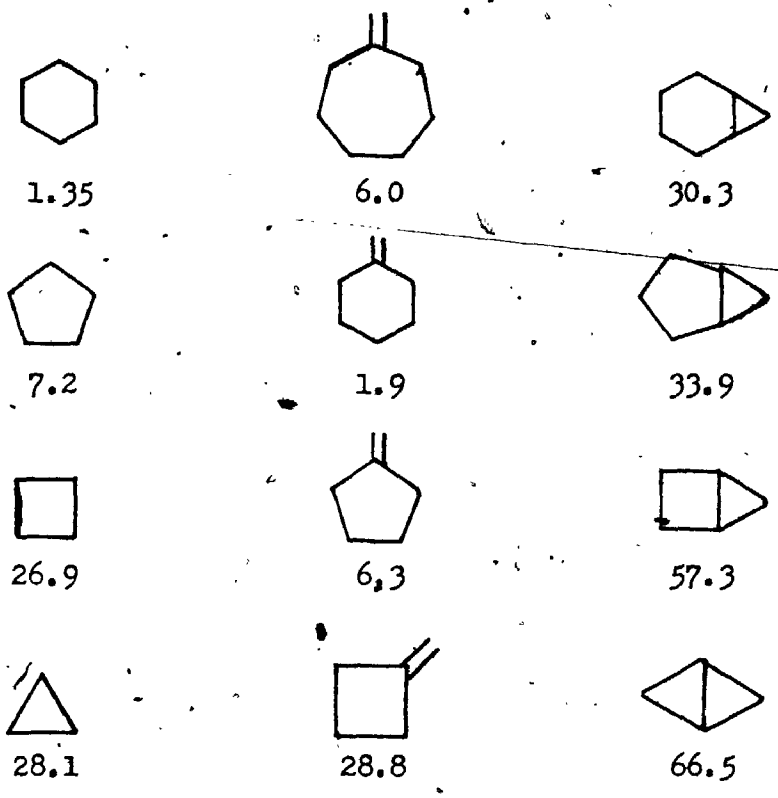
127

pentanone enolizes faster than cyclohexanone,[74] then, at first glance, the Favorskii rearrangement of 2-chlorocyclopentanone 69 might be expected to be faster than that of 2-chlorocyclohexanone 18 regardless of which step was rate determining. However, there are two factors working against ring contraction in the former system. Cyclopentyl chlorides undergo S_N2 displacement approximately six times faster than cyclohexyl chlorides[75] and a much greater increase in strain energy is involved in forming 2-oxobicyclo[2.1.0]pentane 128 than in forming 2-oxobicyclo[3.1.0]hexane 129. A first approximation can be obtained

129

128

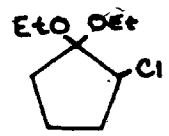
by comparing the strain energy of the hydrocarbon ring with its corresponding bicyclic homolog using Schleyer's strain estimates.[76]



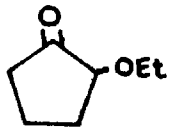
By the cyclopropanone mechanism the five-membered ring must overcome about 20 Kcal/mole more of increased strain energy than the six-membered ring. To explain the failure of the semibenzilic mechanism to occur is more difficult. One can only suggest that side reactions, such as methoxyketone formation, are indeed much more competitive in this system.

Reaction of 2-Chlorocyclopentanone 69 with Other Basic Systems

In an attempt to find more favourable conditions for ring contraction chlorocyclopentanone 69 was treated under other basic conditions. When sodium ethoxide in ethanol was used, two neutral products were obtained. Their position on GLPC and their ir spectra suggested the analogous ketal 130 and ketone 131, but there was no evidence for ethyl



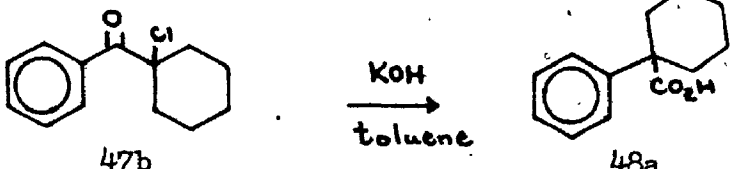
130



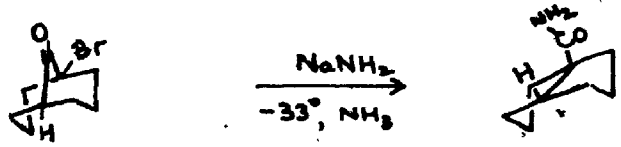
131

cyclobutanecarboxylate 132. On treatment with potassium t-butoxide in t-butanol which was expected to favor cyclopropanone formation as found in the bicyclic [4.3.1] and [5.3.1] systems,[37] 2-chlorocyclopentanone 69 gave viscous, complex mixtures, in both neutral and acidic fractions. There were no volatile products.

Considerable tar formed when chloroketone 69 was treated with a refluxing suspension of powdered KOH in toluene and the acid fraction showed no cyclobutanecarboxylic 70 acid on GLPC. Similarly, reaction of chloroketone 69 with sodium amide in liquid ammonia produced no cyclobutane carboxamide. These latter two base systems have been used successfully on the following compounds to give Favorskii acids via a semibenzilic pathway.[39,77]



47b 48a Ref. 77



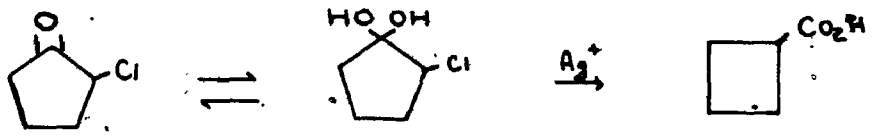
51a 52a Ref. 39

Silver ion might be expected to react with 2-chlorocyclopentanone 69 by a semibenzilic pathway, but neither slightly basic (Ag_2O) nor slightly acidic ($AgNO_3$) conditions produced any cyclobutanecarboxylic acid 70 at steam bath temperature although the chlorocyclopentanone 69 was consumed.

When the conditions employed by Godchot,[50] Kotz,[48] and Favorskii[49] are included in this list of failures, the only conclusion that one can make is that the ring contraction cannot compete successfully with other side reactions regardless of the solvent, base or temperature.

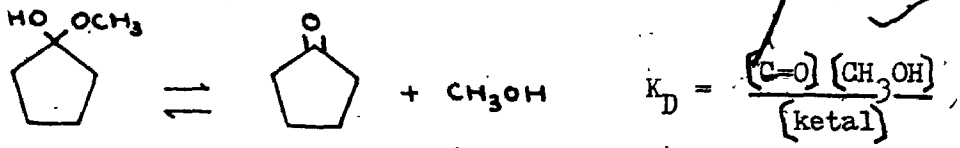
The Reaction of Bromoketals with Silver Ion

The failure of the silver ion to rearrange chlorocyclopentanone 69 by a semibenzilic pathway may have been due to a low concentration of the hydrated ketone. The ketone and its hydrate are in equilibrium, but the hydrate alone probably provides the immediate precursor for



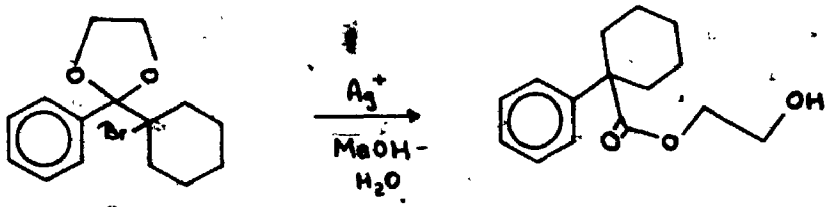
69 70

rearrangement. In comparison to the hemiketal of cyclobutanone and of cyclohexanone, the hemiketal of cyclopentanone has a larger



$$K_D = \frac{[C{=}O][CH_3OH]}{[ketal]}$$

dissociation constant (K_D) 1.11, 2.16 and 15.0 respectively at 25° in methanol.[78] If the side reactions are faster with the five-membered system than with the other rings, the concentration of the hemiketal could be a decisive factor. One answer to this is to preform the ketal function so that the equilibrium, in effect, is entirely to the right. Charpentier-Morize found this a successful measure as illustrated on the following page:[79]



Ref. 79

47c 48b

Accordingly, the ethylene ketal of bromocyclopentanone 132 was treated with silver ion. In acetonitrile the reaction was very sluggish and so methanol was tried. The reaction was considerably faster, as judged by AgBr precipitation, and gave one major compound, 8-methoxycyclopenta-1,4-dioxan 133*, whose structure was assigned after examination of its spectra. The PMR spectrum showed a broad multiplet at 4.0-3.25 δ, and a singlet at 3.2 δ which together integrated for eight protons, and a broad multiplet, 2.0-1.6 δ, which integrated for six protons. The ir spectrum had no carbonyl absorption but did have strong absorption for a methoxy ether (2835 and 1130 cm^{-1}). If a slight excess of pyridine is included in the methanolic silver nitrate solution to quench the nitric acid produced, the reaction is cleaner. If ring contraction had occurrred, the product would have been the orthoester 135 which would have given an integration ratio, high field:low yield, of 7:7. Since the

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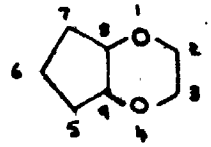
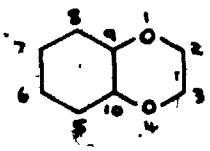
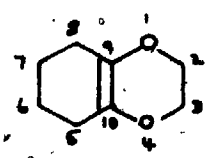


cyclopenta-1,4-dioxan

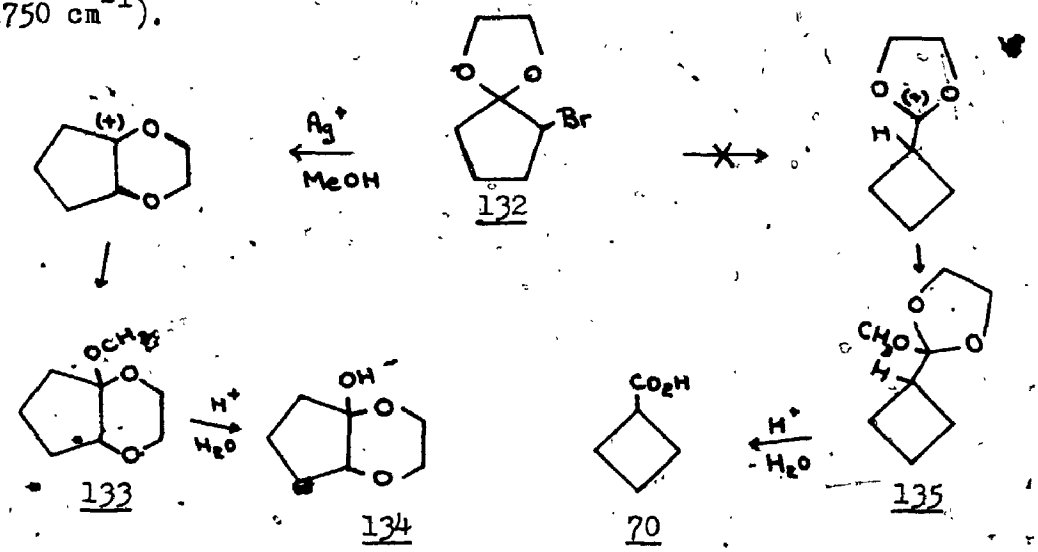


cyclohexa-1,4-dioxan



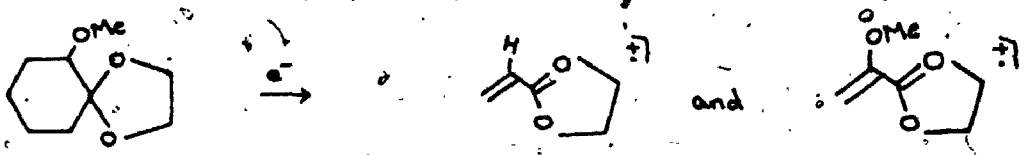
2,3-dihydrocyclohexa-1,4-dioxin

observed ratio was 6:8, it seemed that no ring contraction had occurred. The crude mixture was hydrolyzed, but no acidic fraction was isolated; instead, a major, polar spot, 8-hydroxycyclopenta-1, 4-dioxan 134, appeared on TLC. The ir spectrum showed strong hydroxyl absorption (3620, 3440 cm^{-1}) but only very weak carbonyl absorption (1750 cm^{-1}).



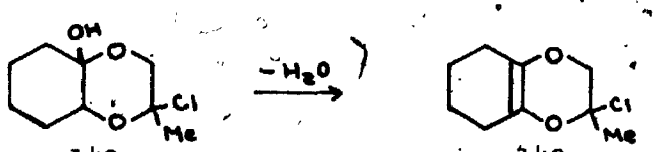
132 133 134 70 135

Since the cyclohexyl ring system is known to contract under many conditions where the cyclopentyl ring will not, the bromo ethyleneketal of cyclohexanone 136 was reacted with silver ion as a comparison. The major product, 9-methoxycyclohexa-1,4-dioxan 137, showed a singlet at 3.3 δ and two broad multiplets, 4.0-3.75 δ and 1.8-1.3 δ, in the PMR spectrum. The ir spectrum showed strong C-O absorption at 2835 and 1150-1050 cm^{-1}. The fragmentation pattern in the mass spectrum indicated that the ethylene ketal moiety had disappeared since it would have given rise to a characteristic peak at m/e 99 and possibly m/e 129, both of which were absent.[68]



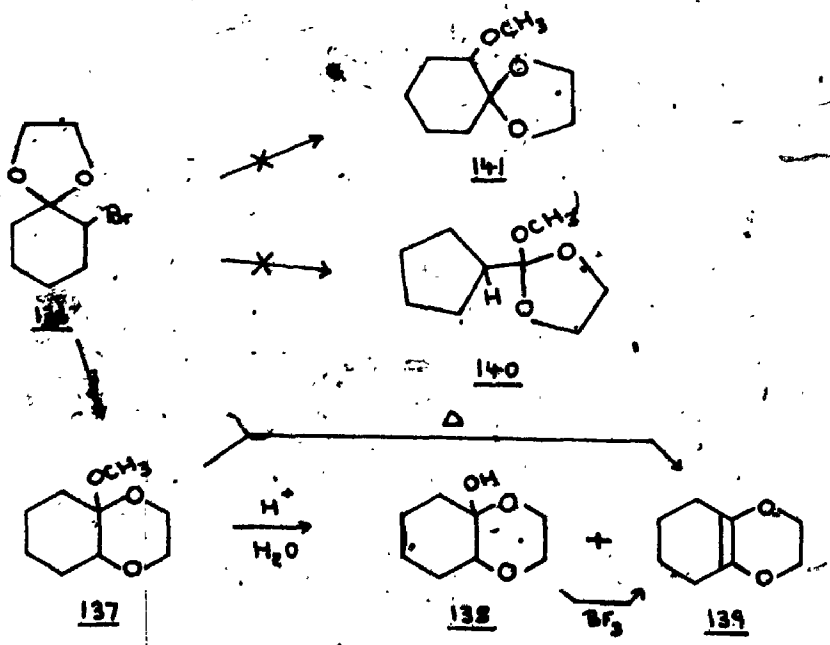
141 m/e 99 m/e 129

On hydrolysis in aqueous acid, the crude material gave no acidic fraction which indicated that orthoester 140 was not formed. Instead, a polar, major product, 9-hydroxycyclohexa-1,4-dioxan 138, was observed besides a non-polar, major product, 2,3-dihydrocyclohexa-1,4-dioxin 139. The ir spectrum showed strong hydroxyl absorption in the 3600 cm^{-1} region and strong C-O absorption at 1110 cm^{-1}. The presence of a product due to dehydration is not surprising, since both the hydroxy and methoxy groups in these compounds are quite labile. A recent publication demonstrates the lability of the 9-OH group.[80] Heating hemiketal 142 slightly above its melting point (59-61°) caused dehydration



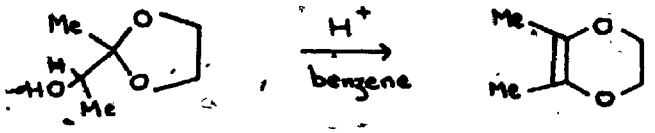
142 143 Ref. 80

An attempt to purify the 9-methoxycyclohexa-1,4-dioxan 137 by preparative GLPC gave only the dioxin 139 as did distillation at atmospheric pressure (165°).

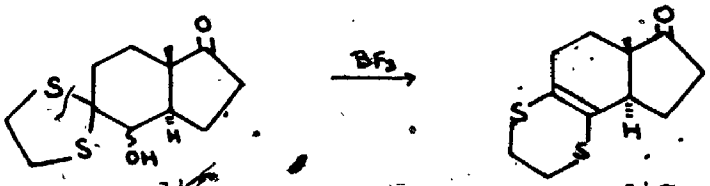


Similarly, 9-hydroxycyclohexa-1,4-dioxan 138 is cleanly converted to dioxin 139 on treatment with BF_3 etherate in acetic acid. The ir spectrum contains only strong C-O absorption, 1100-1300 cm^{-1}, while the PMR spectrum has a sharp singlet at 3.9 δ ($CDCl_3$) for the $-OCH_2CH_2O-$ protons.

It appears then that both the cyclopentyl and cyclohexyl systems prefer to rearrange by a 1,2-oxygen shift rather than by ring contraction. This is in contrast to the example by Charpentier-Morize mentionned earlier (p. 43). However, the success of this last example is probably due to the greater migratory aptitude of the phenyl group in the pinacol rearrangement since related examples with alkyl migrating groups do show the oxygen (sulphur) shift.

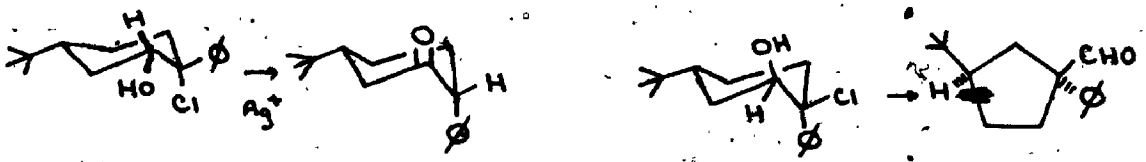


144 145 Ref. 81

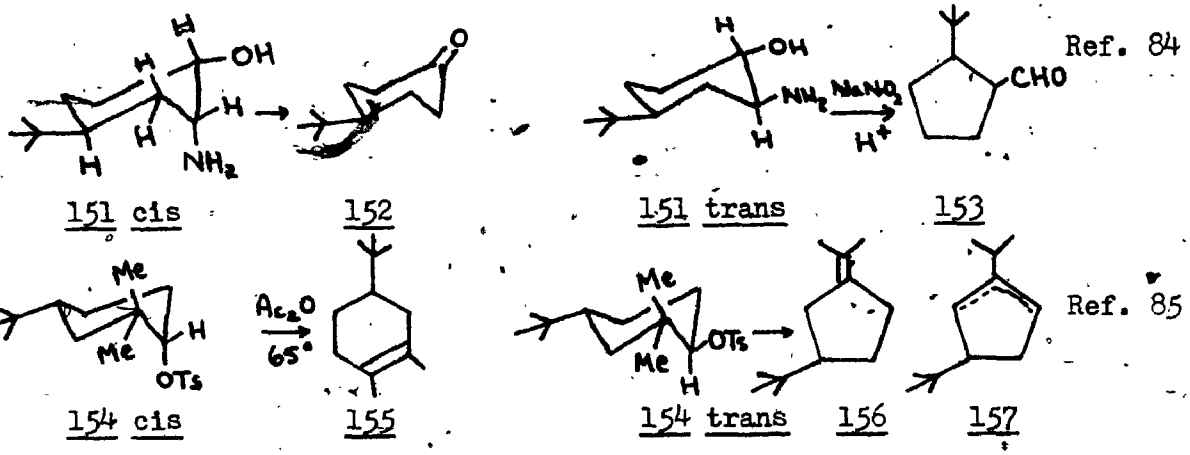


146 147 Ref. 82

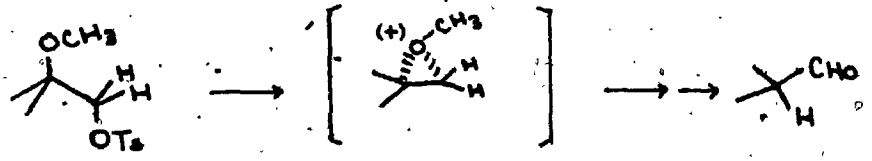
On the other hand, there is evidence that, for ring contraction to occur, the migrating group must be co-planar and anti-parallel with the leaving group. Since no ring contracted product was observed



148 cis 149 148 trans 150 Ref. 83



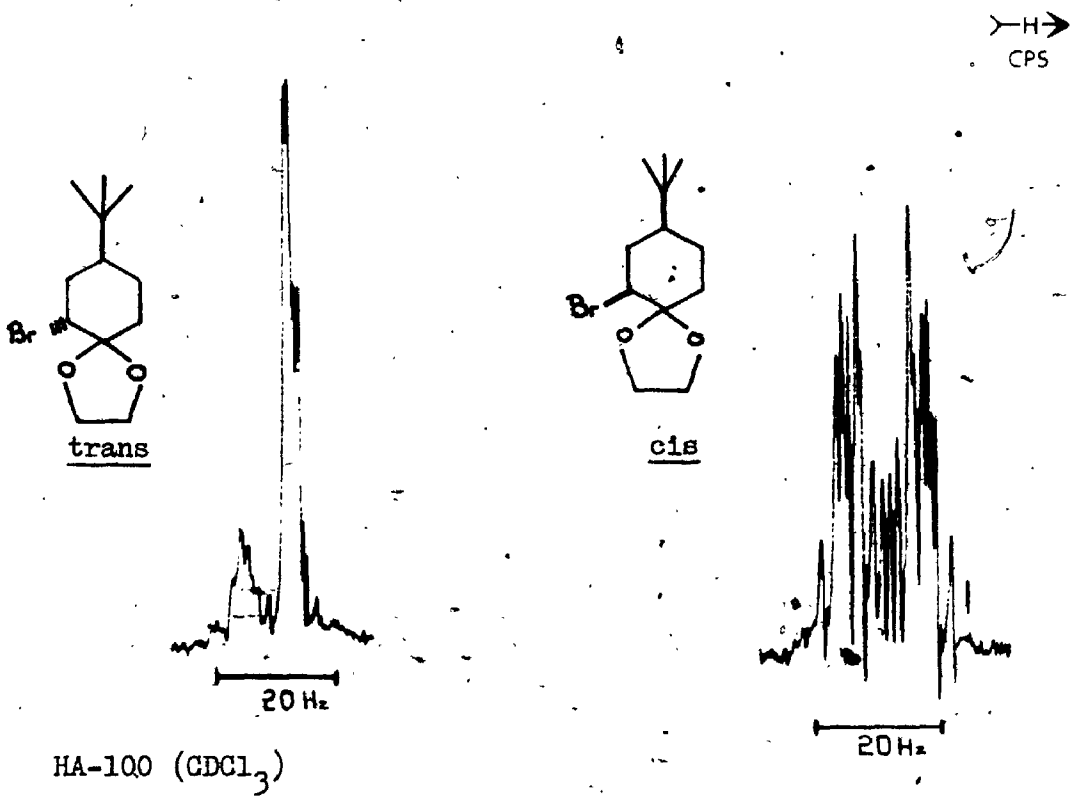
with the α-bromoketals of cyclopentanone 132 and cyclohexanone 136, the reaction with silver ion must be faster with the pseudo-axial bromine conformation. Although the pseudo-axial bromine conformation may be preferred due to greater dipole-dipole repulsion in the pseudo-equatorial bromine conformation, the rate increase is presumably the result of anchimeric assistance from the oxygen atom of the ketal. The equatorial bromine atom receives no anchimeric assistance because of its geometry relative to the ketal unit to overcome the inductive effect of two neighbouring oxygen atoms. This kind of participation from a neighbouring ether bond was demonstrated many years ago by Winstein's group.[86]



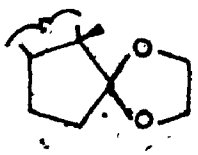
In order to check the importance of the conformation, the isomeric α-bromoketals were prepared from 4-t-butyl cyclohexanone 158. The [redacted]ers were separated by column chromatography on silica gel. The less polar compound 158a, an oil, was assigned the cis structure and the more polar compound 158b, a solid, was assigned the trans

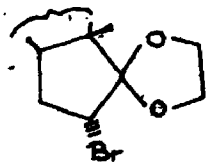
Fig. 1

ABSORPTION PATTERN OF KETAL GROUP OF CIS AND TRANS ISOMERS [158]



structure. Since the -CHBr- proton and the ketal protons were overlapping in the PMR spectrum, the assignment was made by the width of the $-OCH_2CH_2O-$ multiplet (see Fig. 1, above) in comparison with known systems.[87] In the steroid example below, the anisotropy





*Ref. 87.

ketal protons (δ): s, 3.89 m, 4.65-3.85 (includes -CHBr-)

of the C-Br bond is responsible for rendering the magnetic environment of the ketal protons non-equivalent resulting in a broad AA'BB'

type of pattern. In the case of the isomers of 2-bromo-4-t-butyl cyclohexanone ethylene ketal 158, the anisotropy of the C-Br bond would be expected to be more pronounced in the cis isomer than in the trans isomer; hence, the broad singlet (4.0-3.88 δ, $W_{\frac{1}{2}}$=2Hz) was assigned to the trans isomer 158b and the broad multiplet (4.24-3.84 δ, $W_{\frac{1}{2}}$=20Hz) to the cis isomer 158a. Furthermore, in acetone-d_6 the broad multiplet is simplified slightly (4.28-3.90 δ, $W_{\frac{1}{2}}$=8Hz) and a doublet appears further downfield (4.36 δ, J=4Hz, -CHBr-). This doublet is probably half of the pattern expected for the axial proton in the cis isomer.

As expected, the cis isomer reacts with silver ion at a much slower rate than the trans isomer. In 12 hr the cis isomer produced 40% of AgBr; whereas, in 1 hr, the trans isomer produced 68%*; therefore, as first approximation $k_{trans}/k_{cis} \approx 25$.

The crude product from the reaction of the trans isomer 158b with silver ion in methanol showed a strong, methoxy singlet (3.13 δ), as found in the PMR spectra of the cyclopentyl 133 and cyclohexyl 137 systems, but this was entirely missing in the crude product from the reaction of the cis isomer. Instead, the crude product from the cis isomer shows broad, complex peaks between 4.2 and 3.1 δ. On hydrolysis, the crude product of the cis isomer produced an acidic fraction the methyl esters of which showed three spots on TLC; whereas, the crude product of the trans isomer, a neutral oily solid 159, gave no acidic fraction on hydrolysis. The products from the cis isomer were

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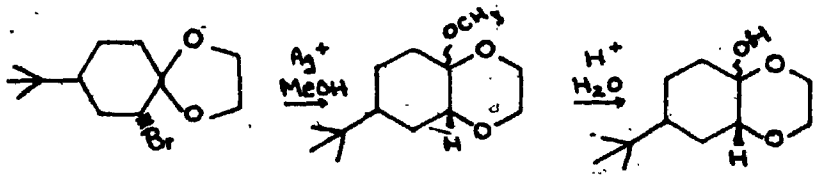
* This assumes the trans impurity is completely reacted in 12 hr and the cis impurity produces negligible AgBr in 1 hr.

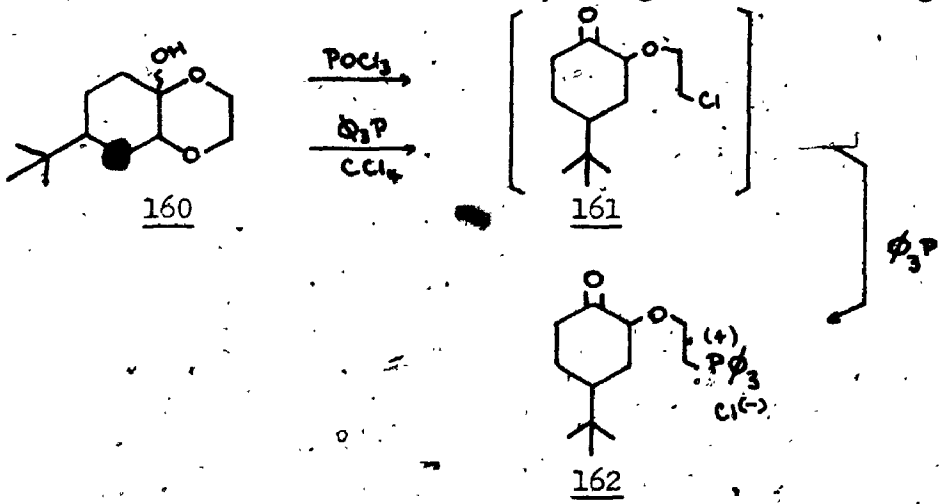
not examined further, but the oily solid 160, 9-hydroxy-6-t-butyl cyclohexa-1,4-dioxan, was purified by re-crystallization.



158b 159 160

The PMR spectrum of dioxan 159 showed a doublet of doublets at 3.52 and 3.32 δ (J=12Hz and 3Hz) which suggested an axial proton. Unfortunately, this pattern cannot be seen in the hemiketal 160 because of the complexity of peaks from the other $-OCH_2CH_2O-$ protons. In either case no attempt was made to define the stereochemistry at the 9-position. The hemiketal 160 showed strong hydroxyl absorption at 3620, 3590 and 3480 cm^{-1} and C-O absorption at 1110 cm^{-1} in the ir spectrum. The mass spectrum gave a very strong parent ion at m/e 214 and a peak at m/e 196 which suggested loss of H_2O.

This hemiketal 160 was not dehydrated with $POCl_3$ or triphenylphosphine in carbon tetrachloride, but gave the same single product

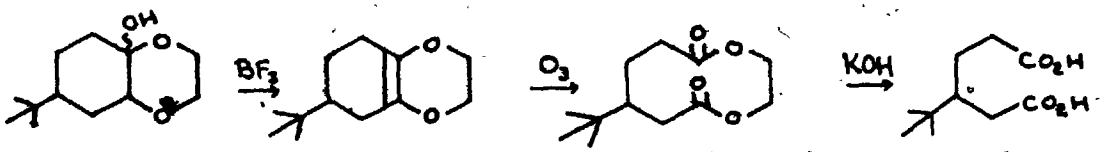


160 161 162

in both cases. It was not examined further, but by analogy with related systems[88,89] and its behavior with triphenylphosphine in

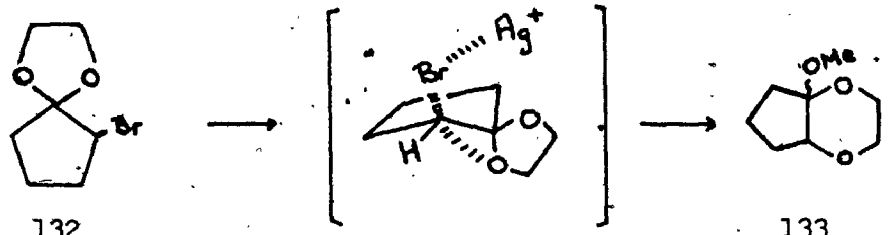
carbon tetrachloride the ketone structure 161 is suggested. The hemiketal 160 was readily dehydrated with BF_3 etherate in acetic acid at room temperature or by azeotropic distillation of water from benzene containing a catalytic amount of p-toluenesulphonic acid. The enol ether 163, 2,3-dihydro-4-t-butyl cyclohexa-1, 4-dioxin, had strong C-H absorption (2980, 2890 cm^{-1}) and C-O absorption (1200 cm^{-1}) in the ir spectrum but no carbonyl or hydroxyl absorption. The PMR spectrum showed a singlet at 3.9 δ ($-OCH_2CH_2O-$), a multiplet between 2.18 and 1.75 δ (allylic), a multiplet between 1.75 and 1.05 δ ($-CH_2-$) and a singlet at 0.85 δ (t-butyl) which supports the assigned structure.

Ozonolysis of the enol ether 163 gave a syrupy oil 164 with strong carbonyl absorption (1740 cm^{-1}) in the ir spectrum. When this oil was hydrolyzed with KOH in alcohol-water it gave 3-t-butyl-adipic acid 165, m.p. 115-117°, which was identical with an authentic sample prepared by nitric acid oxidation of 4-t-butylcyclohexanone.



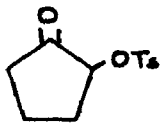
160 163 164 165

The ring contraction of 2-bromocyclopentanone ethylene ketal 132 by silver ion in methanol was probably unsuccessful because reaction with the pseudo-axial bromine conformation is faster than with the pseudo-equatorial bromine conformation which is needed for ring contraction.



132 133

The results from the 2-chlorocyclopentanone 69 and bromoketal 132 experiments suggest that in order to contract the five-membered ring a pseudo-equatorial conformation for the leaving group must be assured. This conformation favours the semibenzilic pathway and minimizes intermolecular nucleophilic displacement. In this regard, 2-tosyloxycyclopentanone 166 or other substituted phenyl sulfonates are worth trying. The increased bulk of the leaving group should provide sufficient energy difference between the conformers to



166

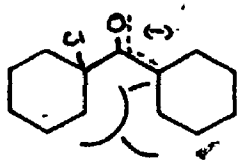
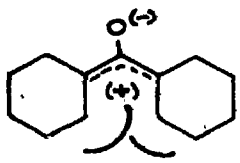
assure a pseudo-equatorial conformation. At the same time, the system has an excellent leaving group.

CHAPTER III

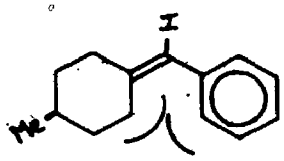
THE REARRANGEMENT OF α-CHLORODICYCLOHEXYL KETONE

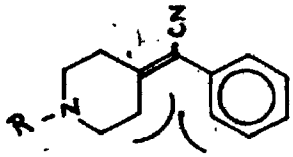
Introduction

The examination of space-filling models suggests that the enolate of chlorodicyclohexyl ketone 167 and the oxyallyl ion resulting from solvolysis of the enolate experience considerable steric interaction between the two rings. There are many examples in the literature

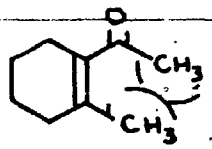
which show that non-bonded interaction of this type, referred to as 1,3 allylic interaction,[90] can prevent co-planarity of the interacting groups. For example, the ultraviolet spectra of olefins 169 and 170 suggest that the benzene rings are out of the plane of the olefins by

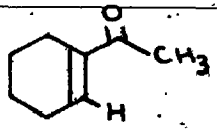

169


170

Ref. 90

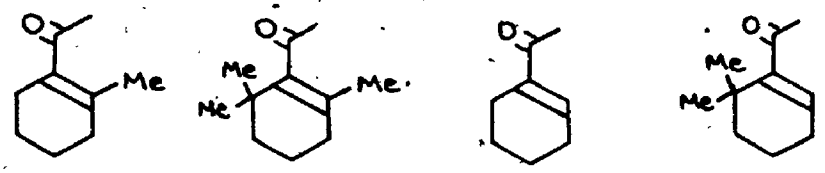
~35°. Likewise, the ϵ_{max} of enone 171 is only 1400 compared to a


171


172

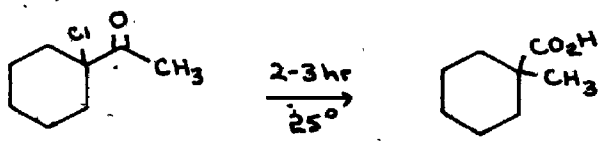
Ref. 91

value of $\sim 10^4$ for enone 172.[91] This is considered to be due to lack of planarity of the carbonyl and olefinic bonds due to repulsive interaction of the two methyl groups. Similarly, the $^{13}C{=}O$ downfield shift of enones 171 and 173 from that of enones 172 and 174 is consistent with decreased conjugative interaction which suggests a reduced planar arrangement of the carbonyl group and the double bond.[92]

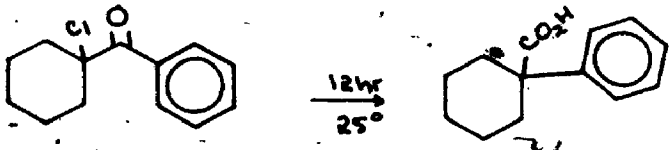


171 173 172 174 Ref. 92

Perhaps the steric crowding in the chlorodicyclohexyl ketone system is illustrated in the sluggishness of its reaction with base. Chloroketones 34 and 47b can be rearranged at room temperature by KOH in ether in 2-3 hr and 12 hr, respectively.[34] Under these conditions

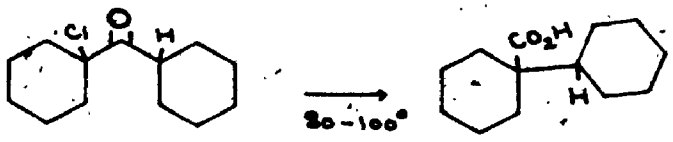


34 175 Ref. 34



47b 48a

chlorodicyclohexyl ketone 167 does not react. It requires more vigorous conditions, namely, KOH in refluxing dioxane.[93]



167 168 Ref. 93

Although one can suggest more than one reason for this higher

activation energy, the fact that it exists suggests that our hypothesis outlined in the objectives section of Chapter One may be correct and warrants investigation. Chlorodiisopropyl ketone 176 is an analogous system and, up to a point, was studied in parallel with chloroketone 167.

176 177

Attempted Rearrangement of Chlorodicyclohexyl Ketone 167 and Chloro diisopropyl Ketone 176 under Various Conditions

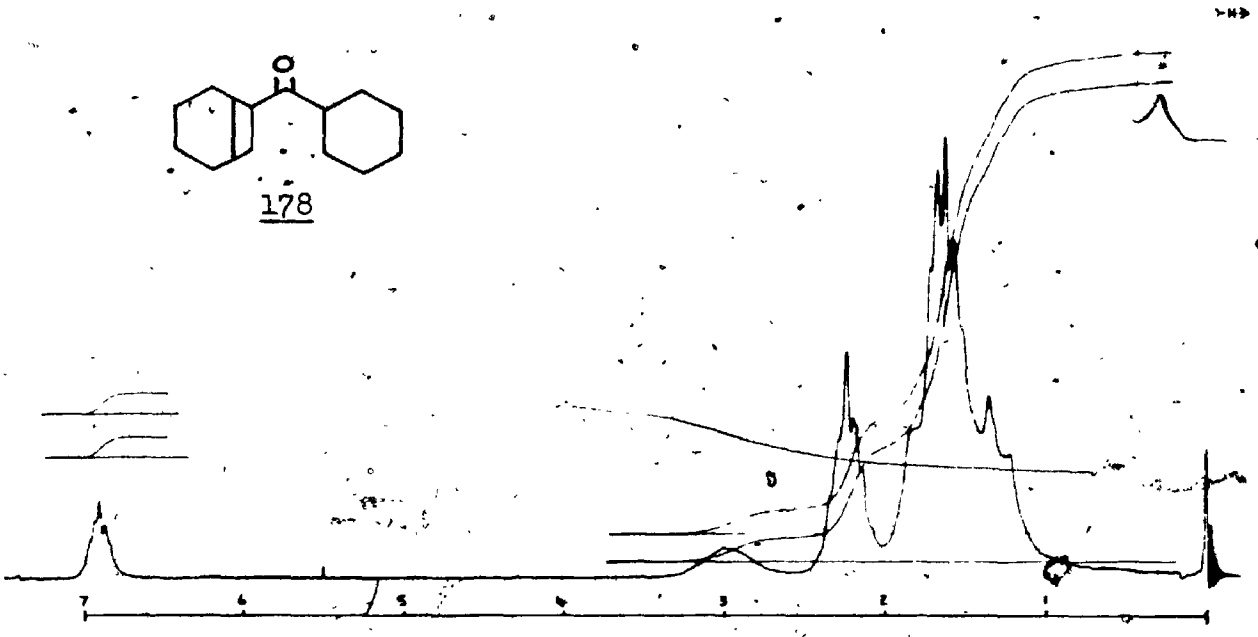
The reactions of chloroketones 167 and 176 with KOH in dioxane were repeated and found to produce the corresponding acids in 70% and 36% yields, respectively. A search was then undertaken for improved reaction conditions, preferably homogeneous. Unfortunately, all such conditions examined (Exptl., Table III, p. 138) resulted in reduced yields of Favorskii acid or none at all. Reaction of chloroketone 167 with silver ion in refluxing aqueous methanol gave no Favorskii acid 168, but instead recovered starting material and enone 178. Since these are conditions which favor a semibenzilic pathway with other

167 178

haloketones,[37,42] the result was not encouraging. The structure of enone 178 was suggested by its PMR spectrum (Fig. 2) which showed an olefinic multiplet (1H) at 6.95 δ and the U.V. spectrum which showed an

Fig. 2

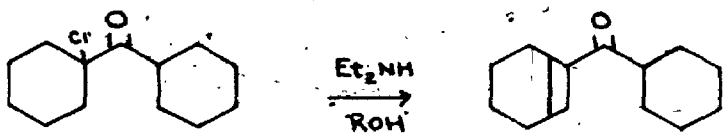
60 MHz Spectrum of Enone 178



178

T-60 ($CDCl_3$)

absorption maximum at 235 nm (ϵ = 8,000) in ethanol. The ir spectrum had carbonyl and olefinic absorption at 1660 and 1635 cm^{-1}, respectively. Riviere found that the enone was the sole product when chlorodicyclohexyl ketone 167 was treated with diethylamine.[94]

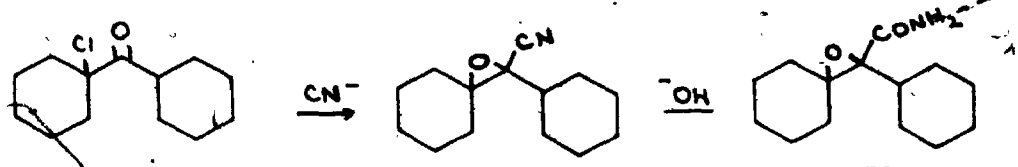


Ref. 94

167 178

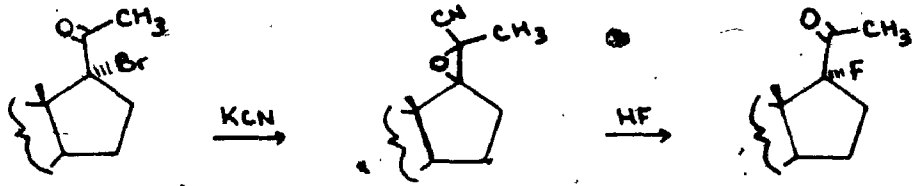
When chloroketone 167 was treated with NaCN in refluxing methanol, conditions which Warnhoff and Toong found to induce rearrangement of rigid bicyclic bromoketones by a semibenzilic pathway,[40] a single product, a neutral liquid, was isolated (80%) whose ir spectrum had

no carbonyl absorption, but showed cyano absorption at 2260 cm^{-1}. Structure 179 was assigned to this material and substantiated by base-catalyzed hydrolysis to the crystalline amide 180, m.p. 154-



167 179 180

155°. The ir spectrum of the amide 180 showed amino absorption at 3100 cm^{-1} and carbonyl absorption at 1685 cm^{-1}. The PMR spectrum was not particularly helpful, but the mass spectrum showed a strong parent peak of m/e 237 and elemental analysis gave correct figures for the formula, $C_{14}H_{23}NO_2$. The reaction of cyanide ion with aliphatic chloroketones to give glycidonitriles was demonstrated to be general by Italian workers in 1948.[95] Deghenghi and Gaudry found it to be a useful reaction for effecting the exchange of halogen without loss of stereochemistry in a steroidal haloketone.[96]



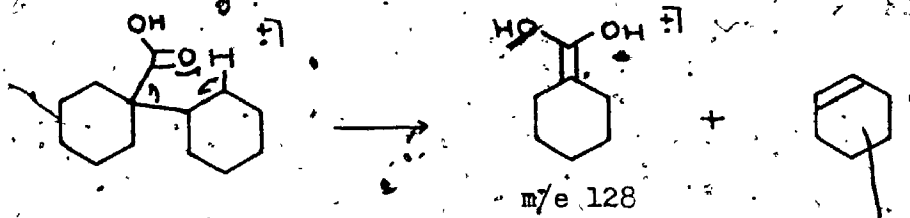
181 182 183 Ref. 96

By addition of 20% (v/v) methanol to the suspension of powdered KOH in dioxane, the homogeneity of the reaction was markedly improved without a reduction in yield of the Favorskii acid. These conditions were used to study the reaction pathway.

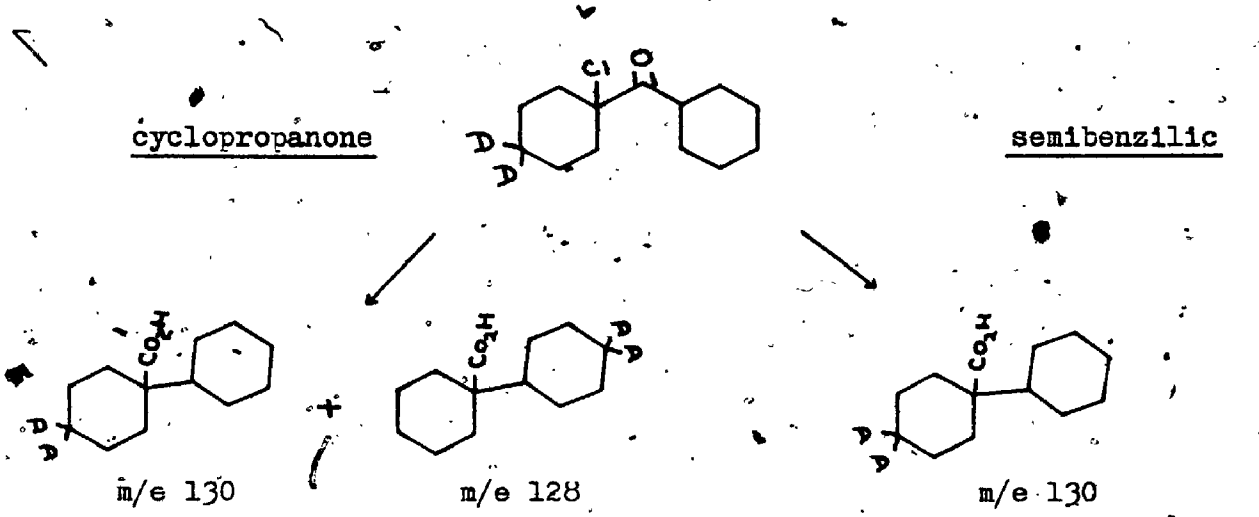
In methanol-O-d, the cyclopropanone mechanism must give acid with at least one C-deuterium atom incorporated; whereas, the semibenzilic pathway will produce an acid without exchange of protons, provided that enolization does not occur prior to rearrangement. When

chloroketone 167 was treated with NaOD in dioxane-methanol-O-d, deuterium analysis of the resulting acid showed 0.75D per molecule. On the other hand, when chloroketone 167 with 98% of the α-proton exchanged for deuterium was treated with NaOH in dioxane-methanol, the Favorskii acid had 0.02D per molecule. If one bears in mind the isotope effect, $^{kH}/_{kD} \sim 5$, for protonation of the carbanion formed by cleavage of the cyclopropanone,[37] then these results are consistent with a cyclopropanone mechanism. However, there was still the possibility that exchange occurred prior to rearrangement.

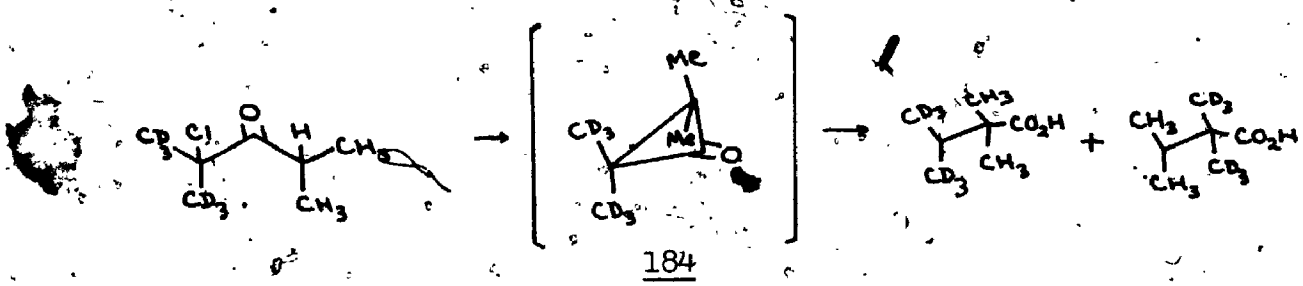
It was noticed during these experiments that the base peak of the mass spectrum of 1-cyclohexylcyclohexane carboxylic acid 168 was m/e 128 which was assumed to arise by the well known McLafferty rearrangement illustrated below. If the Favorskii rearrangement of chloro-



ketone 167 occurred by a semibenzilic pathway, labelling the ring bearing the chlorine atom with deuterium would cause this base peak to shift to a higher m/e value. On the other hand, if the mechanism involved a cyclopropanone system, the result would be an equal distribution of the deuterated cyclohexyl ring in the two possible locations in the product. In this case, there would be two equally intense peaks, one at m/e 128 and one at a higher m/e value. Since there were no other peaks for several mass units on either side of m/e 128, the assignment of mechanism would be straightforward even if both pathways were involved. The same idea is applicable to the



chlorodiisopropyl ketone system except that analysis by PMR spectroscopy would be possible. One difficulty with the latter system not encountered in the dicyclohexyl system would be the secondary β-isotope effect of unknown magnitude during the ring cleavage of 184.[97]



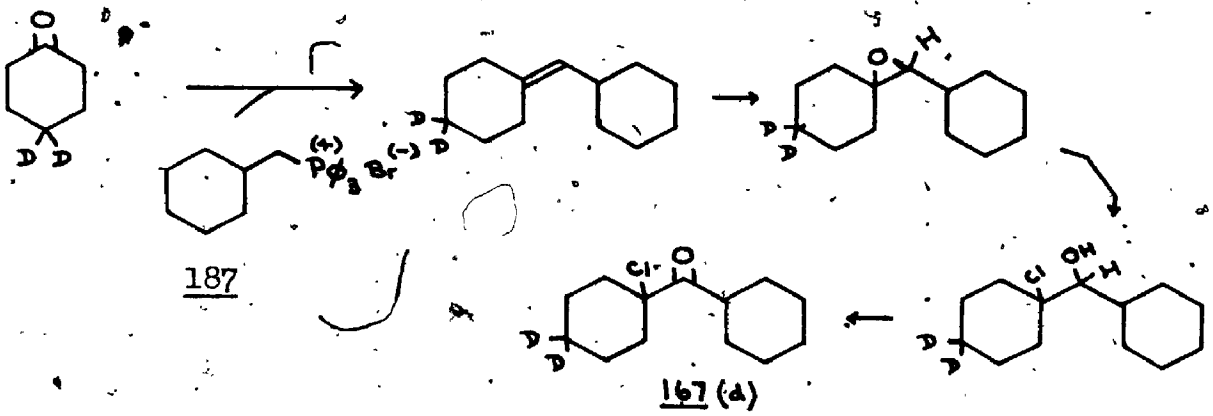
184

Nevertheless, this method could unequivocally allow distinction between the two reaction mechanisms.

Attempted Synthetic Routes to 1-Chlorodicyclohexyl Ketone-4,4-d_2 167 and to 1-Chloro-1,1-dimethyl-d_3-methyl Isopropyl Ketone 176

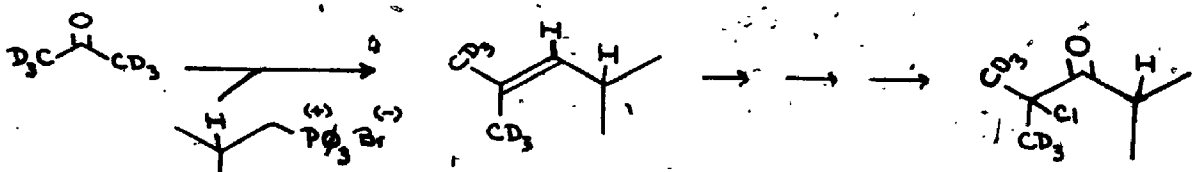
The Wittig Route

The first approach, outlined below, involved initial formation of an olefin by means of the Wittig reaction. The phosphonium salts



187

167 (d)

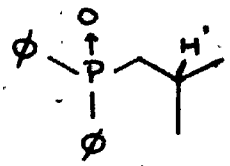


185

176 (d)

were readily prepared by heating benzene solutions of the alkyl bromide and triphenylphosphine in sealed glass tubes at 110-125°.

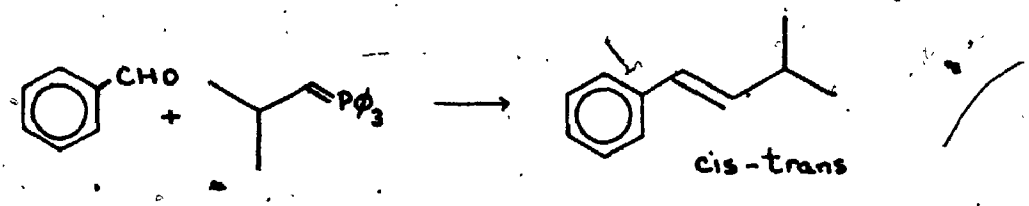
The phosphorane of isobutyltriphenylphosphonium bromide 185 was prepared by Corey's method with "dimsyl" ion.[23] On treatment with acetone, the red colour rapidly faded, but aqueous workup gave a precipitate of isobutyldiphenylphosphine oxide 186 (75%). The pentane



186

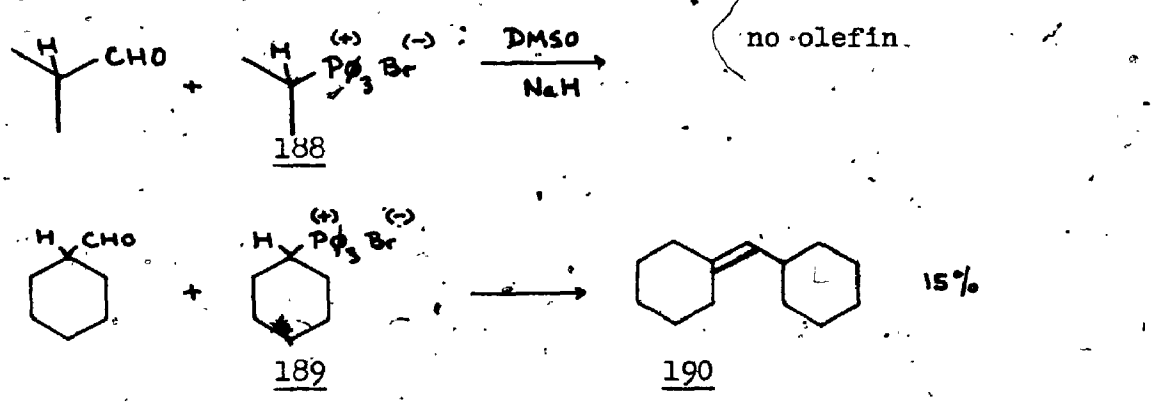
extract showed a strong benzene singlet and a complexity of high field peaks, but only very weak olefinic absorption. Longer reaction times did not change this result. When the phosphorane was generated in ether with n-butyl lithium, no olefin was produced. The difficulty lies in the use of acetone since a mixture of cis and trans olefins could be

prepared from benzaldehyde under the same conditions. The same



problem arises with cyclohexanone since no olefinic product could be produced on reaction with the phosphorane generated from hexahydrobenzyltriphenylphosphonium bromide 187.

The Wittig reaction was then attempted with isobutyraldehyde plus isopropyltriphenyl phosphonium bromide 188 and cyclohexanecarboxaldehyde plus cyclohexyltriphenylphosphonium bromide 189 as illustrated:



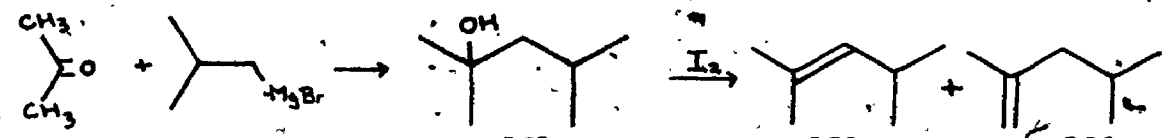
The reaction with isobutyraldehyde failed, but the reaction with cyclohexanecarboxaldehyde was partially successful since it gave a 15% yield of olefin 190. However, this low yield is a poor basis for a synthetic scheme; therefore, other routes were examined.

The reason for the failure of the Wittig reaction in this series is perhaps due to repulsive steric interactions. In his review[98] Maercker notes that "if the reaction between the ylide and the carbonyl compound is sterically hindered, enolization becomes the main reaction. This reaction is particularly pronounced with easily enolizable ketones such as cyclohexanone". The fact that the red colour of the phosphorane

rapidly faded on addition of ketone but formed no olefin suggests that enolization of the ketone is rapid. The same situation has been observed for acetone.[98,99]

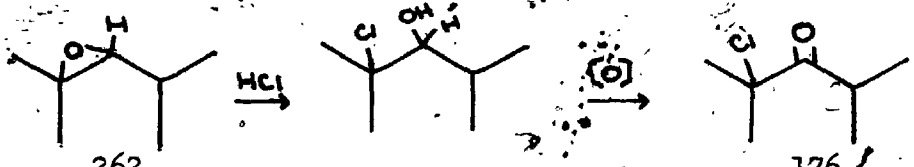
The Grignard Route

A second route was examined only briefly since it is only applicable to the diisopropyl system. This involved the addition of isobutyl Grignard reagent to acetone followed by dehydration to give a mixture of olefins. The Grignard reaction gave 2,4-dimethylpentan-



191 192 193

2-ol 191 in 30% yield after purification. This alcohol was readily dehydrated by heating in the presence of a catalytic amount of iodine. The olefins were isolated in 80% yield and consisted of a 4:1 mixture of a 2,4-dimethylpent-2-ene 192 and its isomer 193. Both olefins were



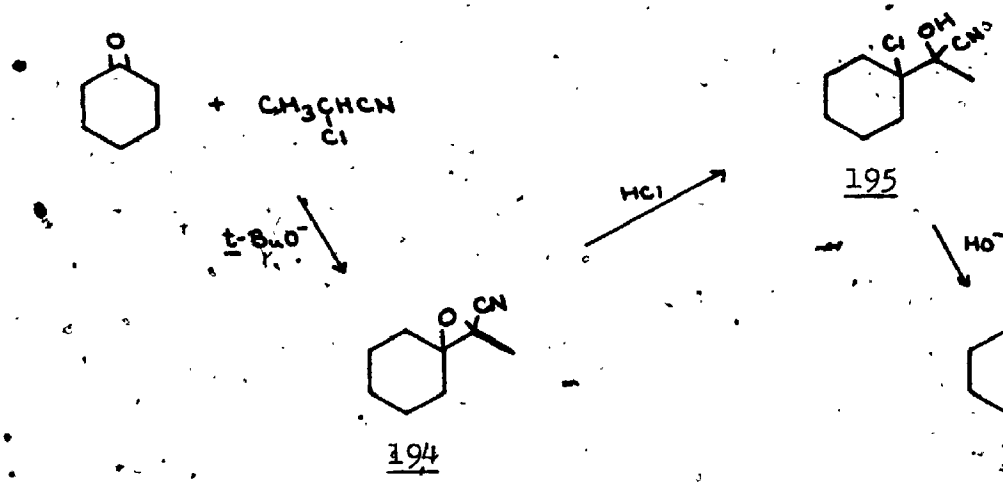
262 176

cleanly converted to their epoxides by m-chloroperbenzoic acid. The epoxide mixture in acetonitrile was treated with gaseous HCl at -78° to effect ring opening and then the crude product of this reaction was oxidized with Jones reagent. The resulting crude product was shown to contain chloroketone 176 as a major product by comparison of its GLPC and PMR spectrum with those of an authentic sample. No attempt was made to maximize yields since this route, although feasible, proved unnecessary

(see p. 72).

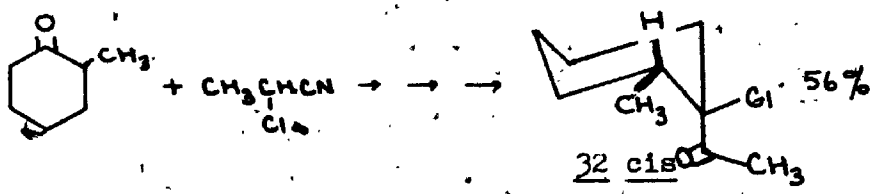
Stork's Route

In 1960 Stork and co-workers developed a route to chloroketones using the condensation of α-chloronitriles with ketones. Opening the epoxide ring of the resulting glycidonitrile with HCl would allow selective positioning of the chlorine atom.[100] This method is illustrated below for the preparation of 1-chlorocyclohexyl methyl ketone 34 in 54% overall yield from cyclohexanone. When 2-methylcyclohexanone is used



Ref. 100

only cis-1-acetyl-1-chloro-2-methylcyclohexane 32 is produced. If the condensation occurs from the least hindered side of the methylcyclo-

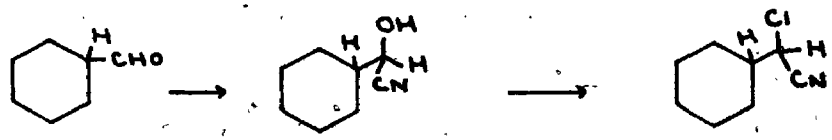


Ref. 100

hexanone, then the epoxide ring opens in trans-fashion with HCl-$ZnCl_2$-ether.

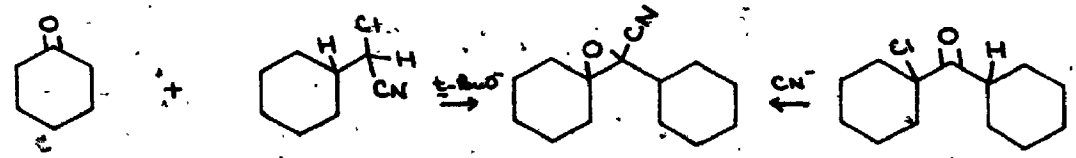
In order to prepare the dicyclohexyl system by this route α-chlorocyclohexylacetonitrile 197 was required. This compound was conveniently prepared in 78% yield by treatment of cyclohexanecarboxal-

dehyde cyanohydrin 196 with triphenylphosphine in carbon tetrachloride. Condensation with cyclohexanone gave glycidonitrile 179 in 85% yield



196 197

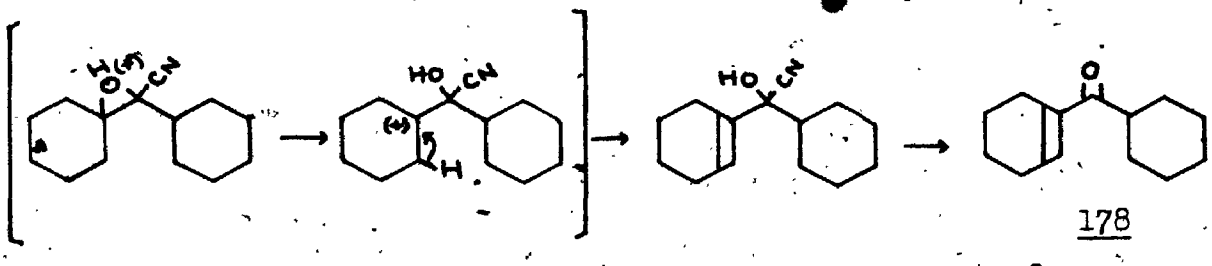
after purification by column chromatography. The material was identical



197 179 167

in all respects with the product from the reaction of chlorodicyclohexyl ketone 167 and NaCN.

When the glycidonitrile 179 was treated with HCl gas in ether at 0° and then with aqueous base, the crude product contained only trace amounts of chloroketone 167. The major product was enone 178 presumably formed by the following route since the chloroketone 167 is stable under workup conditions. The presence of $ZnCl_2$ did not

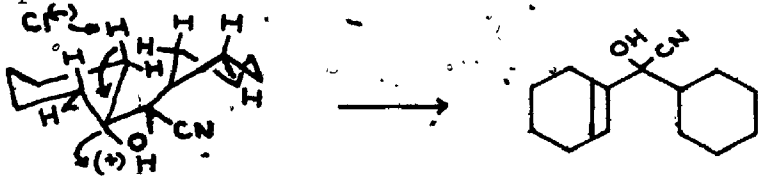


178

produce chloroketone 167. Lowering the temperature to -70° simply stopped all reaction, and reaction for 1.2 hr at -55° gave again predominantly enone 178. Different solvents were tried (CH_3CN, HOAc, $CHCl_3$, CCl_4) but without success. In the more polar solvents, acetonitrile and acetic acid, the reaction gave enone 178 with small amounts of starting material 179. Tetraethyl ammonium chloride was added to the reaction

mixture to increase the concentration of chloride ion with the hope of favouring addition to the carbonium ion, but no chloroketone was observed. In fact, tetraethyl ammonium chloride alone in refluxing acetonitrile or hot acetic acid (85°) followed by basic workup was sufficient to effect enone formation. In acetonitrile, the chloride ion is probably acting as a base.

The only difference between glycidonitrile 179 and Stork's examples is substitution of a cyclohexyl group for a methyl group; therefore, the formation of enone rather than chloroketone must be dependent on steric factors. The stereospecificity of the ring opening to give only cis chloroketone 32 suggests that the chloride ion is involved in the transition state. Possibly, in the dicyclohexyl case, the chloride ion is prevented from approaching as close as needed to form a chlorine-carbon bond, but gets sufficiently close to aid in proton removal.

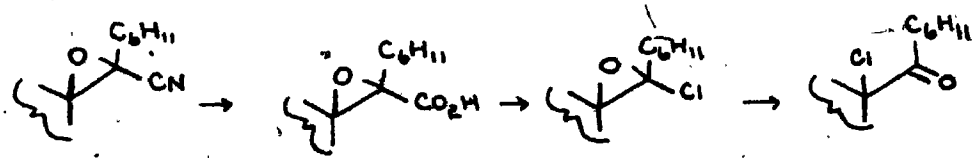


At this point, other routes were tried, but eventually a modification of Stork's route led to the desired chloroketone as explained on p. 71.

α-Haloepoxide Route

It occurred to us that even if the glycidonitrile 179 could not be directly converted to chloroketone 167 it might still be a useful intermediate if it could be hydrolyzed to the glycidic acid 198. The Hunsdiecker reaction could be used to convert the acid to the halide.

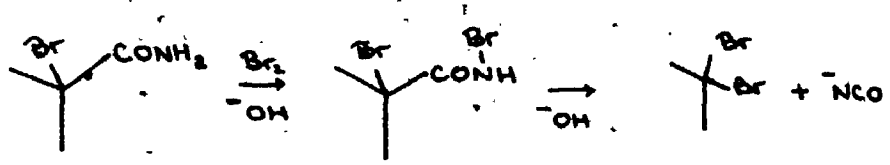
Since α-haloepoxides are thermally unstable and acid sensitive, rearranging under either of these conditions to haloketone,[101] this would provide an alternative route to chlorodicyclohexyl ketone 167.



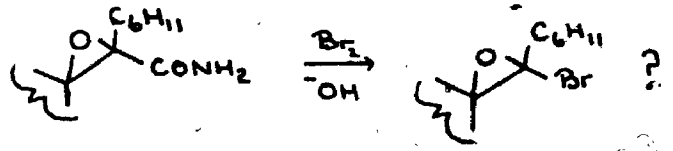
179 198 199 167

Since base-catalyzed hydrolysis had been found to stop at the amide stage even on prolonged heating and because acid-catalyzed hydrolysis presumably caused ring opening of the epoxide, it was decided to try diazotisation of the glycidamide 180. When a solution of amide 180 in acetic acid was treated with 20% aqueous $NaNO_2$, the amide precipitated and gave no reaction. Further attempts with $NaNO_2$ in acetic acid alone gave only recovered amide 180. The failure of the diazotization reaction was surprising because it has proved to be a useful method of hydrolyzing hindered amides.[102,103] Similarly, Wolfrom's procedure for hydrolyzing an amide,[104] nitrosyl chloride in chloroform, gave no acidic material. The crude residue contained at least three other compounds besides starting material 180. In ethanol or methanol, the nitrosyl chloride produced a very complex mixture of products; therefore, this reaction was not pursued.

In 1963, Stevens and co-workers showed that α-bromohaloamides in the presence of base, or α-bromoamides in the presence of halogen and base, rearranged to give geminal dihalides.[105] We attempted to extend this to glycidamides with the hope of preparing



Ref. 105



180

α-haloepoxides. A suspension of glycidamide 180 in aqueous base treated with chlorine showed very little reaction even after several days. To improve homogeneity, the reaction was tried in methanol at 0°. When Br_2 was added to a solution of the glycidamide 180 in methanol containing sodium methoxide, a crystalline product could be isolated in 20% yield by preparative TLC. The crude product from the reaction showed a methoxy singlet in its PMR spectrum, but this peak was missing in the PMR spectrum of the purified product. Furthermore, the ir spectrum of the crude product had carbonyl absorption at 1756 cm^{-1} ($CHCl_3$), but the isolated solid had a broad, perhaps a double, carbonyl absorption between 1720 and 1712 cm^{-1} ($CHCl_3$). Analysis showed nitrogen and oxygen in a ratio of 1:3. The following scheme summarizes what was thought to have happened.* Unfortunately, structure 200 requires a parent ion of m/e 253; whereas, both electron impact and chemical ionization gave m/e 252. This last

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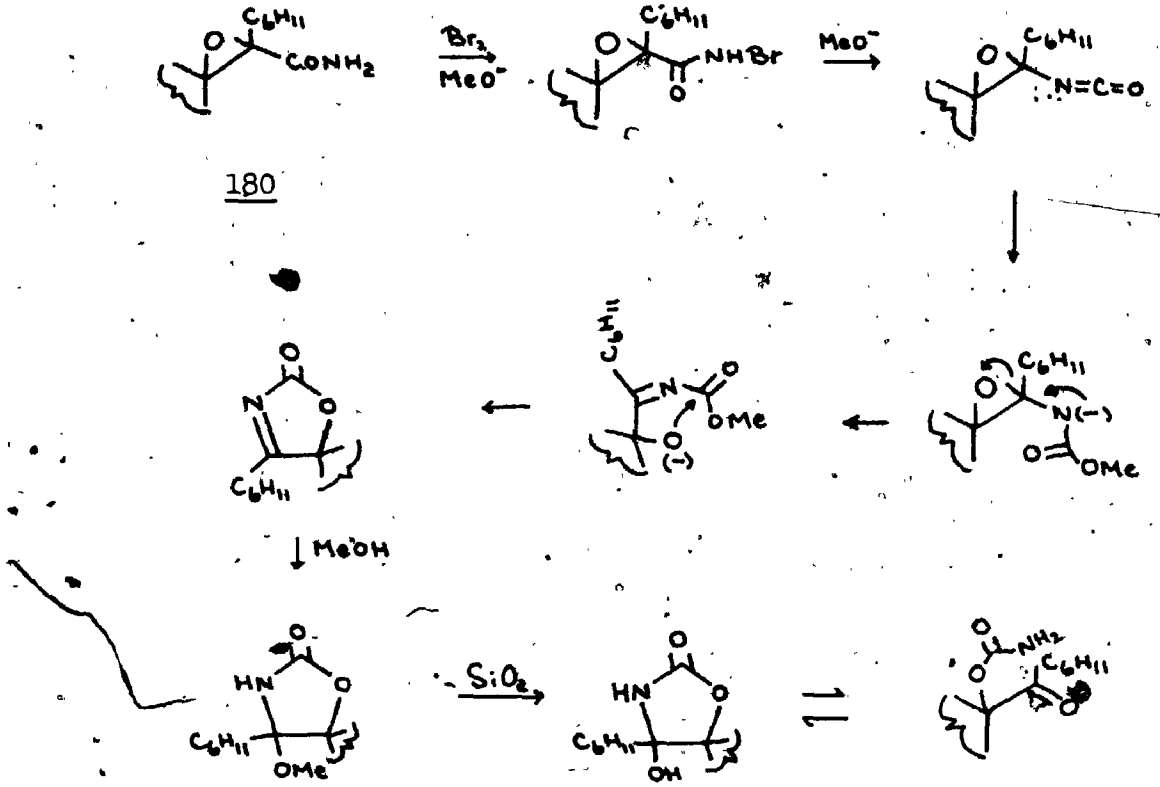
* A recent publication[106] has shown Br_2-MeO^- to be an excellent reagent for the Hofmann rearrangement, but the reagent is not stable above -20°.



180

crude product

purified product 200

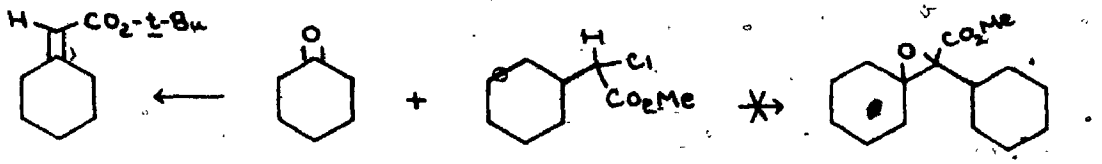
value cannot be the parent ion since the product definitely contains a single atom of nitrogen. Whether m/e 252 represents P^+-1 or P^++1 was not determined. If structure 200 were correct, base-catalyzed hydrolysis would give α-hydroxydicyclohexyl ketone 201 which might have served as precursor for α-chlorodicyclohexyl ketone 167.

A preliminary attempt to hydrolyze the compound 200 using aqueous base and dimethoxyethane at room temperature gave only recovered starting material after several hours. Furthermore, attempts to convert hydroxyketone 201 to chloroketone 167 using thionyl chloride, HCl in chloroform or triphenyphosphine in carbon tetrachloride gave only starting material 201 or a mixture of starting material 201 and enone 178. These results discouraged

continuation of the approach using the Hofmann degradation before structure 200 was definitely established.

Darzen's Condensation and Miscellaneous Routes

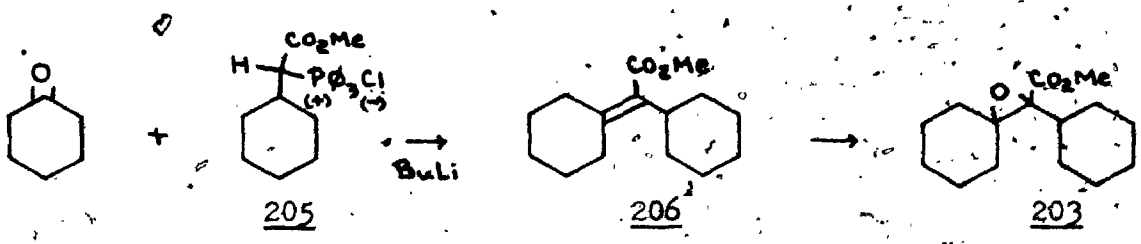
Since the glycidonitrile 179 could not be hydrolyzed to the corresponding glycidic acid, an attempt was made to form glycidic ester 203 directly from cyclohexanone. The Darzen's condensation of



204 202 203

cyclohexanone and methyl 2-chlorocyclohexylacetate 202 was attempted with t-butoxide, but it gave no glycidic ester 203. The major compound isolated from the mixture had carbonyl absorption in the ir spectrum ($CHCl_3$) at 1705 cm^{-1}, showed an olefinic multiplet (1H) at 5.41 δ and a t-butyl singlet (9H) at 1.48 δ and was tentatively assigned structure 204. The failure of the Darzen's condensation was probably due to the increased steric requirement of the carbomethoxy group over that of the cyano group since the pKa values of 197 and 202 are approximately the same.

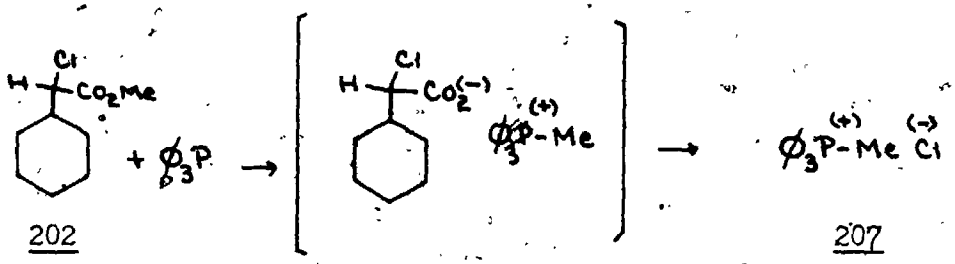
Another route which was considered is outlined below:



205 206 203

Although the phosphonium salt 205 is bulkier than those used earlier, it would have the advantage of producing a more stable (less basic) phosphorane which might have reduced the competing enolization of the

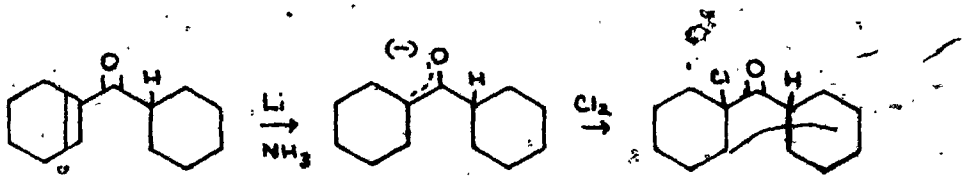
ketone. Unfortunately, phosphonium salt 205 could not be formed. When chloroester 202 was heated with triphenylphosphine in benzene in a sealed glass tube at 150°, a white solid was formed (70%) which was identified as methyl triphenylphosphonium chloride 207. Presumably, an α-halo carboxylate phosphonium salt forms initially and then eliminates chloride ion to form an α-lactone which gives rise to a



202 207

complex mixture of compounds. It is interesting in this regard that the ethyl ester shows no reaction at all under the same conditions. This approach was not continued.

The only synthetically useful reaction product derived from the glycidonitrile 179 was the enone 178, so it was decided to attempt enolate formation by $Li-NH_3$ reduction of the enone 178. The enolate could then be quenched with chlorine to give chloroketone 167. Work by House and co-workers has demonstrated that metal enolates

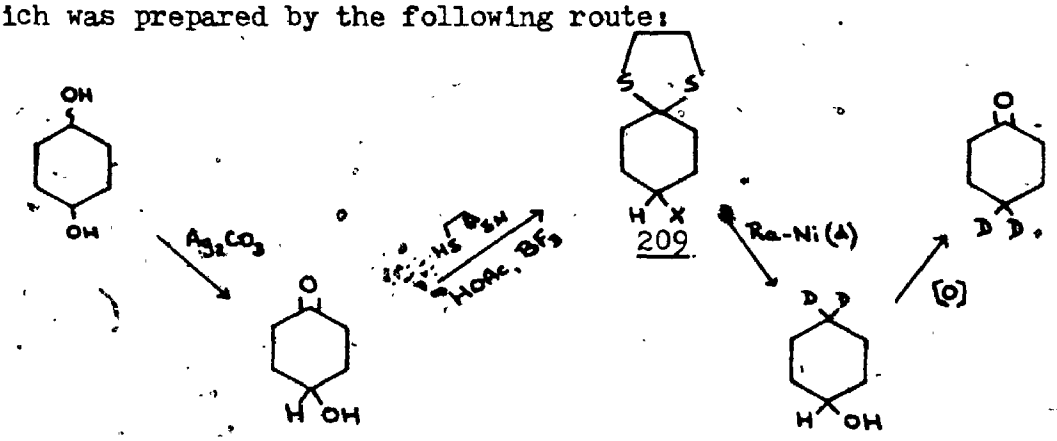


178 167

prepared in aprotic, oxygen-free media will retain their structural and stereochemical integrity for at least several hours.[107] Hence, there should be no problem with ring equilibration during preparation of the enolate. This route proved successful and its details are presented in the next section.

Synthesis of 1-Chlorodicyclohexyl Ketone-4,4-d_2 167(d)

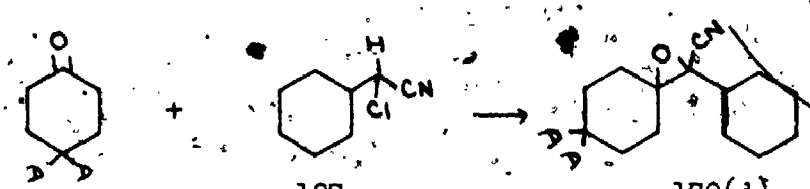
The first part of the synthesis required labelled cyclohexanone which was prepared by the following route:



By using Fetizon's procedure,[108] 1,4-cyclohexanediol was selectively oxidized to 4-hydroxycyclohexanone 208 in 60% yield after purification by column chromatography. The ir spectrum showed hydroxyl absorption at 3620 and 3400 cm^{-1} and carbonyl absorption at 1720 cm^{-1}. In the PMR spectrum, the proton at position 4 gave rise to a multiplet at 4.15 δ. When a mixture of hydroxyketone 208 and 1,2-ethanedithiol in acetic acid was treated with BF_3 etherate, two compounds were produced which were readily separated by column chromatography. The less polar compound (50%) was a colourless oil which had carbonyl absorption at 1728 cm^{-1} but no hydroxy absorption in the ir spectrum and was assigned the monoacetate structure 209a. The more polar compound (13%) was a crystalline solid which showed no carbonyl absorption but had hydroxyl absorption at 3600 and 3440 cm^{-1} in the ir spectrum and was assigned the hydroxy thioketal structure 209b. The PMR spectra supported the proposed structures.

A suspension of deuterated Raney nickel in an ethanol-O-d_1

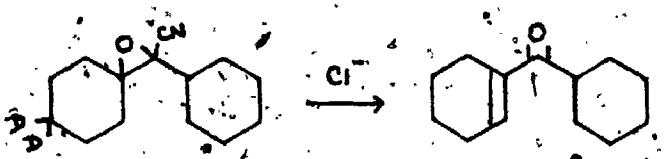
solution of acetoxythioketal 209a was refluxed for 1.5 hr. The isolated, crude cyclohexanol-4,4-d_2 was oxidized with Jones reagent to yield cyclohexanone-4,4-d_2. This ketone was condensed with α-chlorocyclohexylacetonitrile 197 without purification. The crude condensation product was chromatographed on a column of silica gel to yield epoxynitrile-4,4-d_2 179(d) slightly contaminated with



197 179(d)

α-chloronitrile 197 in 67% yield from acetoxythioketal 209a.

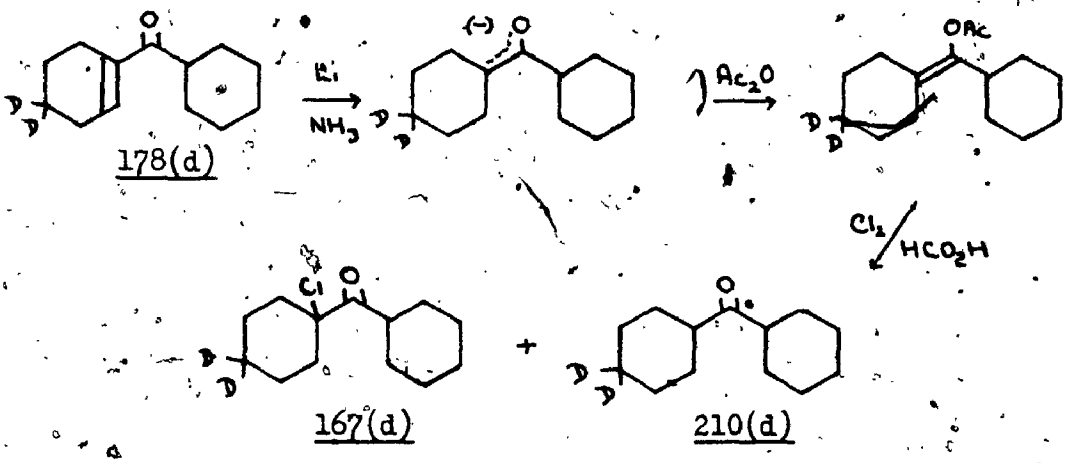
The epoxynitrile-4,4-d_2 179(d) was quantitatively converted to 4,4-d_2-cyclohex-1-enyl cyclohexyl ketone 178(d) by reflux in a solution of tetraethyl ammonium chloride in acetonitrile for 22 hr. A solution of the crude enone-4,4-d_2 178(d) in anhydrous ether



179(d) 178(d)

was added to a deep blue solution of lithium in liquid ammonia. After the colour had faded (1.5 hr), the ammonia was evaporated and the grey residue was suspended in ether and treated with a large excess of acetic anhydride in order to trap the enolate. Exploratory experiments had shown that more chloroketone was formed by chlorinating the enol acetate rather than the enolate itself. After removal of the ether, the residue was taken up in a small volume of formic acid and added dropwise to a cold solution of chlorine (5% excess) in formic acid. The isolated, crude oil showed three spots on TLC corresponding

to chloroketone 167(d), dicyclohexyl ketone 210(d) and an unidentified, more polar compound. Analysis by GLPC showed chloroketone 167(d) and ketone 210(d) in the ratio 45:55. Purification by column chroma-



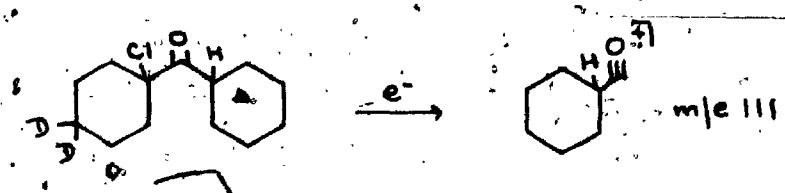
178(d) 167(d) 210(d)

tography gave 1-chlorodicyclohexyl ketone-4,4-d_2 167(d) in an overall yield of 8% from acetoxythioketal 209a.

Deuterium analysis by mass spectroscopy of both chloroketone-4, 4-d_2 167(d) and dicyclohexyl ketone-4,4-d_2 210(d) gave the following percentage distribution of deuterium for each: (See Fig. 3, p. 77)

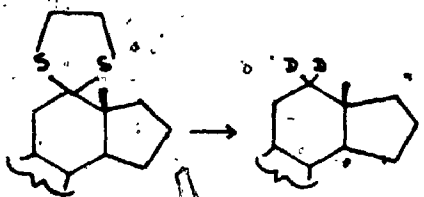
3.9 (d_0), 24.8 (d_1), 55.5 (d_2), 10.5 (d_3), 4.2 (d_4), 1.1 (d_5).

Examination of the fragment ion, m/e 111, from chloroketone-4,4-d_2 167(d) proved that no equilibration of the two rings had taken place during preparation since this peak was virtually unchanged from that of non-deuterated material.

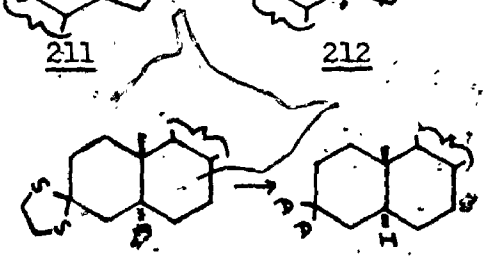


In retrospect, the presence of species with more than 2 is to be expected. Djerassi and co-workers have shown that additional label is incorporated during the desulfurization of a thioketal by

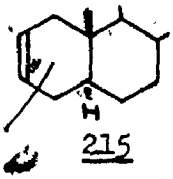
Raney nickel.[109] For example:



211 → 212 : 1% d_1, 18% d_2, 72% d_3, 8% d_4, 1% d_5



213 → 214 : 18% d_2, 48% d_3, 18% d_4, 11% d_5, 5% d_6



215 : 8% d_1, 28% d_2, 33% d_3, 19% d_4, 7% d_5, 1% d_6

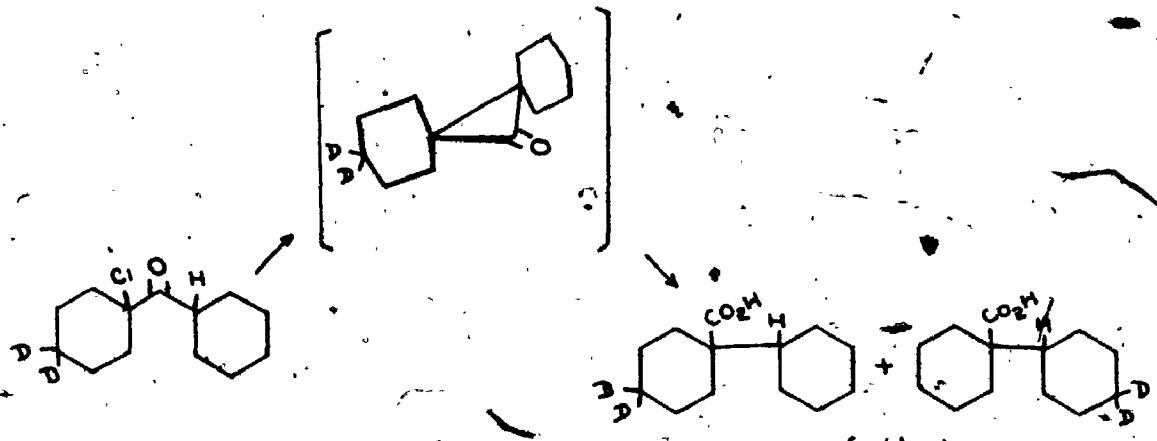
However, the additional label is localized to the carbons adjacent to the thioketal centre. In the mass spectrum of the deuterated olefin 215 above, the peak derived from the retro Diels-Alder cleavage is virtually unchanged from that of the non-deuterated olefin.[109] With respect to the formation of cyclohexanone-4,4-d_2, this means that the label will be at carbons 3, 4 and 5. Hence, there will be a negligible isotope effect on the McLafferty fragmentation of the Favorskii acid-d_2 168(d).

The Favorskii Reaction of 1-Chlorodicyclohexyl Ketone-4,4-d_2 167(d)

Chloroketone-4,4-d_2 167(d) was treated with NaOH in dioxane-methanol as before to give 1-cyclohexylcyclohexane carboxylic acid-d_2 168(d) (72%) as a colourless solid. Deuterium analysis by mass spectroscopy showed the following percentage distribution in the ion due to the McLafferty rearrangement:

51 (d_0), 13.9 (d_1), 27.4 (d_2), 6.9 (d_3), 2.3 (d_4), 0.6 (d_5)

Comparison of this distribution with that of the chloroketone (p.74) indicates complete equilibration of the two rings within experimental error during the Favorskii rearrangement of 1-chlorodicyclohexyl ketone-4,4-d_2 167(d). Furthermore, the acyl cleavage fragment from dicyclohexyl ketone-d_2 210(d) has a pattern which is practically superimposable on that of the McLafferty fragment (see Fig. 3, p.77) This would only be true if the rearrangement had involved a symmetrical



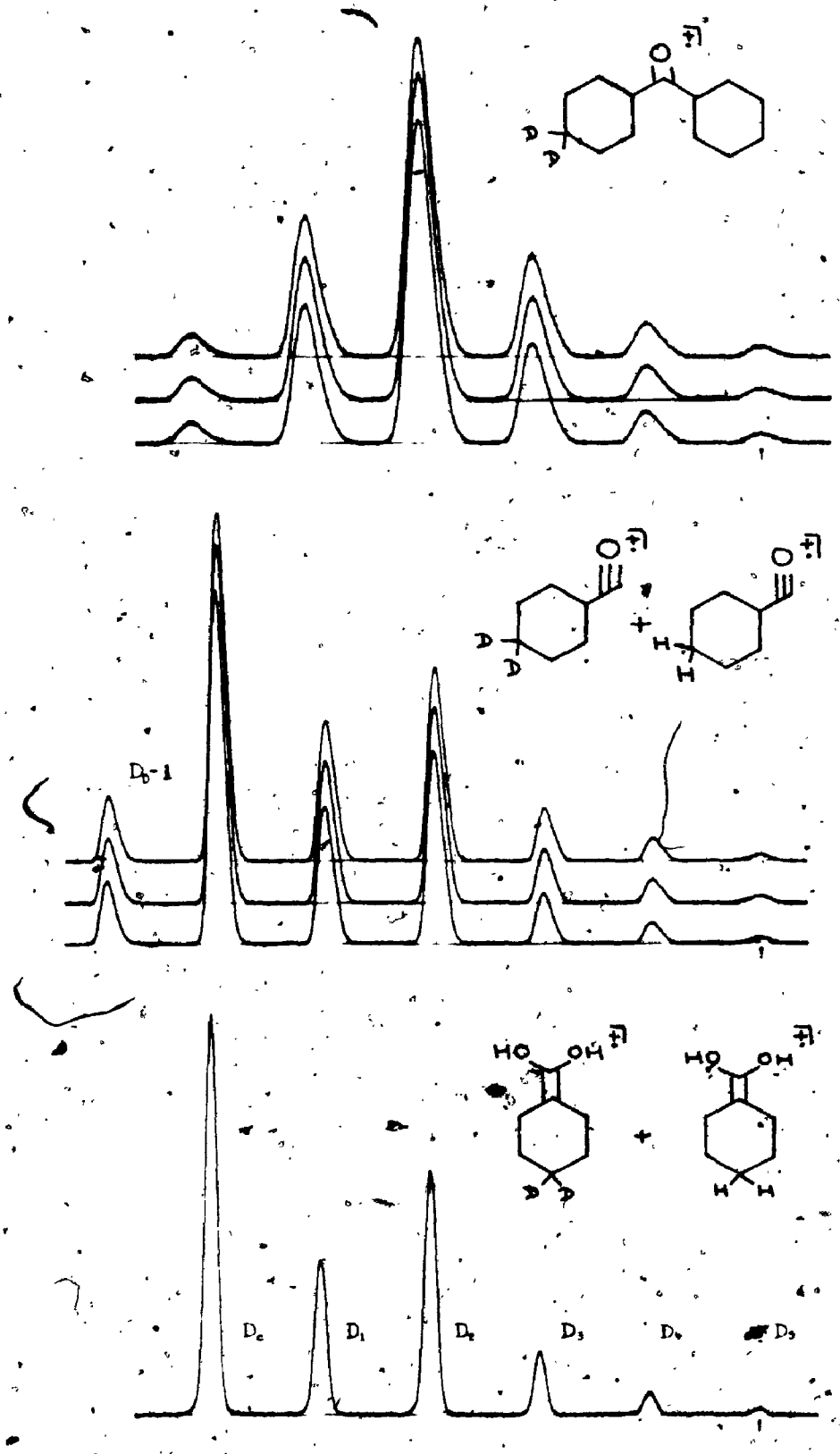
167(d) 168(d)

intermediate. There was no reason to believe that chlorodiisopropyl ketone would have behaved differently; therefore, this study was concluded.

Although space filling models indicated a considerable barrier to rotation of the two rings in 167, it is likely that they exaggerate the magnitude of this barrier or else the rings do not need to be "very co-planar" at any stage before a cyclopropanone is formed.

Fig. 3

Deuterium Distributions by Mass Spectroscopy

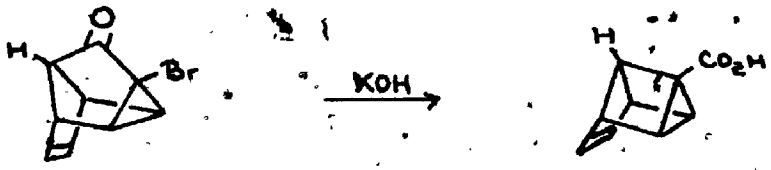


CHAPTER IV

Attempted Favorskii Rearrangement of Representative α-Bromocyclopropyl Ketones

Introduction

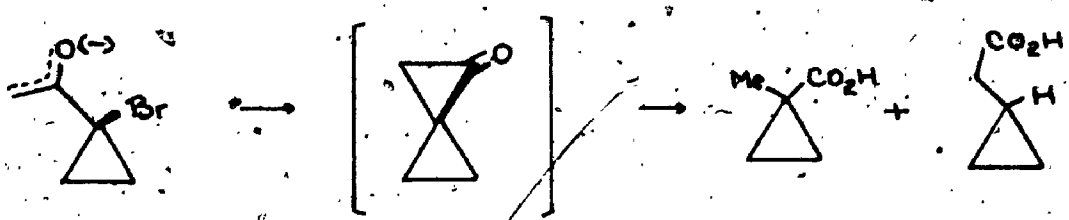
The rearrangement of α-bromocyclopropyl ketones with base is of interest for diverse reasons. Although Klumpp, et al.[47] isolated Favorskii acid 217 from bromo-ketone 216, in general, the reactivity of these bromo-ketones with base is unknown. Assuming the Favorskii

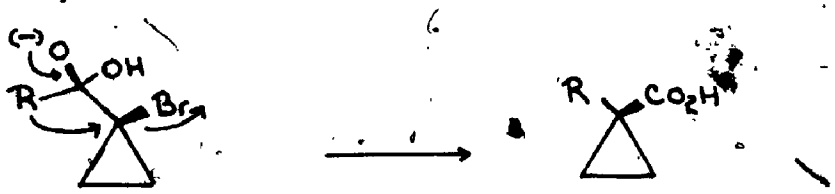


Ref. 47

216 217

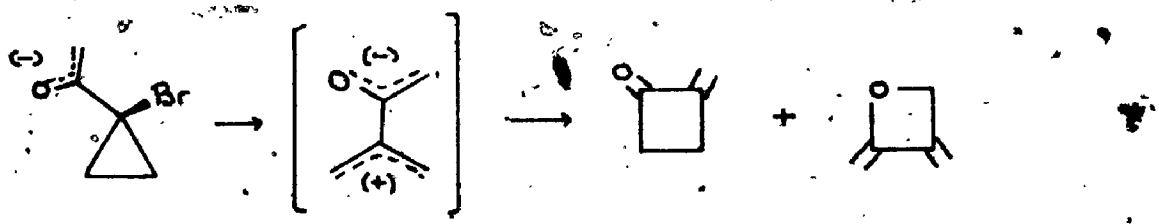
rearrangement is a general phenomenon, one could not say with any certainty whether the reaction could be expected to go via a semibenzilic or a cyclopropanone mechanism although the system illustrated above argues for a semibenzilic pathway. The cyclopropanone pathway would require a strained spiro-intermediate while the semibenzilic pathway would require an S_N2 displacement at a cyclopropyl carbon. The



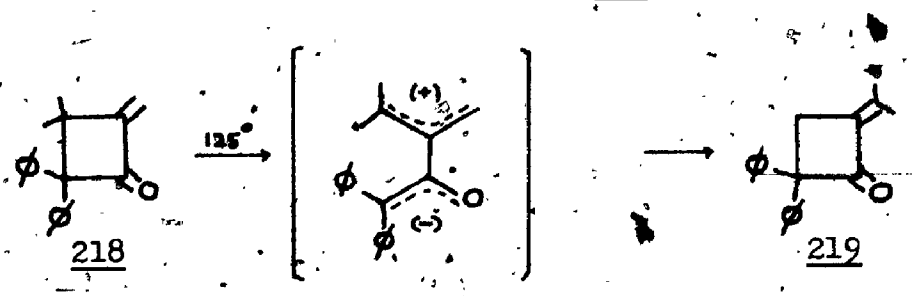


intermolecular S_N2 reaction at cyclopropyl carbon has long been known as a particularly unfavourable one and, although the displacement would be intramolecular, there were no examples available at the beginning of this work.

Furthermore, if solvolysis of the halogen to form an oxyallyl intermediate were a necessary step in the Favorskii rearrangement, one might see evidence of this in the form of cyclobutanone or oxetane products since solvolysis of halide at a cyclopropyl centre proceeds with concerted ring opening.[112,113,114] For example,



the cyclobutanone 218 is thought to rearrange through a dipolar species to the isomeric cyclobutanone 219.[115]

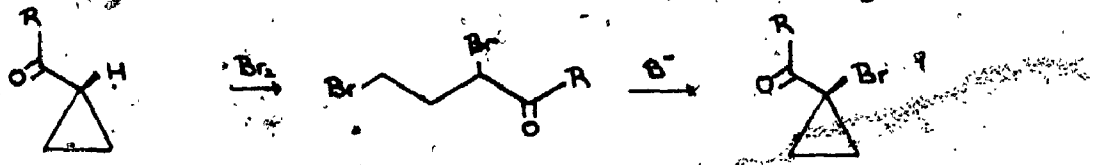


218 219 Ref. 115

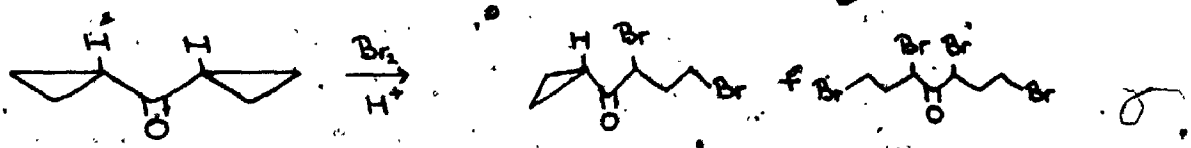
The bromoketones examined were methyl, phenyl and cyclopropyl α-bromocyclopropyl ketones, partly because the parent ketones are readily available and partly because they represent a range of possibilities at the α-carbon. The first problem was to devise a general synthetic route.

Synthesis of α-Bromocyclopropyl Ketones

The successful synthesis of these bromoketones was based on two earlier observations: bromine was found to cleave the cyclopropyl ring in cyclopropyl phenyl ketone to give presumably a α,γ-dibromoketone[74] and base was found to produce cyclopropyl rings from γ-bromoketones[116]. Since the α-proton of α-bromoketones is the most acidic, it seemed likely that a combination of the steps--first, ring opening and then, ring closing--would give the desired bromoketone.



On reaction with bromine in acetic acid in the presence of HBr, dicyclopropyl ketone 220 gave two products in the ratio 86:14. The major product was isolated by distillation and examined by ir and PMR spectroscopy. The shift of the carbonyl absorption to higher wave numbers and the doublet of doublets at 4.76 δ representing one proton indicated an α-bromoketone. The rest of the spectrum supported

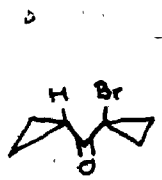


220 221 222

structure 221. When dibromoketone 221 was treated with refluxing aqueous NaOH solution for thirty minutes, a single neutral product was isolated in 80% yield. The mass spectrum showed a single bromine atom, and the spectroscopic data, in particular the AA'BB' doublet of multiplets at at 1.62 and 1.40 δ representing two protons each (Fig. 4, p. 81) supported structure 223.

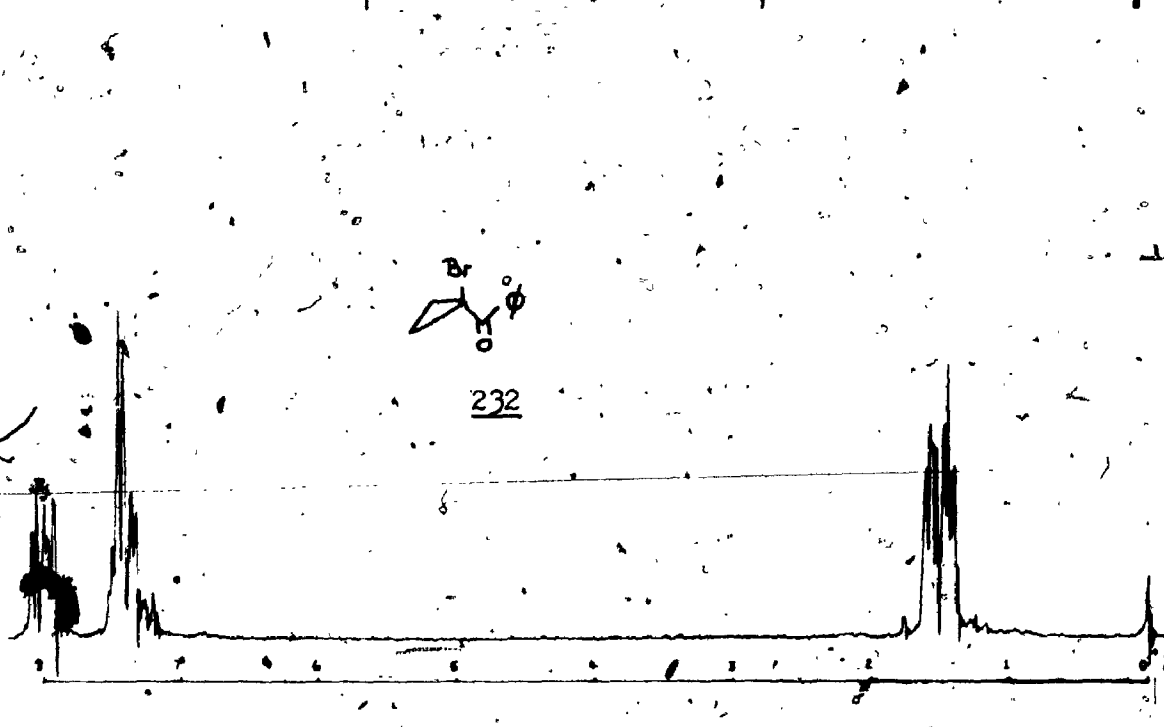
Fig. 4

PMR Spectra of Cyclopropyl Bromoketones



223

229



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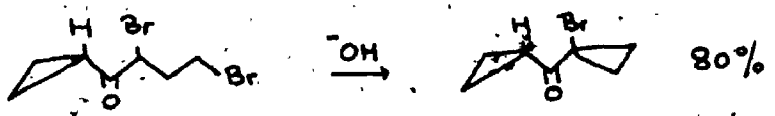
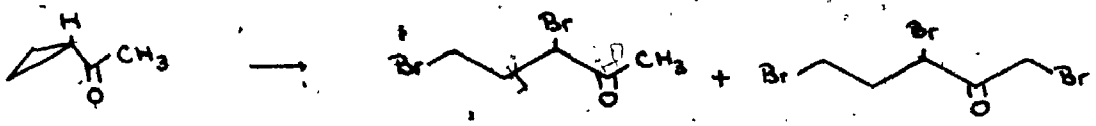


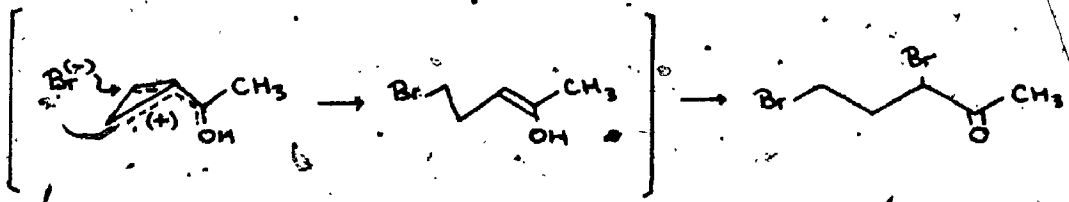
221 223

When HBr gas was bubbled through an equimolar mixture of bromine and ketone 224 in carbon tetrachloride, the colour rapidly faded and a single major product was isolated. The structure of the product was easily assigned as 3,5-dibromopentan-2-one 225 by examination of the PMR spectrum.

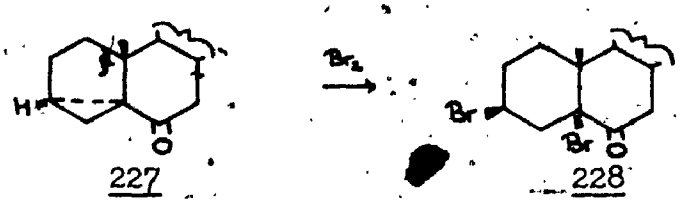


224 225 226

It was suspected initially that bromination might take place preferentially at the methyl group, but this was not the case. This is probably due to the fact that the initial carbonium ion formed is strongly delocalized into the cyclopropyl ring and rapidly attacked



by bromide ion. In support of this mechanism, Kohen, et al., have observed that bromination of cyclosteroid 227 gives a 3β-bromo



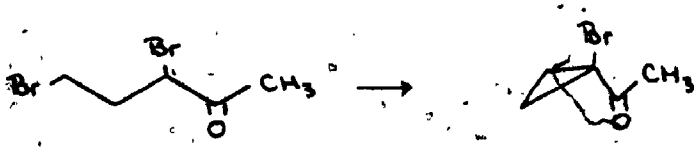
227 228

Ref. 117

substituent.[117] The tribromoketone 226 is probably formed after ring

opening since it is practically eliminated when any excess of bromine is avoided.

The ring closure proved to be more exacting with 3,5-dibromopentan-2-one 225 than with dibromoketone 221 since refluxing aqueous NaOH solution gave polymeric material with only 5% of α-bromocyclopropyl methyl ketone 229. Whether this is due to the greater sensitivity of

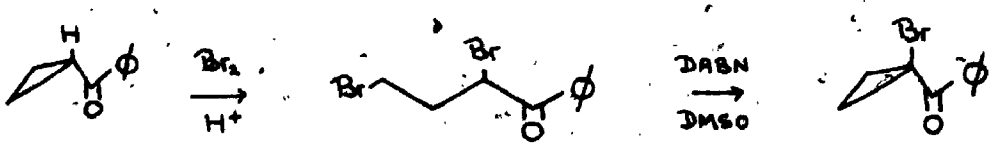


225 229

bromoketone 229 to base or to competing side reactions with dibromoketone 225 was not determined. Instead, a search was begun for a suitable reagent to effect ring closure. A reasonably strong base with low nucleophilic properties was required so a series of tertiary amines were examined of which 1,4-diazabicyclo[4.3.0]nonene (DABN) gave the highest yield.

In dimethysulfoxide, DABN reacted with dibromoketone 225 to give a single, volatile, neutral product in 50% yield. The mass spectrum showed a single bromine atom and the PMR spectrum with its characteristic AA'BB' doublet of multiplets at 1.64 and 1.40 δ (Fig. 4, p. 81) permitted assignment of structure 229.

In the same manner, cyclopropyl phenyl ketone 230 was converted to α-bromocyclopropyl phenyl ketone 232 in 74% yield (Fig. 4, p. 81)

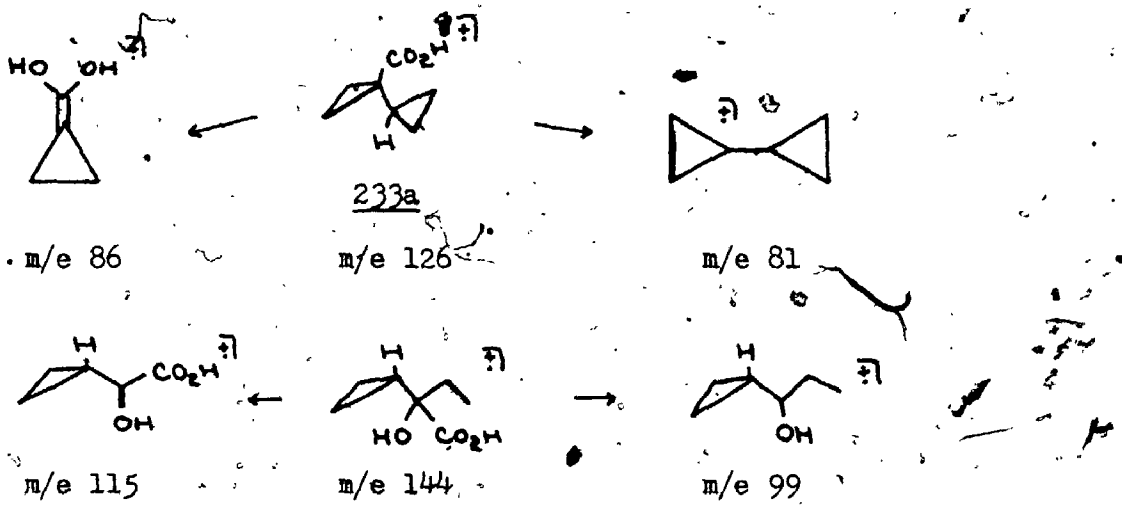


230 231 232

Reactions of α-Bromocyclopropyl Ketones with Base

The failure of α-bromodicyclopropyl ketone 223 to react with cyanide ion in either methanol or 2-methoxyethanol or with silver ion in methanol or water indicates that it lacks the labile character associated with haloketones. After 20 hr in refluxing 10% methanolic hydroxide solution, only 10% of the starting material was consumed and the resulting product was a complex mixture. At room temperature, NaOH in tetrahydrofuran gave no reaction but on refluxing for 42 hr, besides starting material, a small amount of acidic material 234 was produced which turned out to be the same compound produced in concentrated aqueous base (see below). The corresponding alkoxides in methanol and t-butanol produced complex acid mixtures, but the ethoxide-ethanol system showed a major compound on TLC which was less polar than the others. Furthermore, when this crude acidic mixture was methylated with diazomethane in ether, two overlapping peaks were observed on GLPC. The major compound was isolated by column chromatography and, although it only showed a single spot on TLC, it gave both peaks on GLPC. This material had a very complicated PMR spectrum, but vinyl absorption was evident. To determine whether one of the peaks was due to methyl α-cyclopropylcyclopropane carboxylate 233b, the esters were ozonized in methylene chloride at 0°. If the Favorskii ester were present, it should survive and a single peak would be observed on GLPC. If the esters were cis-trans double bond isomers, they would both be cleaved and both peaks would disappear on GLPC. It was observed that both peaks did disappear and that an aldehyde-ester was produced. The identification was not pursued further.

Attention was then turned to the conditions which Klumpp, et al., had used to effect the Favorskii rearrangement of bromoketone 216.[47] After refluxing a suspension of α-bromodicyclopropyl ketone 223 in 30% aqueous NaOH for 13 hr, an acidic fraction was isolated as a tan oil which crystallized on standing. The crude was readily purified by sublimation to yield white crystals, m.p. 92-93.5°. The 60 MHz PMR spectrum (Fig. 3, p. 86) was too complicated to be the hoped for Favorskii acid since one would expect an AA'BB' doublet of multiplets for the protons on the ring bearing the two substituents. Furthermore, the mass spectrum showed major peaks at m/e 115 and 99 but nothing at m/e 126, 86 or 81, the peaks one might expect for the Favorskii



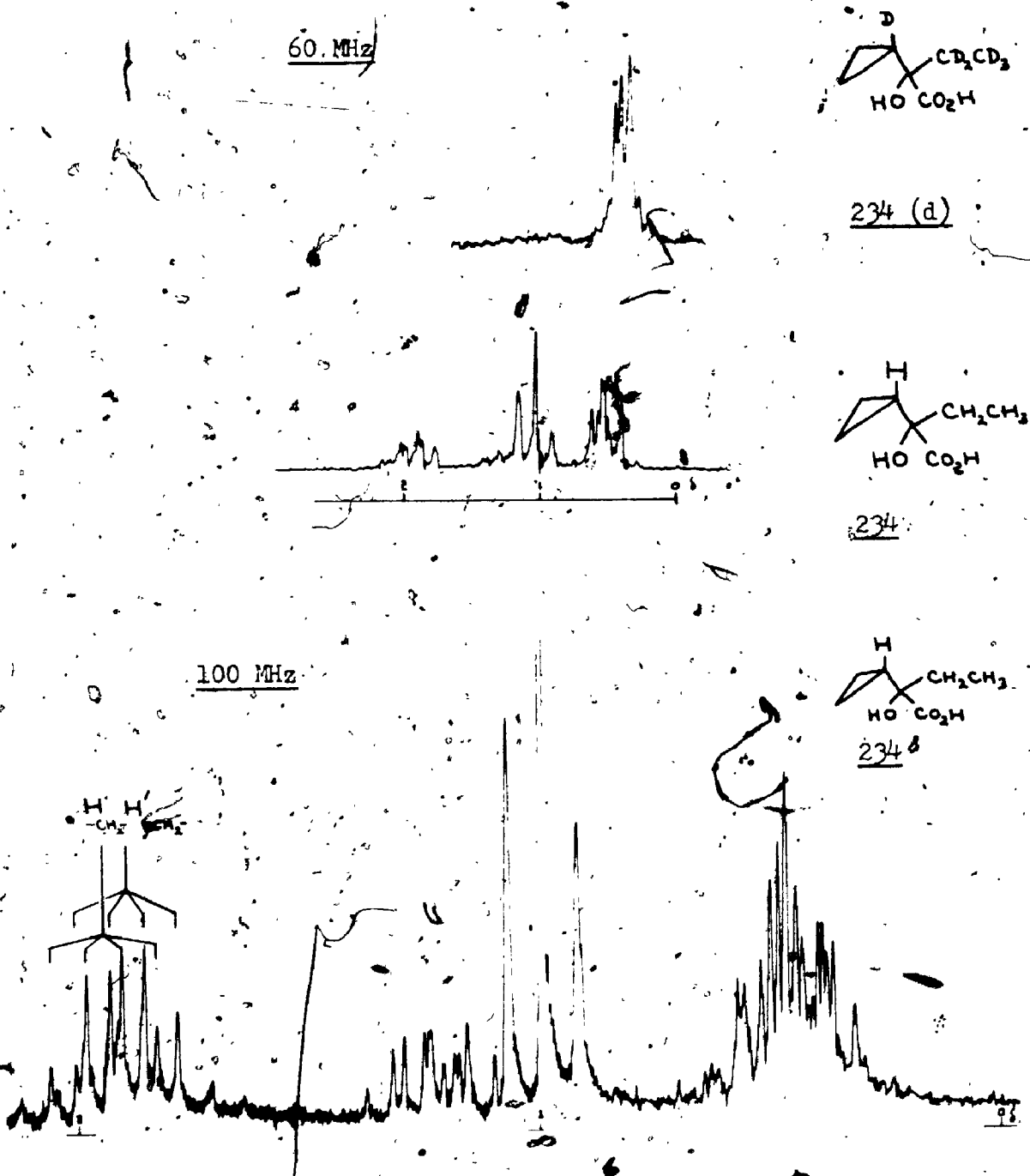
233a

acid 233a. Finally the elemental analysis proved that the product was not the Favorskii acid.

When a sample of the acid was methylated with diazomethane in ether, the ir spectrum of the ester showed hydroxyl absorption. This was supported by the PMR spectrum which had a broad singlet at 2.85 δ. This singlet disappeared on treatment with D_2O. Furthermore, the mass spectrum showed major peaks at m/e 129 and 99. Only one peak (m/e 129) had shifted 14 amu. ($-CH_2-$) from those of the corresponding acid

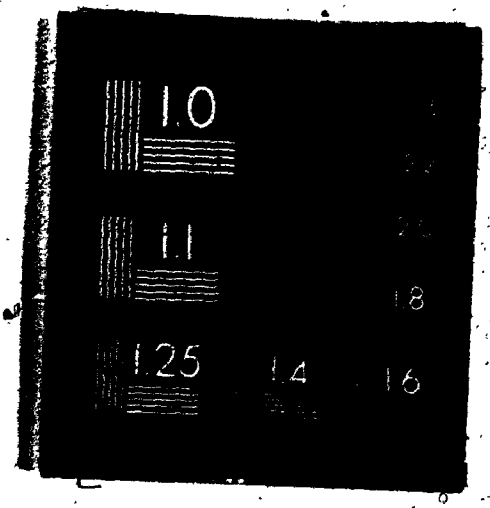
Fig. 5

100 MHz and 60 MHz Spectra of Cyclopropyl Ethyl Glycolic Acid.



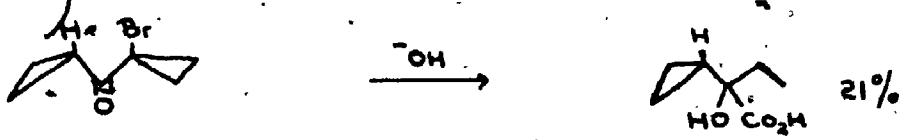
2 3

OF/DE



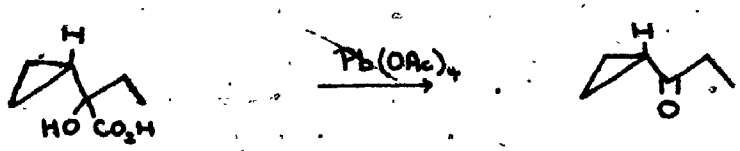
fragments. This indicates that these peaks are formed by separate pathways. Summation of m/e 99 and m/e 59 for the lost carbomethoxy group indicated that the molecular weight of the ester was at least 158. With the elemental analysis, this gave $C_7H_{12}O_3$ as the simplest molecular formula for the acid.

Examination of the 100 MHz spectrum (Fig. 5, p. 86) in concert with spin decoupling results showed overlapping quartets coupled only to a triplet. This suggested an ethyl group with magnetically non-equivalent methylene protons. The remaining two multiplets which were coupled only to each other integrated for 1 proton and 4 protons and suggested a mono-substituted cyclopropane ring. Hence, the product was assigned structure 234, 2-hydroxy-2-cyclopropyl butanoic acid.



223 234

To confirm the assignment, the carboxylic acid was treated with lead tetra-acetate in benzene and found to decarboxylate at room temperature to give the known ethyl cyclopropyl ketone 235 identified by its 2,4-dinitro phenyl hydrazone, m.p. 166-167.5°.[118]

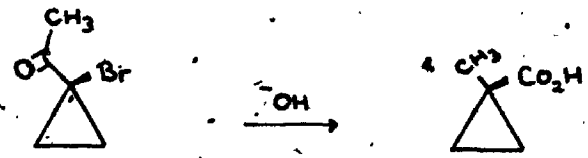


234 235

When α-bromocyclopropyl methyl ketone 229 was treated with refluxing aqueous silver nitrate solution for 4.5 hr, starting material was recovered. On treatment with sodium methoxide in methanol, some starting material remained in the complex neutral fraction, but no

Favorskii acid was present in the acidic fraction to judge from the PMR spectrum which lacked the typical AA'BB' multiplets. In these two respects, the reactivity of the methyl bromocyclopropyl ketone 229 and bromodicyclopropyl ketone 223 are similar. However, when bromocyclopropyl methyl ketone 229 was reacted with refluxing aqueous 30% NaOH solution, a volatile acid was produced in 8% yield whose PMR spectrum (Fig. 6, p.89) suggested that it was the Favorskii acid 236. Furthermore, the mass spectrum gave a parent peak at m/e 100 consistent with that formula.

The p-bromophenacyl ester was prepared and found to give the same melting point as that reported in the literature for the p-bromophenacyl ester of α-methyl cyclopropane carboxylic acid 236.[119]



229 236

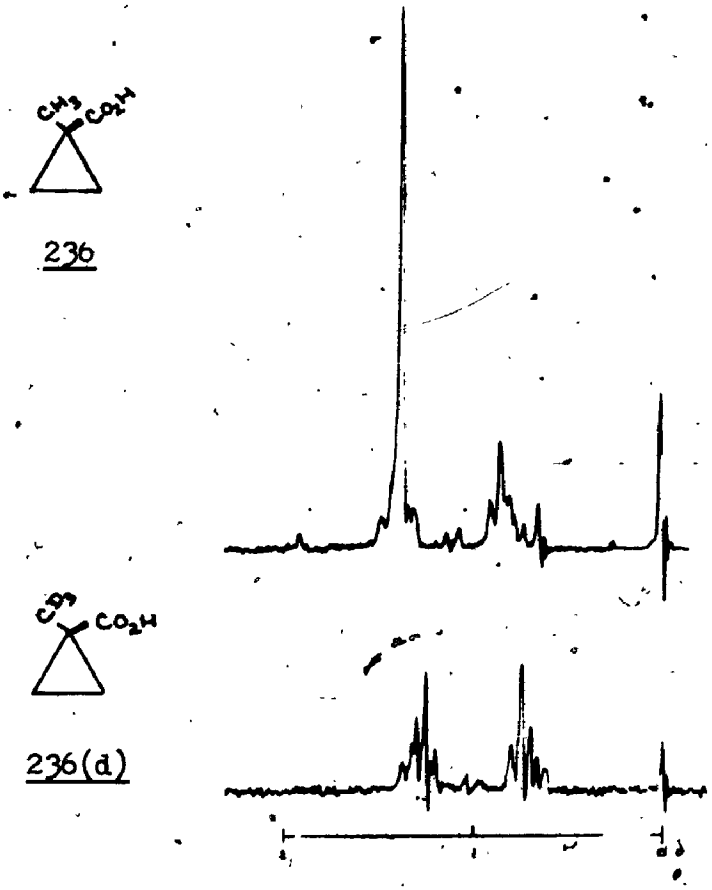
Although the major product of the reaction of bromoketone 229 with 30% NaOH was insoluble polymeric material, the isolated acidic fraction was quite clean. Only one other acid was present besides α-methylcyclopropane carboxylic acid 236 and this appeared to be a condensation product judging by the complexity of the PMR spectrum and the presence of two methoxy signals after treatment with diazomethane in ether. It was not investigated further.

When methyl bromocyclopropyl ketone 229 was reacted with t-butoxide in t-butanol, conditions which favour cyclopropanone formation,[37] no volatile products could be isolated from the viscous acidic fraction.

Finally, phenyl bromocyclopropyl ketone 232 was treated with

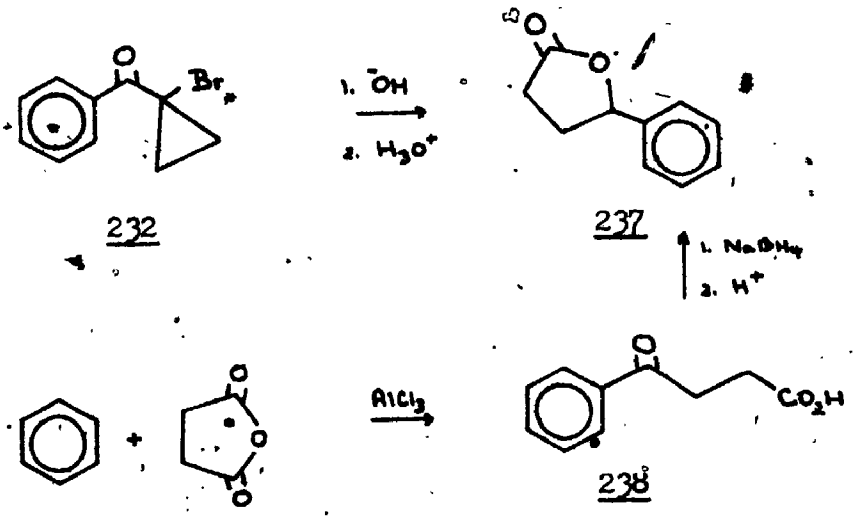
Fig. 6

60 MHz Spectra of α-Methyl Cyclopropane Carboxylic Acid 236*



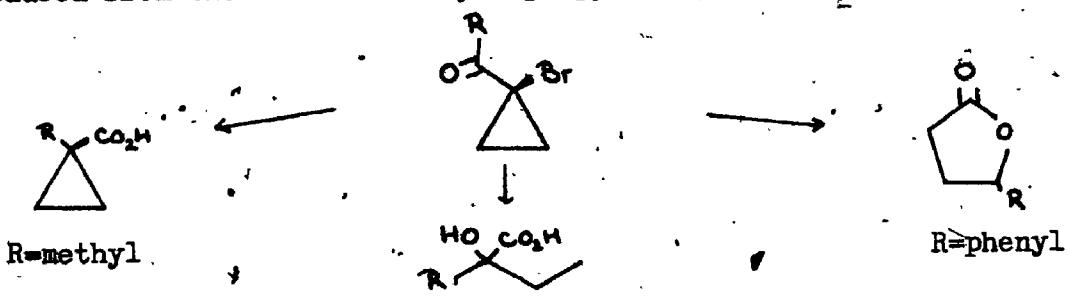
refluxing aqueous 30% NaOH to see whether it would give Favorskii acid or an α-hydroxy acid. The reaction was remarkably clean. It gave a negligible neutral fraction and a single, major product (75%) in the base soluble fraction which was identified as γ-phenylbutyrolactone 237 by comparison with an authentic sample.

* The small change in chemical shifts for the deuterated acid may be a result of concentration, i.e., less dimerization of the $-CO_2H$ units, rather than an isotope effect.



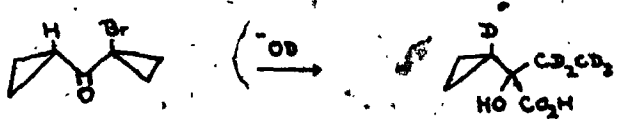
Mechanism of Acid Formation from α-Bromocyclopropyl Ketones

The mechanisms by which three different kinds of acids are produced from the three bromocyclopropyl ketones by aqueous 30%



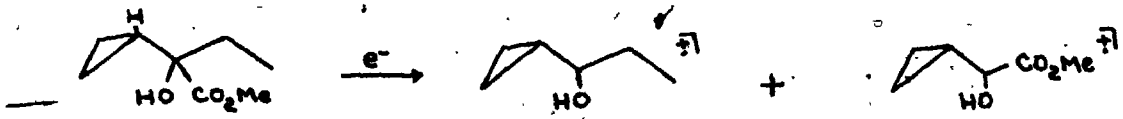
NaOH were not completely elucidated. However, examination of the deuterium content and distribution in these acids produced when the bromoketones were reacted with 30% NaOD-D_2O did suggest feasible schemes.

Bromodicyclopropyl ketone 223 on treatment with 30% NaOD-D_2O gave white crystals of hydroxy acid 234(d) in 21% yield after sublimation. The high field region of the PMR spectrum (Fig. 5, p. 86) showed a single multiplet at 0.40 δ which suggested that only the four beta protons of the cyclopropane ring were not exchanged. The ethyl



223 234(d)

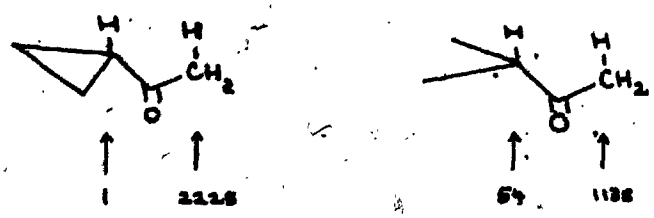
group and the alpha proton of the ring appeared to have been completely exchanged. The mass spectrum of the methyl ester supported this contention. Since the parent ion eliminates the ethyl group (m/e 158 → 129) as one fragmentation mode and the carbomethoxy group (m/e 158 → 99) as another, one can deduce the quantity of deuterium in the ethyl group and in the cyclopropyl ring. Peaks at m/e 104 and 105 indicated



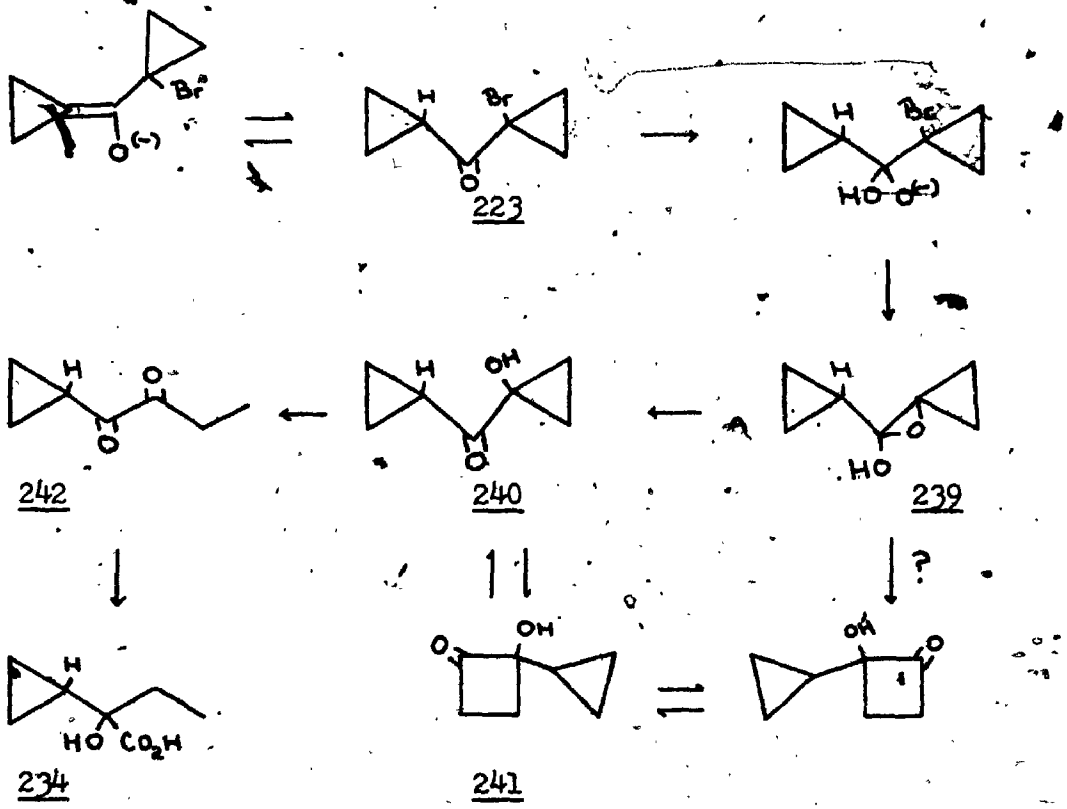
m/e 158 m/e 129 m/e 99

72% d_6 and 28% d_5 while peaks at m/e 129 and 130 contained 78% d_1 and 22% d_0. This shows that the ethyl protons are completely exchanged, whereas, the alpha cyclopropyl proton is only 75% ± 3% exchanged.

The partial exchange of the alpha cyclopropyl proton suggests that it is exchanged before the bromoketone has reacted since the exchange of this type of proton is known to be slower than exchange of the α-protons of other alkyl groups in alkyl cyclopropyl ketones. The structures below show the relative rates of base-catalyzed exchange of the alpha protons:[120]

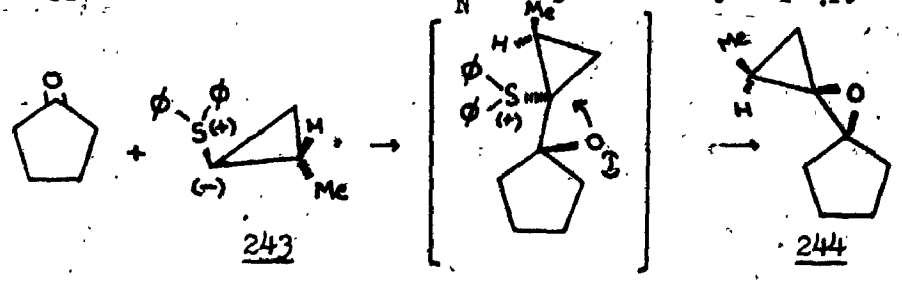


The exchange of all the ethyl protons suggests that both carbons are equivalent and alpha to a carbonyl group at some point during the reaction. A mechanism which is consistent with these results is outlined below:



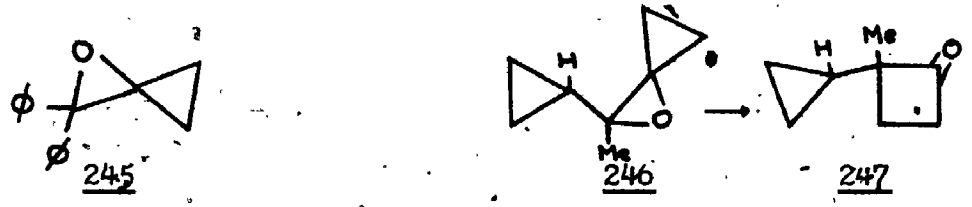
223 242 240 239 234 241

The first reaction is enolization. The deuterium results show that this is slightly slower than oxirane 239 formation which occurs by an intramolecular S_N2 reaction of the anion of the hydrated bromoketone. This second step has analogy in Trost's work on the reaction of diphenylcyclopropyl sulfonium ylides with ketones.[121] His group has recently demonstrated that the stereochemistry of this reaction does supppprt an intramolecular S_N2 step at the cyclopropyl ring.



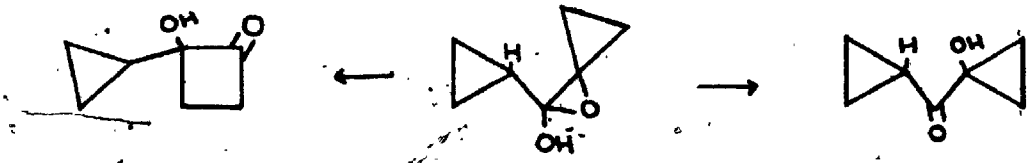
243 244 Ref. 121

The next step, however, is more ambiguous and needs to be settled experimentally. Trost, et al., found that the oxiranes from the reactions above were readily converted to cyclobutanones on warming. In fact, oxiranes 245 and 246 were not isolable since they rearranged



245 246 247 Ref. 121

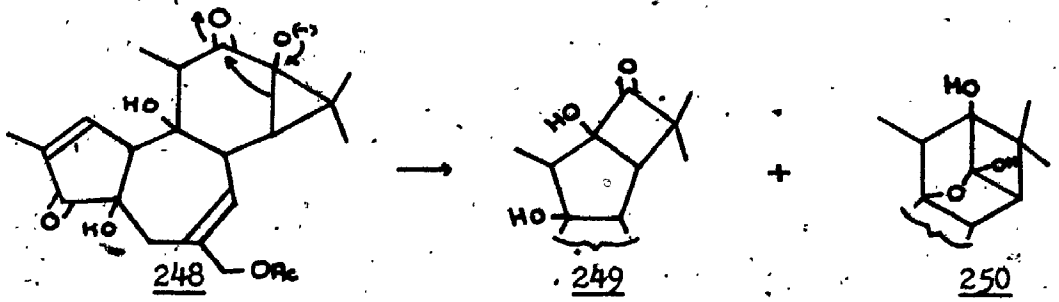
under the conditions of formation. Because compound 239 is both an oxirane and a hemiketal, it is difficult to decide whether ring opening to a hydroxyketone 240 or rearrangement to cyclobutanone 241 would be faster. Although oxirane 239 would rearrange at least as rapidly as



241 239 240

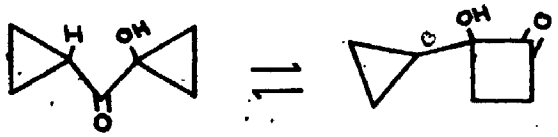
oxirane 246, the cleavage of the hemiketal would be extremely fast and would require less molecular motion than rearrangement.

Cyclopropanols cleave under mildly basic conditions,[122] but they can also produce a 1,2-shift as illustrated beneath:[123]



248 249 250 Ref. 123

Such a shift with hydroxyketone 240 would form a cyclobutanone which would permit rapid exchange of two of the original protons. The remaining two protons would be exchanged after equilibration of the



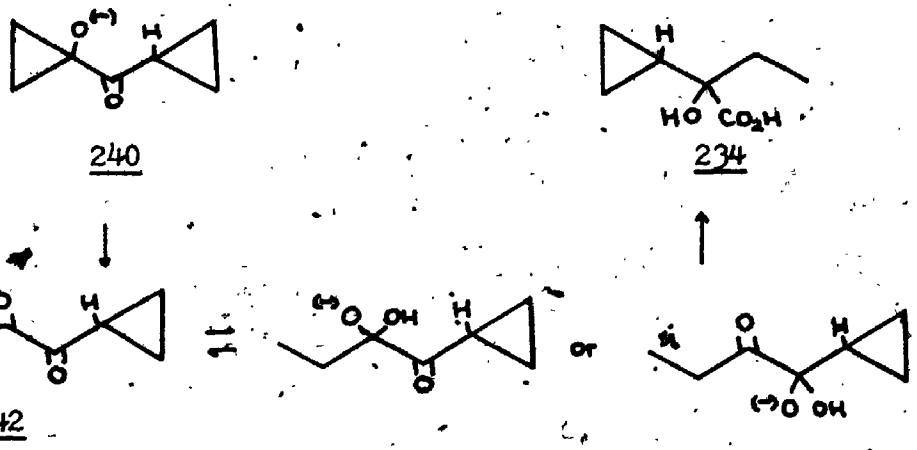
240 241

methylene carbons. This could be due to the reversibility of the ring expansion or a 1,2-alkyl shift known to happen in this kind of system. Urry found that the methyl group in cyclobutanone 251 oscillated at

251

least as fast as the rate of deuterium exchange since the alpha- and beta-protons disappeared at the same rate in the PMR spectrum.[124]

Once the hydroxyketone 240 has been cleaved to the diketone 242, the well-known benzilic acid rearrangement would account for the



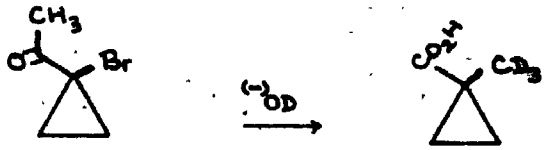
240 234

242

observed product. Protonation of the carbanion produced by ring opening would account for the fifth deuterium that was incorporated in the ethyl group.

When α-bromocyclopropyl methyl ketone 229 was treated with 30% NaOD-D_2O at reflux, the PMR spectrum of the Favorskii acid 236(d)

(Fig. 6, p.89) showed only the AA'BB' system of the cyclopropane ring protons which indicated that the methyl group had been completely exchanged. This was supported by the mass spectrum which showed almost entirely d_3-species.

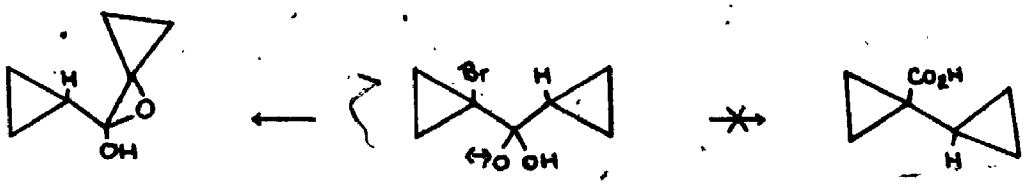


229 236(d)

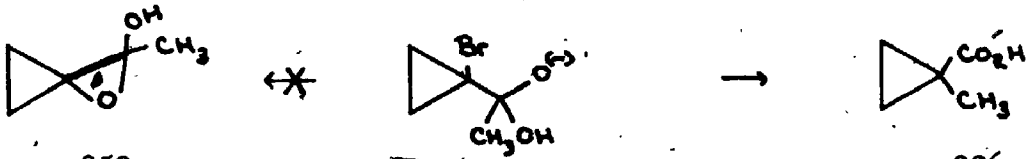
If the reaction proceeds by a cyclopropanone intermediate, then, loss of bromide, not enolate formation, is the rate determining step. However, there is no cyclopropyl acetic acid 252 in the crude acidic fraction as judged by the PMR spectrum. This acid would be the alternative cleavage product of the intermediate spiro-cyclopropanone. Streitweiser and Taylor measured the relative kinetic acidities of cyclopropane and methane and found that cyclopropane exchanged its protons 32 times as fast as methane.[110] A difference of this order in kinetic acidity of the two products would be expected during cleavage

of the spiro-cyclopropanone. This means that the cyclopropanone would give a mixture of acids containing predominantly cyclopropyl acetic acid. Its absence can be interpreted as support for the semibenzilic mechanism.

The question remains why methyl bromocyclopropyl ketone 229 produces an alkyl group migration in preference to an oxirane ring while cyclopropyl bromocyclopropyl ketone 223 produces an oxirane ring in preference to an alkyl group migration.



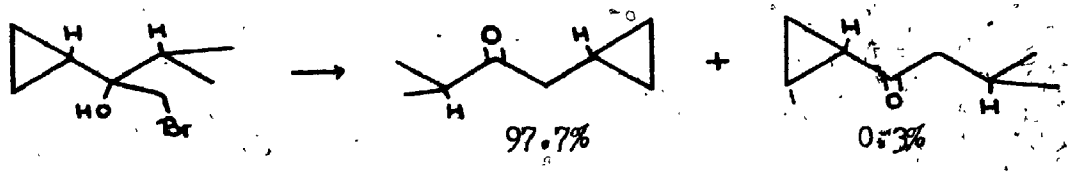
239 233a



253 236

The examination of space-filling models offers no obvious steric reason. Although rather unsatisfactory, an alternative possibility is the relative migratory aptitude of these two substituents. When migrating to a positive centre, the observed rates are as follows:[125,126]

phenyl > cyclopropyl > methyl



97.7% 0.3%

254 256 255

When migrating from a carbon adjacent to a negative oxygen centre, as in the benzilic acid rearrangement, the migratory aptitudes of a phenyl and a methyl group are reversed.[36] Unfortunately, cyclopropyl migration in such a system has not been studied.* If the migratory aptitude of

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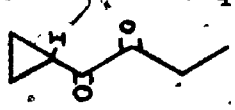
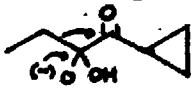
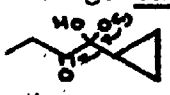
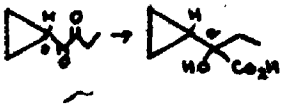
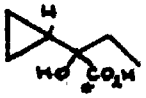
* This is also pertinent to the question of the benzilic acid rearrangement with  . Does it go via ethyl migration  or via cyclopropyl migration  ? If the speculation above is correct then  , not 

the cyclopropyl group is also reversed, i.e. methyl > cyclopropyl, it is possible that the competitive oxirane formation is slower than methyl migration but faster than cyclopropyl migration. In this regard, it is interesting to note the rate difference between the two reactions. Under the same conditions, reaction with methyl bromocyclopropyl ketone 229 is perhaps twenty times faster than reaction with cyclopropyl bromocyclopropyl ketone 223.

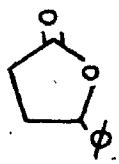
When phenyl bromocyclopropyl ketone 232 was treated with 30% NaOD-D_2O at reflux, γ-phenylbutyrolactone 237(d) was isolated. Its PMR spectrum (Fig. 7D, p.98) showed only phenyl absorption and a broad doublet of doublets at 2.7-1.8δ which integrated for 1.5 protons. The parent ion in the mass spectrum (Fig. 8, p.99) showed a strong peak at m/e 165 and smaller ones at m/e 166 and 167. Curiously, the peak at m/e 166 was smaller than the peak at m/e 167. When the correction for ^{13}C isotope and P^+-1 contribution was applied, the peak at m/e 166 was essentially zero. This left a d_3-species (78 ± 3%) and a d_5-species (19 ± 3%) for the parent ion.

The methylene protons of γ-phenylbutyrolactone 237 exhibit two complex multiplets in the HA-100 spectrum which integrate in the ratio, 3:1. The alpha protons would be expected to be at lower field than the beta protons; however, the anisotropic effect of the benzene ring on the vicinal methylene group causes the cis proton to shift to lower field; hence, the ratio, 3:1. A comparison of the PMR spectra (Fig. 7, p.98) of deuterated and non-deuterated γ-phenylbutyrolactone 237 suggested that the beta methylene protons were the ones which had only undergone partial exchange.

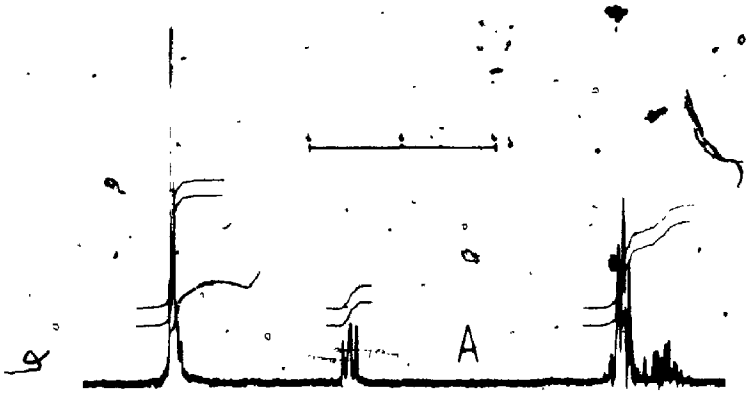
To clarify this point, the samples were treated with approximately

Fig. 7

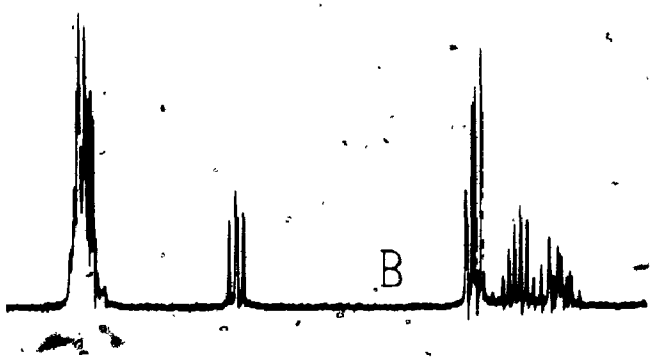
100 MHz Spectra of γ-Phenylbutyrolactone 237



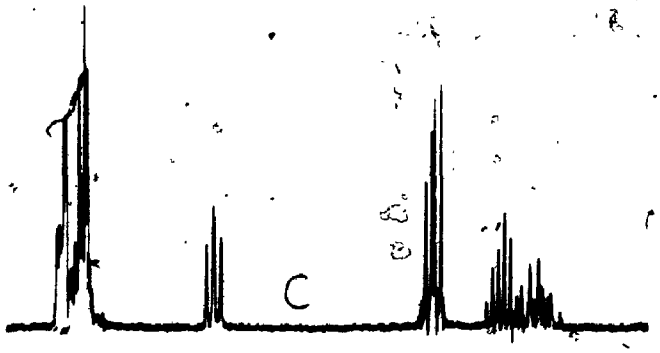
237

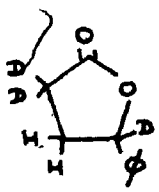


+ Eu^{3+}(fod) 1x



+ Eu^{3+}(fod) 2x





237(d)

+ Eu^{3+}(fod) 2x

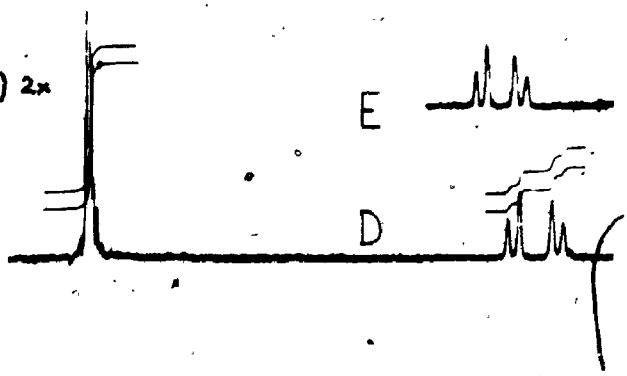
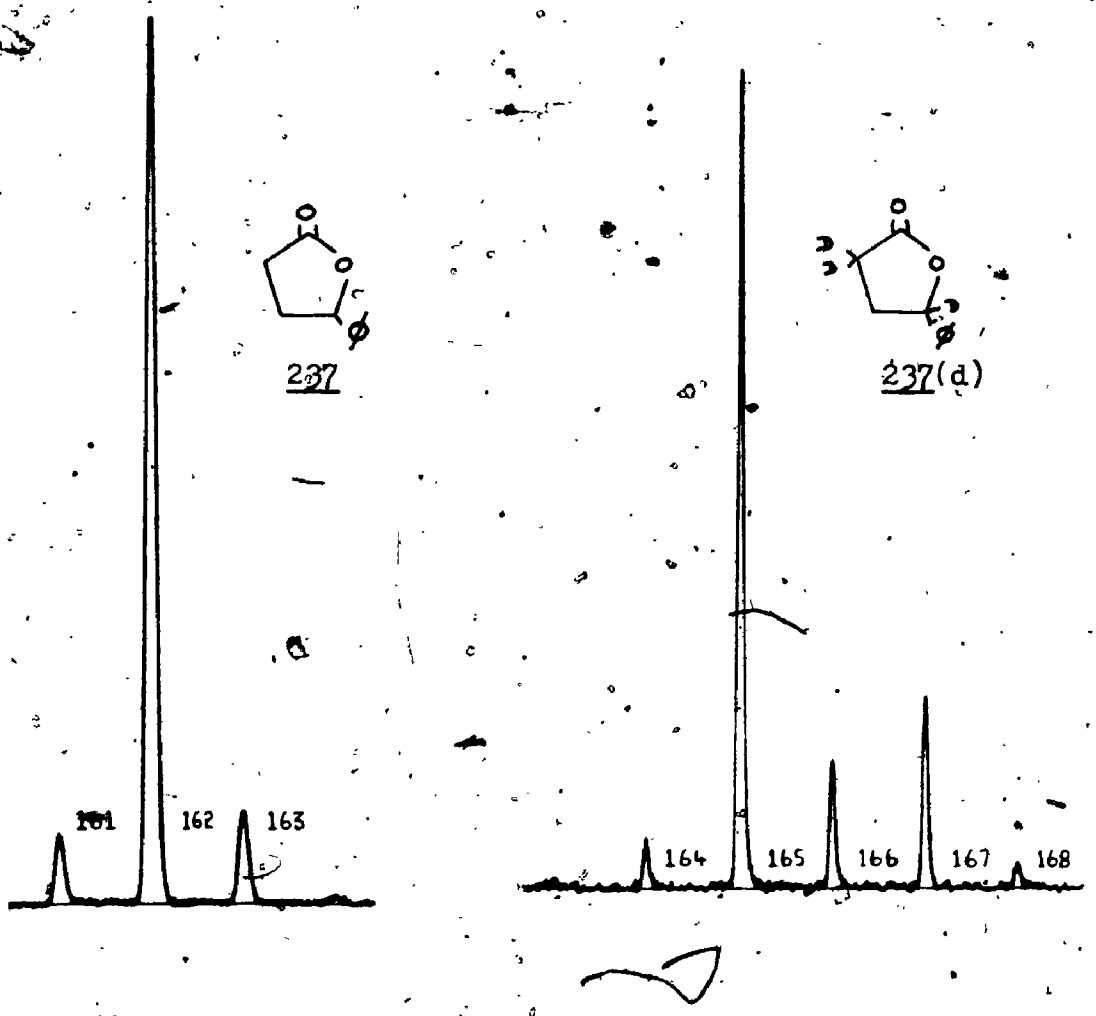


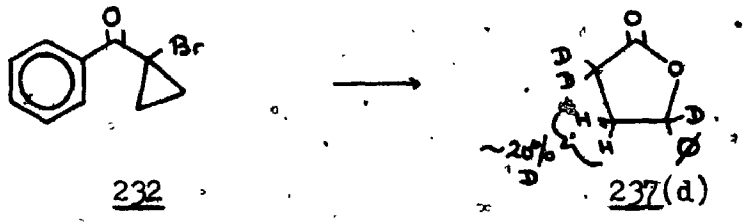
Fig. 8

Parent Ion of γ-Phenylbutyrolactone 237



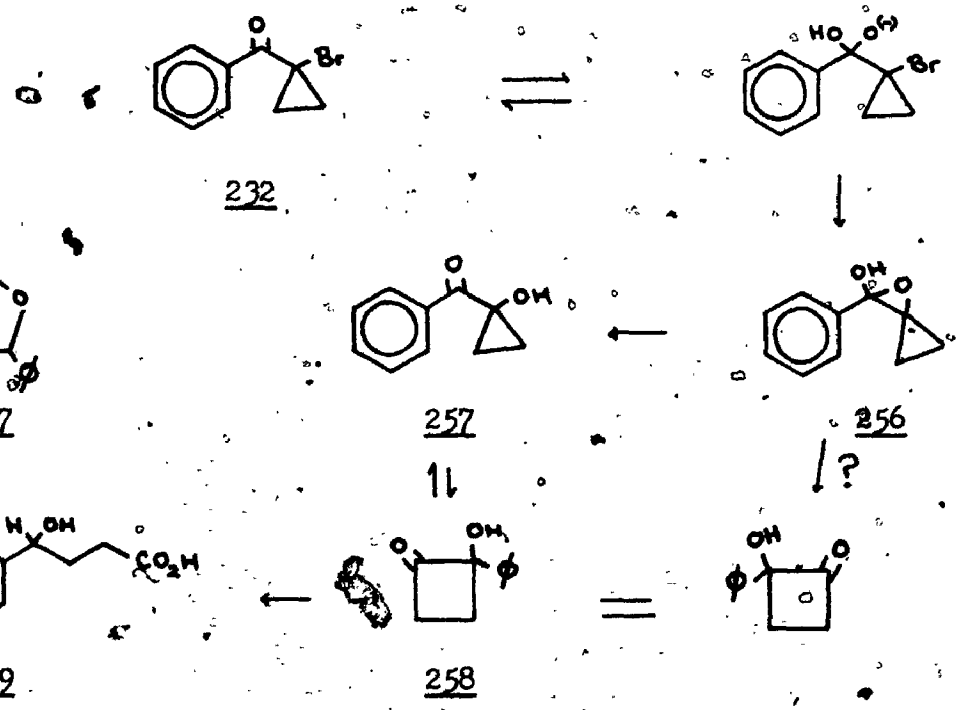
equivalent amounts of Eu^{3+}(fod). By analogy with other systems, the carbonyl alpha protons would be expected to shift further to lower field than the beta protons. In Fig. 9, p. 98, one can see that the high field portion of the spectrum of the non-deuterated sample splits into three multiplets with the ratio, 2:1:1, on addition of europium shift reagent. The two higher field multiplets correspond in position to the doublet of doublets in the deuterated sample. Therefore, one can

conclude that the alpha protons are completely exchanged while the beta protons are only partially exchanged in the deuterated sample of



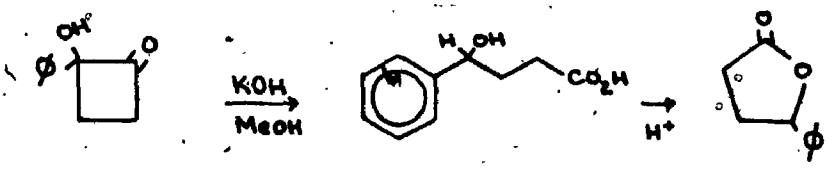
232 237(d)

γ-phenylbutyrolactone 237(d). The mechanism which best explains these results is outlined below:



As in the case of bromodicyclopropyl ketone 223, an oxirane is the initial intermediate which leads to the substituted hydroxy cyclobutanone 258 via the cyclopropanol 257. However, because of the increased acidity of the substituted alpha carbon and, perhaps, as suggested earlier, because of the lower migratory aptitude of the phenyl group, alpha cleavage is competitive with the 1,2-shift. Since base-catalyzed exchange of the alpha protons is faster than both, one sees a ratio of d_5 to d_3 which represents the relative rates of ring cleavage

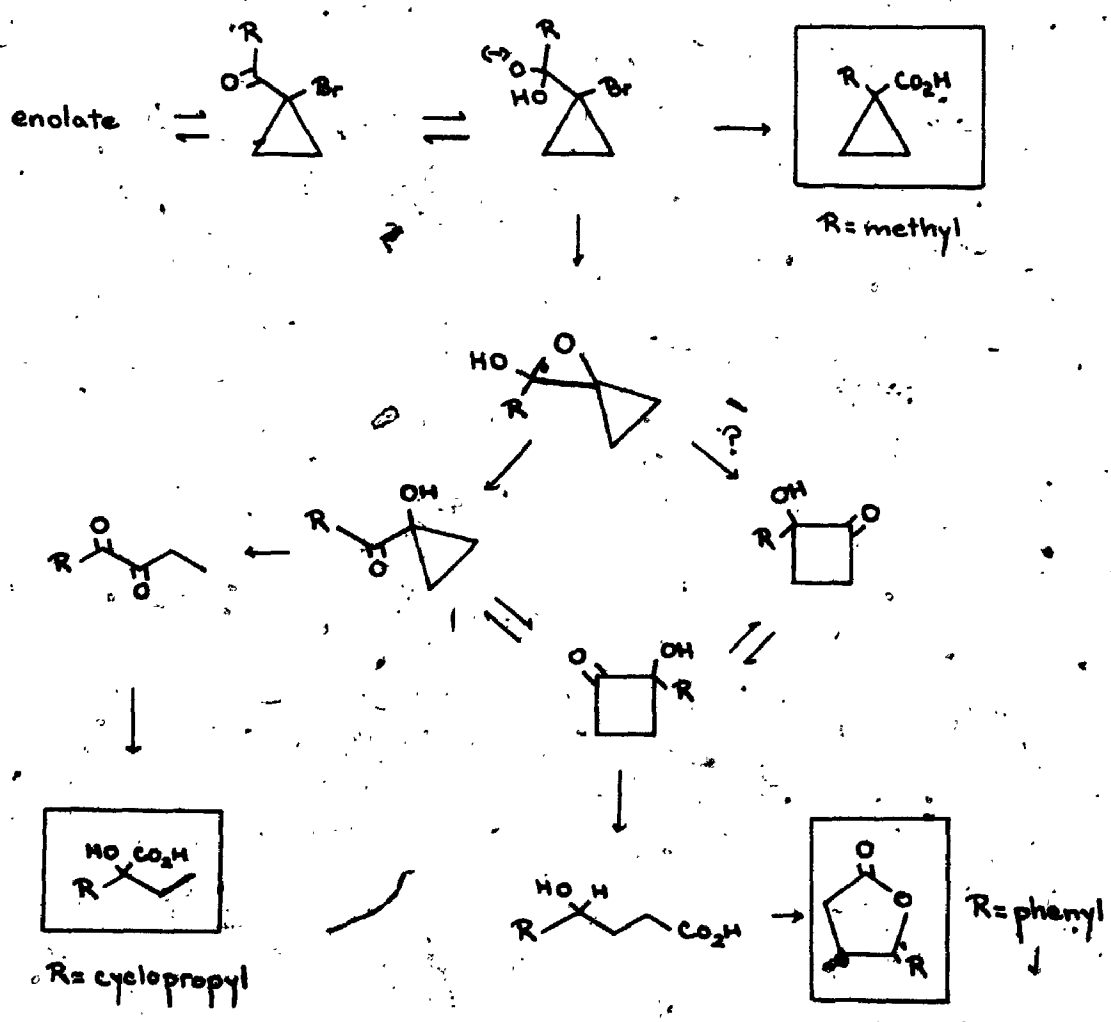
and 1,2-shift (~4:1). Stevens and Weier have observed that the 2-hydroxy-2-phenyl cyclobutanone 258, one of the proposed intermediates above, does indeed give γ-phenylbutyrolactone 237 on treatment with refluxing methanolic KOH.[127]



Ref. 127

258 237

A general scheme can now be written for the reaction of bromocyclopropyl ketones with aqueous hydroxide ion.



Experimental

General

All melting points were done on a Reichert-Kofler microscope hotstage and are corrected. Infrared spectra were recorded on Beckman IR-20A or IR-10 spectrophotometers with carbon tetrachloride or chloroform as solvent. Ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer with 95% ethanol as solvent. Proton magnetic resonance (PMR) spectra were recorded on Varian T-60, A-60 or HA-100 spectrometers with carbon tetrachloride or deuteriochloroform as solvent. Tetramethylsilane (TMS) was the internal reference, and all chemical shifts are reported as δ values. PMR integrations are reported only for pure materials and, in these cases, the number of protons is included in the PMR data. Otherwise, only the major signals and their interpretations were given. Routine mass spectra were recorded on the Varian M-66 spectrometer using perfluoroalkanes for calibration. Gas liquid chromatography (GLPC) was performed on a Glowall Model 400 with 1.8m x 3.4 mm spiral glass columns for routine analysis and 1.8 m x 10 mm spiral glass columns for preparative scale work. Column packing was 5% diethylene glycol succinate (DEGS) on Chromosorb "P" unless otherwise stated. Fractional distillations were done on a Nestor & Faust 18" semimicro spinning band column. Thin layer chromatography (TLC) was performed on 2.5 cm x 7.5 cm slides coated with Stahl GF-254 (Brinkman Instruments) silica gel with calcium sulfate binder. The plates were developed by spraying and charring with 5%

phosphomolybdic acid (PMA) in ethanol. Thick layer chromatography was done on 20 cm x 20 cm glass plates coated with 25 g of Stahl GF-254 silica gel. The wet coating was dried at 90° overnight after partially drying at room temperature. Bands were visualized under uv light or by adsorption of iodine vapor. Sealed tube reactions were done in a Fischer Hi-temp wax bath. Microanalyses were done in the laboratories of A.B. Gygli, Toronto, Ontario and Chemalytics, Tuscon, Arizona, U.S.A.

"Aqueous workup" was done by quenching the reaction mixture in a large excess of water and extracting with ether (2-3x). In the case of a basic reaction medium, this was followed by acidification of the aqueous layer with concentrated HCl and extraction with ether. Ether layers were dried by washing with saturated salt solution and standing over anhydrous $MgSO_4$. This treatment was followed by filtration and distillation of the ether. Solvent residue was removed on a rotatory evaporator (Rotavap) at reduced pressure. British Drug Houses Silica Gel was used for column chromatography. Bulb to bulb distillation involved the use of a glass tube with a bulb at one end and a second bulb 7-10 cm up the tube. The terminal bulb containing sample was heated and the vapour was condensed in the second bulb. Solvent abbreviations include:

DME for dimethoxyethane

PE68(96) for petroleum ether of boiling range

60-80° (30-60°)

HOAc for acetic acid

EtOAc for ethyl acetate

DABN for 1,5-diazabicyclonon-5,6-ene

DUBN for 1,5-diazabicycloundec-5,6-ene

Preparation of 2-Chlorocyclopentanone 69

A solution of chlorine (85 g, 1.2 mol) in carbon tetrachloride (1000 ml) (determined by quenching a 1 ml aliquot in 20 ml of 20% KI solution and titrating to a colourless starch-iodide endpoint with 0.1 N $Na_2S_2O_3$) was added dropwise (2-3 hr) to a solution of cyclopentanone (100 g, 1.19 mol) in CCl_4 (1250 ml) at ice temperature. After the yellow colour had faded, the solvent plus HCl was distilled off on a steam bath and the last traces were removed on a Rotavap. The residue was distilled on a spinning band column and the fractions closest to b.p. 58-60° at 3.5 Torr (lit.[48] b.p. 77-80° at 10 Torr) were kept for use. Yields varied from 45 to 55%. The percentage of unchlorinated ketone impurity was easily checked by GLC and was usually in the range of 3-8%.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1752 cm^{-1} (C=O)

PMR spectrum: δ_{TMS}^{neat} 4.03 (1H, m, -CHCl-)

Preparation of Methyl Cyclobutanecarboxylate 118

Cyclobutanecarboxylic acid chloride (2.0 g, 17 mmol) (Aldrich Chemical Co.) was added slowly to a solution of pyridine (1.3 g) in methanol (10 ml) and the reaction mixture was refluxed for 45 min before an aqueous workup.

The residue was distilled under reduced pressure.

IR spectrum: $\nu_{max}^{CCl_4}$ 2870 (C-H of MeO), 1732 (ester C=O), 1430 and 1360 (C-H of $-CO_2Me$)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 3.62 (s, 3H, -OMe)

Stability of Methyl Cyclobutanecarboxylate 118 to $MeO^-/MeOH$

Methyl cyclobutanecarboxylate 118 (1.0 g, 9.0 mmol) was added to a solution of sodium methoxide (0.6 g of sodium, 0.026 g. atom) in methanol (12 ml) and stirred at room temperature (12 hr). Aqueous workup gave a colourless liquid (0.9 g).

GLPC (80°): 1 peak (methyl cyclobutanecarboxylate)

Reaction of 2-Chlorocyclopentanone 69 with $MeO^-/MeOH$ at 0°

2-Chlorocyclopentanone 69 (5.0 g, 42 mmol) in an equal volume of methanol (spectral grade, Fisher) was added dropwise (40 min) to a stirred solution of sodium methoxide (2.4 g of sodium, 0.10 g atom) in methanol (30 ml) maintained at ice temperature.[51] A blood red colour developed initially which changed to yellowish-brown and became progressively darker as noted by Favorskii.[49] After complete addition (1 hr), the reaction medium was left at room temperature for 12 hr. Aqueous workup resulted in a tarry material (0.75 g) which was insoluble both in ether and water. Acidification of the aqueous layer resulted in further insoluble tar separation (0.5 g).

The combined ether extracts of the basic aqueous layer yielded a brown oil 116 + 117 (2.4 g) with a camphoraceous odour.

GLPC (100°): 2 peaks (1:1), no methyl cyclobutanecarboxylate 118 by direct comparison with an authentic sample

TLC (EtOAc-PE68, 30:70): 2 major spots

IR spectrum: $\nu_{max}^{CCl_4}$ 2830 (C-H of MeO); 1740, 1720 (weak C=O); 1050, 1085 and 1120 (C-O)

The combined ether extracts of the acidified aqueous layer gave a dark brown syrup (0.4 g).

TLC (EtOAc-PE68, 75:25): 6-7 spots, not examined further

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/MeOH at 0° slow addition

The reaction was conducted as before except the substrate solution was added over a period of 2.5 hr and the reaction medium was held at 0° for the entire reaction period (14.5 hr) before the aqueous workup.

The neutral fraction was a light yellow oil 116 + 117 (2.7 g) with a camphoraceous odour.

GLPC (100°): 2 peaks (less polar 117 : a more polar 116, 5.6:1)

The acidic fraction was an orange-brown syrup (1.5 g) which was similar to the acidic material from the previous experiment (p. by TLC. It was not investigated further.

TLC (EtOAc-PE68, 75:25): 6-7 spots

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/MeOH at -20°

The procedure has been outlined in the previous experiment except the temperature of the reaction was maintained between -25° and -15°.

The acidic fraction was an orange-brown syrup (0.26 g).

IR spectrum: $\nu_{max}^{CCl_4}$ 3500, 3100 (-OH); 1746, 1710 (broad C=O)

The neutral fraction was a light yellow oil 116 + 117 (3.7 g) with a camphoraceous odour. The less polar compound 117 had the same retention time as cyclopentenone 71 but comparison by ir spectroscopy proved that

it was not the same.

GLPC (100°): 2 peaks (no methyl cyclobutanecarboxylate by comparison with an authentic sample) 117 : 116, 1:1.3

TLC (EtOAc-PE68, 40:60): 2-3 spots

IR spectrum: $\nu_{max}^{CCl_4}$ 3630, 3500, (-OH); 2830 (C-H of -OMe), 1747 (C=O); 1050, 1085, 1120 (C-O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 3.17, 3.22 and 3.41 (s,-OMe)

Reaction of 2-Chlorocyclopentanone 69 with MeO-/MeOH at Reflux

The procedure was that outlined previously (p. 105) except the sodium methoxide-methanol solution was maintained at reflux (14 hr). Aqueous workup produced a large amount of insoluble brown material.

The neutral fraction was an amber liquid 117 (700 mg).

GLPC (100°): 1 peak

IR spectrum: $\nu_{max}^{CCl_4}$ 3600-3300 (-OH), 2835 (C-H of -OMe), 1745 (C=O); 1050, 1085, 1120 (C-O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 3.18, 3.25 (s,-OMe), 4.08 (broad d.)

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/MeOH (low concentration)

A solution of 2-chloroeyclopentanone 69 (2.0 g, 17 mmol) in methanol (25 ml) was added dropwise (3 hr) to a solution of sodium methoxide (1 g of sodium, 0.04 g. atom) in methanol (125 ml) kept under dry nitrogen at -15°. The reaction was stirred for 22 hr and, then, quenched by an aqueous workup.

The acidic material (40 mg) was almost negligible and was not investigated further.

The neutral fraction was a pale yellow oil, 116 + 117 (1.6 g).

GLPC (100°): 2 peaks (117 : 116, 1:1.7)

IR spectrum: $\nu_{max}^{CCl_4}$ 2830 (C-H of -OMe), 1748 (C=O); 1050, 1085, 1125 (C-O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 3.18, 3.25 and 3.46 (s, -OMe)

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/Ether

A solution of 2-chlorocyclopentanone 69 (5.0 g, 42 mmol) in an equal volume of anhydrous ether was added (0.75 hr) dropwise to a suspension of sodium methoxide (5.7 g, 0.11 mol) in ether (30 ml) at dry-ice temperature and the reaction mixture was stirred overnight (12-14 hr). Aqueous workup produced a large amount of tarry products.

The neutral fraction was a brown syrup 116 lacking the camphoraceous odour of products from previous experiments.

GLPC (100°): 1 peak

IR spectrum: $\nu_{max}^{CCl_4}$ 3630, 3540 (weak -OH), 1742 (strong C=O)

The acidic fraction was a thick brown syrup which was not investigated further.

IR spectrum: $\nu_{max}^{CCl_4}$ 1740, 1715 (C=O)

Preparative GLPC of Neutral Products from the MeO^-/MeOH Experiments

The crude oil 116 + 117 (400 mg) in dry ether (2 ml) was injected in successive aliquots (50 ml) onto a column (5% DEGS, 100°) fitted with a splitter (50:1 ratio) and a heated exit tube (100°). Samples were

collected in glass tubes cooled to dry-ice temperature.

Fraction	Time Interval (min)	Weight (mg)	Analysis (GLPC, TLC)
1	0-4	10	many compounds
2	4-6.5	5	two compounds
3	7-9	47	one major compound and trace impurities
4	9-18	14	two compounds

Total recovery was only 20% and only fraction 3, 116, appeared reasonably pure.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2830 (C-H of -OMe), 1748 (C=O), 1123 (C-O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 3.7 (m,-proton), 3.53 (s,-OMe), 2.5-1.6 (brd.m).

A 2,4 dinitrophenylhydrazine derivative 119 was prepared from fraction 3, m.p. 162-178°, with some crystals melting around 122°.

TLC (Benzene-EtOAc, 9:1): 4 spots (1 major, 3 minor)

The major product, a yellow solid of m.p. 165-179°, was isolated by TLC (prep.) and recrystallized from methanol. The PMR spectrum ($CDCl_3$) showed an almost equal mixture of syn- and anti-isomers with two sharp methoxy singlets at 3.57 and 3.48 δ. The phenyl proton pattern was very similar to that illustrated in Fig. 9 (p. 196).

Mass spectrum: m/e 294 (P^+)

Analysis: Calc. for $C_{12}H_{14}N_4O_5$ (MW294): C,48.98; H,4.80; N,19.04

Found: C,49.14; H,4.89; N,18.89

Thick Layer Chromatography of Neutral Products of MeO^-/MeOH Reactions

Crude neutral material 116 + 117 (350 mg) was spotted equally on four silica gel plates and developed once with EtOAc-PE36, 40:60. Iodine

showed two well-separated bands. The bands were cut out, eluted with ether, filtered and the solvent removed by Rotavap.

The less polar band gave 150 mg of liquid 117 with a camphoraceous odour. On GLPC, it corresponded to the peak of shorter retention time.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2840 (C-H of -OMe); 1045, 1085, 1122 (C-O).

The more polar band gave 15 mg of liquid 116 which corresponded to the peak of greater retention time on GLPC.

IR spectrum: ν_{max}^{CHCl} 1745 (C=O) and 1125 (C-O)

Column Chromatography of Neutral Products of MeO^-/MeOH Reaction

Crude neutral material 116 + 117 (1.2 g) was chromatographed on a column of silica gel (60 g) with EtOAc-PE36 10:90. The column development was followed by GLPC analysis of the eluent. The first material to come off was 2-chlorocyclopentanone dimethylketal 117.*

PMR spectrum: δ_{TMS}^{neat} 4.08 (brd.d,1H); 3.25, 3.19 (s,6H,-OMe) and 2.2-1.6 (brd.m,6H,$-CH_2$)

The second material to come off was a minor one whose ir spectrum resembled that of 2-chlorocyclopentanone 69.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1748 (C=O)

Hydrolysis of 2-Chlorocyclopentanone Dimethylketal 117

The least polar material (380 mg) taken from the column in the previous experiment was stirred vigorously (4 hr; 25°) in water (5 ml) containing a drop of concentrated HCl. The reaction medium was extracted

* When injected neat onto the GLPC column, this material decomposed, thereby, accounting for the poor recovery on preparative GLPC.

with pentane, washed with saturated salt solution and dried over $MgSO_4$. Evaporation of the solvent gave a colourless liquid 69 + 117 (200 mg).

GLPC (100°): 2 peaks (2-chlorocyclopentanone 69 plus some unreacted dimethylketal 117)

IR spectrum: $\nu_{max}^{CHCl_3}$ 1752 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 4.16 (m,1H) and 2.6-1.8 (brd.m,7H)

Reaction of 2-Chlorocyclopentanone 69 with MeOH

A drop of 2-chlorocyclopentanone (20 mg) was added to methanol (1 ml) and allowed to stand at room temperature for 1 hr. Aliquots were taken regularly and injected onto the GLPC column. Only one peak appeared which corresponded to starting material 69.

Fractional Distillation of Neutral Products of MeO^-/MeOH Reactions

A solution of freshly distilled 2-chlorocyclopentanone 69 (8.7 g, 0.07 mol) in methanol (25 ml) was added dropwise (1 hr) to a solution of sodium methoxide (5 g of sodium, 0.2 g.atom) in methanol (125 ml) at 0°. Aqueous workup was carried out within fifteen minutes of complete addition. The neutral fraction was a pale yellow oil 116 + 117 (5.5 g) whose GLPC, IR spectrum and PMR spectrum were the same as before, p. TLC (EtOAc-PE68, 30/70) showed two major spots, R_f=0.66 and 0.28. This crude material was distilled at reduced pressure on a semi-micro spinning band column (20 cm) with a reflux ratio of 9:1. (See Table I.)

TABLE 1

Fractional Distillation of Neutral Products of MeO^-/MeOH Reactions

Yield	Fract.	T°C	Torr.	GLPC*	Analysis (IR, PMR and TLC)
1.9 g	1	37.5-40.5°	2.9	1:15	The 1750 cm^{-1} (C=O) and 1409 cm^{-1} ($-CH_2C=O$) bands decreased while the 1333 cm^{-1} (CH_3O-) and 1050, 1085 1125 cm^{-1} (C-O) bands increased with the decreasing amount of compound 116. TLC showed a decreased in the more polar spot in later fractions. The PMR spectra showed a decrease in the methoxy singlet at 3.36 δ and an increase in the methoxy doublet at 3.19 and 3.14 δ as the ketal 117 percentage increased.
	2	40.5-42°	"	1.3:1	
	3	42-43.5°	"	2.3:1	
1.3 g	4	43.5-45°	"	4.2:1	
	5	45-46°	"	ketal only	
	6	46°--	"	ketal only	

Column Chromatography of Distilled Material (Table 1)

Fractions 1 to 3 were combined (1.86 g) and chromatographed on silica gel (120 g) with ether-pentane, 10:90. The first material eluted was 2-chlorocyclopentanone dimethylketal 117 (427 mg) which was distilled bulb to bulb under vacuum.

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* GLPC peak height ratio, ketal 117 : ketone 116

Mass spectrum: m/e 164, 166 (P^+); 133, 135 (P^+-31, -OMe); 101 (P^+-63, 65, α-cleavage, 100%)

The second material was 2-chlorocyclopentanone 69 identified by GLPC and ir spectrum. The third material was 2-methoxycyclopentanone 116 (437 mg) contaminated with a small amount of 2-chlorocyclopentanone 69. This was also distilled bulb to bulb under vacuum.

Mass spectrum: m/e 114 (P^+), 84 (P^+-30), 58 (P^+-56, α-cleavage, 100%), 55 (P^+-59)

Reaction of 2-Chlorocyclopentanone 69 with 0.1M MeO^-/MeOH[51]

2-Chlorocyclopentanone 69 (2.0 g, 17 mmol) in methanol (18 ml) was added dropwise to a solution of sodium methoxide (0.6 g of sodium, 0.03 g.atom) in methanol (200 ml) at room temperature. Fifteen minutes after complete addition, an aliquot checked on GLPC showed no starting material but two product peaks. The ratio of peak heights of 117:116 is 1:2.2 which is less than usual. The reaction was worked up as usual.

The neutral fraction gave an amber liquid 116 + 117 (500 mg).

IR spectrum: $\nu_{max}^{CCl_4}$ 1750 (C=O), 1408 (C-H of $-CH_2C=O$); 1050, 1085, 1125 (C-O)

PMR spectrum: δ_{TMS}^{neat} 3.3 (s, -OMe)

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/MeOH (fast addition)

A freshly distilled sample (all metallic parts of spinning band columns taped with teflon) of 2-chlorocyclopentanone 69 (0.5 g, 4.0 mol) in methanol (1 ml) was added rapidly (5 sec) to a stirred solution of sodium methoxide (0.25 g. of sodium, 0.010 g.atom) in methanol (8 ml) at 0°. An aliquot was taken within 10 sec of addition and quenched with

H_2O and the ether extract injected onto the GLPC column.

GLPC (100°): 1 peak (2-methoxycyclopentanone 116, no 2-chlorocyclopentanone 69)

Reaction of 2-Chlorocyclopentanone 69 with MeO^-/MeOH (repeated)

2-Chlorocyclopentanone 69 (1.0 g, 9.0 mmol) in methanol (3 ml) was added (30 min) dropwise to a stirred solution of sodium methoxide (0.80 g.of sodium, 0.035 g.atom) in methanol (20 ml) at 0°.

Just prior to complete addition, a sample of the chloroketone solution was injected onto the GLPC column. Two peaks were evident: 2-chlorocyclopentanone 69 and 2-chlorocyclopentanone dimethylketal 117. Aqueous workup of the reaction medium soon after complete addition gave a neutral fraction which had two peaks 116 + 117 but no starting material 69.

Preparation of 2-Bromocyclopentanone 69b

Bromine (50 g, 0.32 mol) in CCl_4 (200 ml) was added dropwise to a solution of cyclopentanone (20 g, 0.24 mol) in CCl_4 (250 ml) at 0°. The colour faded rapidly. The CCl_4-HBr was distilled off leaving a dark brown residue which was distilled under vacuum on the spinning band column. During this distillation it was observed that the colourless liquid which dripped from the condenser turned reddish-brown on contact with the metallic part of the reflux ratio valve. The valve was screwed out to avoid contact.

The fraction b.p. 60-62° (3.0 Torr) (lit.[139] b.p. 60° at 2 Torr) was collected.

Attempted Favorskii Reactions with 2-Chlorocyclopentanone 69 and 2-Bromocyclopentanone 69b

See Table 11.

Preparation of 2-Bromocyclopentanone Ethylene Ketal 132

Cyclopentanone (25 g, 0.21 mol) was brominated (48 g of Br_2) in ethylene glycol (350 ml) and gave a colourless liquid (47 g) after aqueous workup.

The crude oil was distilled under reduced pressure and gave a liquid[132], b.p. 53-54° (0.15 Torr), which decomposed quite readily at room temperature.[128]

GLPC (150°): 1 peak

PMR spectrum: δ_{TMS}^{neat} 4.15 (t), 4.09 (brd.m), 2.4-1.7 (m)

IR spectrum: $\nu_{max}^{CCl_4}$ 1320, 1340, 1350, 950, 970 (sharp indicative bands)

Precise Mass Determination. Calc'd: 205.99412 (Br^{79})

Found: 205.99832

Reaction of 2-Bromocyclopentanone Ethylene Ketal 132 with $AgNO_3/CH_3CN$

Bromocyclopentanone ethylene ketal 132 (4.2 g, 0.020 mol) in acetonitrile (10 ml) was added dropwise (1 hr) to a refluxing solution of $AgNO_3$ (3,4 g, 0.020 mol) in acetonitrile (40 ml) under a blanket of dry N_2. A precipitate gradually developed. After 3 hr, the reaction medium was cooled to room temperature, filtered (1.3 g of AgBr, 35%), poured into an excess of water and extracted with ether. The ether layer was washed with water, saturated NaCl solution and dried ($MgSO_4$).

TABLE 11

Reactions of 2-Chlorocyclopentanone 69 and 2-Bromocyclopentanone 69b under Various Conditions

Substrate	Concentration	Reaction Conditions	Neutral Products	Acidic Products
69	1.0 g (9.0 mmol) 5 ml EtOH	0.5 g Na (0.02 g. atom) 20 ml EtOH 1 hr 0°	TLC: 2 spots GLPC: 2 peaks IR (CCl_4): 1745 (C=O) 1000-1200 (C-O)	not examined
69	2.0 g (18 mmol) 25 ml t-BuOH	5 g K^+ t-BuO^- 125 ml t-BuOH 14 hr 25°	TLC: 5-7 spots IR ($CHCl_3$): 1740 (C=O) 1642 (C=C) PMR ($CDCl_3$): 3.64 (m, J=6Hz) 2.2 (s) 1.06-1.29 (m)	IR ($CHCl_3$): 3600-3000 ($-CO_2H$) 1750-1710 (C=O) thick brown syrup (not examined further)
69	2.0 g (17 mmol)	2.0 g KOH (powder) 90 ml toluene[77] 1 hr reflux	TLC: 5-7 spots GLPC: starting ketone 69	Tar (0.7 g) and yellow syrup GLPC (120°): no cyclobutanecarboxylic acid 70 by comparison with authentic sample

TABLE 11 (Cont'd)

Substrate	Concentration	Reaction Conditions	Neutral Products	Acidic Products
69	20 mg	2.5 ml 5% $AgNO_3$ (H_2O) 15 min 90°	GLPC: 2 peaks (starting ketone 69 plus minor, less polar peak)	GLPC: no cyclobutane-carboxylic acid 70
69	50 mg	200 mg Ag_2O 3 ml H_2O + 1 ml MeOH	GLPC: 2 peaks (minor peak is starting ketone 69)	GLPC: no cyclobutane-carboxylic acid 70
69	2.0 g (18 mmol)	1.0 g Na (0.04 g.atom) 200 ml NH_3 $FeCl_3$ (catalyst) 45 min -80°	TLC: no cyclobutane-carboxamide by comparison with authentic sample	
69	2.0 g (18 mmol) 50 ml DME	4.2 g Na^+MeO^- 50 ml DME (dry) 6 hr reflux	GLPC: 3 peaks (starting ketone 69 plus 2 less polar peaks)	oily orange solid m.p. 86-112° (not examined further) GLC: no cyclobutane-carboxylic acid 70
69	1.0 g (9 mmol) 1 ml MeOH	2.0 g NaCN 10 ml MeOH 45 min reflux	poor recovery IR (CCl_4): 1738 (C=O) (continued on next page)	poor recovery

TABLE 11 (Cont'd)

Substrate	Concentration	Reaction Conditions	Neutral Products	Acidic Products
69			1660 (C=C) (neither cyclopentenone 71 nor 2-cyclopentylidenecyclo-pentanone by comparison of ir spectra)	
69	2.0 g (12 mmol) 5 ml MeOH (reacts at 25°)	0.8 g Na (0.035 g. atom) 20 ml MeOH 1 Hr 0°	GLPC: 4 peaks IR (CCl_4): 1742 (weak C=O) 2850 (C-H of MeO-) 1045, 1075, 1115 (C-O)	not examined

Evaporation of the ether layer gave a pale yellow liquid 132 (2.3 g).

GLPC (100°): 3 peaks (ketal 132 and 2 minor peaks)

TLC (EtOAc-PE36, 10:90): 3 spots (ketal 132 and 2 minor, polar spots)

Reaction of 2-Bromocyclopentanone Ethylene Ketal 132 with $AgNO_3$/MeOH

2-Bromocyclopentanone ethylene ketal 132 (1.7 g, 8.0 mmol) in methanol (13 ml) was added dropwise (35 min) to a refluxing solution of $AgNO_3$ (2.25 g, 13.0 mmol) in methanol (35 ml). A precipitate formed rapidly. After complete addition (2 hr), the reaction medium was worked up as before (1.6 g AgBr, 65%). Evaporation of the ether gave a yellow syrup 133 (750 mg).

TLC: 4 spots (1 major, 3 minor polar spots)

GLPC (100°): 2 peaks (less polar:more polar, 2:1)

IR spectrum: $\nu_{max}^{CCl_4}$ 2835 (C-H of -OMe), 1755 (weak C=O), 1130 (C-O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 4.2-3.4 (m), 3.39 (s,-OMe), 2.0-1.8 (m)

This crude material was absorbed on a column of alumina (21 g, Woelm, neutral, activity 1) and eluted with a gradually increasing concentration of EtOAc in PE36.

The major fraction was a yellowish oil 133 (170 mg).

IR spectrum: $\nu_{max}^{CCl_4}$ 2835 (C-H of -OMe), 1050-1150 (strong C-O), no C=O

Precise Mass Determination Calc'd: 158.09418

Found: 158.09582

Preparation of 2-Bromocyclohexanone Ethylene Ketal 136

As outlined for cyclopentanone (p. 115),[128] cyclohexanone (9.8 g,

0.10 mol) was brominated in ethylene glycol. Workup afforded a whitish oil 136 (19.2 g) which was distilled bulb to bulb (40° at 0.15 Torr) (lit.[128] b.p. 90.5-92.5 (5 Torr)) and which crystallized on refrigeration.

GLPC (100°): 1 peak

IR spectrum: no C=O function

PMR spectrum: δ^{neat}_{TMS} 4.3-3.9 (m, $-OCH_2CH_2O-$)

Reaction of 2-Bromocyclohexanone Ethylene Ketal 136 with $AgNO_3$/MeOH

As outlined for the cyclopentyl system (p. 119) an equimolar ratio of $AgNO_3$ (3.4 g, 0.020 mol) and ketal 136 (4.4 g, 0.020 mol) was refluxed in methanol (3.2 g, AgBr, 85%). Workup afforded a colourless oil 137 (2.1 g), b.p. 54-56° (0.1 Torr). Liquid-liquid extraction of the aqueous layer with ether gave more of the oil (1.0 g).

TLC (EtOAc-PE36, 10:90): 3 spots

GLPC (100°): 2 major peaks

IR spectrum: $\nu^{CCl_4}_{max}$ 2835 (C-H of -OMe) 1050-1150 (C-O)

PMR spectrum: δ^{neat}_{TMS} 3.18 (s, -OMe)

A portion of the crude oil 137 (1 g) was dissolved in 95% EtOH-3% aqueous HCl (25 ml, 1:1) and heated on a steam bath (1 hr). The reaction medium was saturated with salt and extracted with ether. The PMR spectrum of the crude 138 shows the loss of the methoxy peak but no low field peak as expected for a carboxylic acid proton

IR spectrum: $\nu^{CCl_4}_{max}$ 3560-3450 (-OH) and 1735 (weak C=O)

The remainder of the crude oil 137 (2 g) was chromatographed on silica gel (90 g) with PE36 diluted with increasing concentration of ethyl

acetate. Fractions of 30 ml were taken followed by GLPC. Five fractions were combined (700 mg) since TLC (EtOAc-PE36, 10:90) showed a single major spot 137 which corresponded to the major spot of the crude product.

IR spectrum: $\nu_{max}^{CCl_4}$ 2835 (C-H of -OMe), 1050-1150 (C-O), ~ 1739 (trace C=O)

This combined fraction was rechromatographed on silica gel with benzene-ether to purify it further. The ir spectrum showed no C=O impurity.

GLPC (130°): 1 peak

TLC (EtOAc-benzene, 1090): 1 spot

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 4.0-3.75 (m, $-OCH_2CH_2O-$), 3.3 (s, $-OCH_3$), 1.8-1.3 ($-CH_2-$)

Mass spectrum: m/e 172 (P^+) 141 (P^+-CH_3O) 83, 85 (metastable 100%)

Precise Mass Determination Calc'd: 172.10982

Found: 172.10743

When this material 137 was distilled bulb to bulb (165°) at atmospheric pressure, another compound 139 was formed which had the same PMR spectrum as the major volatile fraction from preparative GLPC (5% DEGS, 150°).

TLC (EtOAc-benzene, 10:90): 1 spot (less polar than 137)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 3.96 (s), 2.1-1.8 (m), 1.8-1.4 (m) (integration, 1:1:1)

Precise Mass Determination Calc'd: 140.08364

Found: 140.08458

Reaction of 2-Bromocyclohexanone Ethylene Ketal 136 with Silver Benzoate

2-Bromocyclohexanone ethylene ketal 136 (2.2 g, 10 mmol) was stirred

into a suspension of silver benzoate[129] (2.3 g, 10 mmol) in methanol-acetonitrile (50 ml, 1:1). The reaction was stirred at room temperature (12 hr) and then checked on TLC. Since there had been very little change, the reaction was continued at reflux (50 hr). After cooling to room temperature, the suspension was filtered and distilled to remove solvent. The residue was dissolved in ether and refiltered to remove any silver salt.

GLPC (150°): 2 peaks (ketal 136 plus a minor, less polar peak, which was not identified

Reaction of 2-Bromocyclohexanone Ethylene Ketal 136 with $AgNO_3$/MeOH-pyridine

2-Bromocyclohexanone ethylene ketal 136 (2.2 g, 10 mmol) was added to a solution of $AgNO_3$ (1.7 g, 10 mmol) in methanol (40 ml) containing pyridine (0.8 g, 10 mmol). This solution was purged with argon and refluxed (20 hr). After filtration to remove AgBr (1.4 g, 80%), the bulk of the solvent was removed by distillation and the remainder was poured into an excess of water, extracted with ether and dried. Evaporation of solvent gave a pale yellow oil 137 (600 mg).

TLC (EtOAc-PE68, 25:75): 3 spots (1 major, R_f=0.25 and 1 minor R_f=0.35 plus a trace of ketal 136)

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 4.0-3.3 (m,$-OCH_2CH_2O-$), 3.14 (s,$-OCH_3$); 2.0-1.2 (m,$-CH_2-$), integration (low field: high field=1:1)

Reaction of 2-Bromocyclopentanone Ethylene Ketal 132 with $AgNO_3$/MeOH-pyridine

The procedure was the same as that outlined for the cyclohexyl system above except the reaction was refluxed for 5.5 hr. The reaction

mixture was filtered to remove AgBr (1.4 g, 75%) and worked up as before. Evaporation of the ether gave a pale yellow liquid 133 (500 mg).

TLC (EtOAc-PE68, 25:75): 2 spots (1 major spot, R_f=0.38 and a trace of ketal 132)

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 4.0-3.25 (m, $-OCH_2CH_2O-$), 3.2 (s, $-OCH_3$), 2.0-1.6 (m, $-CH_2-$), integration (low field: high field = 4:3)

Hydrolysis of the Product 133 from the Reaction of $AgNO_3$ with 2-Bromocyclopentanone Ethylene Ketal 132

Crude oil 133 (110 mg) from the preceding reaction was stirred at room temperature in a solution of DME (1 ml) and 5% aqueous HCl acid (2 ml) for 16 hr. Workup involved pouring the reaction mixture into saturated NaCl solution, extracting with ether and extracting the ether layer with 5% NaOH solution. The basic, aqueous layer was then acidified to pH 2 and extracted with ether. The ether layers were dried, filtered and distilled to remove solvent.

No acidic fraction was found.

The neutral material was a yellowish oil 134 (20 mg).

TLC (EtOAc-PE68, 25:75): 5 spots (1 major spot, R_f=0.08 plus 4 less polar, trace materials)

IR spectrum: $\nu^{CCl_4}_{max}$ 3620, 3440 (strong -OH), 1750 (weak C=O) and 1115 (C-O)

Mass spectrum: m/e 126 (P^+-H_2O), 99, 70, no parent ion

Precise Mass Determination Calc'd: (P^+-H_2O): 126.06800

Found: 126.06920

Hydrolysis of the Product 137 from the Reaction of $AgNO_3$ with 2-Bromocyclohexanone Ethylene Ketal 136

Crude oil 137 (110 mg) (p. 121) was treated as above and worked up by pouring into saturated salt solution.

No acidic fraction was found.

The neutral fraction gave a pale yellow liquid (90 mg).

TLC: 3 spots (1 major spot 138, R_f=0.09 and 1 major spot 139, R_f=0.7 plus a trace spot)

IR spectrum: 3620, 3590, 3470 (-OH) and 1110 (C-O)

Mass spectrum: m/e 141 (P^+-OH), 140 (P^+-H_2O), 99 (100%), no parent ion

Reaction of 2-Bromocyclohexanone Ethylene Ketal 136 with $AgNO_3/H_2O$-DME

2-Bromocyclohexanone ethylene ketal 136 (2.2 g, 10 mmol) was stirred in a refluxing solution of $AgNO_3$ (2.5 g, 15 mmol) in 50 ml of water and 15 ml of DME containing pyridine (0.80 g, 10 mmol) for 5 hr. The starting material gradually went into solution and a precipitate formed (AgBr, 2 g, 100%). The reaction was worked up as before, p.122.

The acidic fraction (150 mg) and neutral fraction (200 mg) gave the same spots on TLC which reflects both the solubility of the products in aqueous medium and the lack of acidic products. The TLC and ir spectrum matched those of the hydrolysis product from the previous experiment.

The aqueous phase was extracted continuously with ether for 65 hr. A purplish-brown oil separated in the ether layer. The solvent was evaporated. The residue (1.2 g) showed only two spots on TLC which corresponded to the two major spots in the hydrolysis product 138 and 139 above; however, the non-polar spot 139 was the major one.

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 3.94 (s,-OCH_2CH_2O-), 2.2-1.85 (m, allylic), 1.85-1.4 (m,-CH_2-)

Comparison of the PMR spectrum with that of the material recovered from the preparative GLPC (p. 121) indicated that they were the same 139.

Reaction of Hydrolysis Product 138 with $BF_3 \cdot Et_2O$/HOAc

The crude hydrolysis product 138 (60 mg) (p. 124) was stirred at room temperature in acetic acid (3.5 ml) which contained 5 drops of BF_3 etherate.[132] The reaction mixture turned pale green immediately, then yellowish, later amber and finally a deep ruby colour. Aliquots were checked on TLC after 2 hr and after 3.5 hr. The reaction mixture was poured into saturated salt solution and extracted with ether - CH_2Cl_2 (1:1). Evaporation of the solvent gave an amber liquid 139 (33 mg).

TLC: 1 spot (R_f=0.85)

IR spectrum: $\nu^{CCl_4}_{max}$ 3600 (weak-OH), 1745, 1710 (weak C=O), 1100-1300 (intense C-O)

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 3.9 (s,-OCH_2CH_2O-), 2.15-1.85 (m, allylic), 1.85-1.35 (m,-CH_2-)

Comparison of PMR spectra showed that this was the same material as the previous reaction product 139 above and as the product of the preparative GLPC (p.121).

Preparation of Cis and Trans-2-bromo-4-t-butylcyclohexanone Ethylene Ketal 158

The procedure was the same as that used for the cyclohexyl system (p. except the bromination step required a longer time (overnight) because of the low solubility of the ketone in ethylene glycol. The product was

a white liquid (10.1 g, 85%) which crystallized after standing in the refrigerator for several weeks.

TLC (EtOAc-PE36, 10:90): 2 spots (R_f=0.39, R_f=0.49)

GLPC (150°): 2 peaks (overlapping, 55:45)

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 4.3-3.9 (m,-OCH_2CH_2O- and -CHBr-), 2.3-1.3 (m,-CH_2-), 0.86 (s,t-butyl)

Crude material (6 g) was chromatographed on a column of silica gel (300 g) with benzene and its separation followed by GLPC and TLC analysis. In each case, the purest fractions were combined.

The less polar cis isomer 158a (1.65 g) was a colourless oil whose GLPC showed 11% of the more polar trans isomer 158b. This material was used without further purification.

PMR spectrum[130,131]: $\delta^{CCl_4}_{TMS}$ 4.24-3.84 (m), 2.4-1.2 (m,-CH_2-), 0.9 0.9 (s,t-butyl)

: $\delta^{acetone\text{-}d_6}_{TMS}$ 4.36 (d, partial -CHBr-), 4.38-3.9 (m,-OCH_2CH_2O-

Mass spectrum: m/e 278, 276 (P^+), 197 (P^+-Br), 179, 177 (α-cleavage) 99 (α-cleavage, 100%).

The more polar trans isomer 158b (2.7 g) was colourless, slightly oily crystals, m.p. 35-50° whose GLPC showed 15% of the less polar cis isomer 158a. Recrystallization from pentane at -40° gave a white flaky solid, m.p. 54-57°.

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 4.14-4.0 (m,-CHBr-), 4.0-3.88 (m,-OCH_2CH_2O-), 2.3-1.2 (m,-CH_2-), 0.87 (s,t-butyl)

Mass spectrum: m/e 278, 276 (P^+), 197 (P^+-Br), 179, 177 (α-cleavage), 99 (α-cleavage, 100%)

Anal. Calc'd for $C_{12}H_{21}BrO_2$ (MW277): C, 51.65; H, 7.53

Found: C, 51.86; H, 7.29

Reaction of Cis-2-bromo-4-t-butylcyclohexanone Ethylene Ketal 158a with $AgNO_3$/MeOH-pyridine

The crude, equatorial bromo-isomer 158a (0.275 g, 1.0 mmol) was dissolved in 4 ml of methanol containing 80 mg of pyridine and 170 mg of $AgNO_3$ (1.0 mmol). The solution was stirred at reflux for 12 hr during which time a precipitate of AgBr (89 mg, 50%) gradually formed. The reaction was worked up as before (p.122).

Removal of ether gave a pale yellow liquid (220 mg) whose TLC (benzene) showed that considerable equatorial isomer remained but that the axial impurity had gone.

TLC (25% EtOAc-PE68) showed two products R_f=0.52 and 0.35, both more polar than the ketal 158a (R_f=0.74).

GLPC (150°) showed some equatorial isomer, no axial isomer and two, major, less polar peaks.

The crude material was re-treated with an excess of $AgNO_3$ under the same solvent and temperature conditions for 15 hr. After workup and solvent removal, a pale yellow oil (135 mg) was recovered. GLPC showed no ketal 158a. TLC (EtOAc-PE68, 25:75) showed five spots, all quite intense. The PMR spectrum showed a strong t-butyl signal, but the rest of the spectrum was not like those of the other bromoketal products 133 and 137 in that there was no distinct peak at 3.13 δ (s, CH_3O-).

Hydrolysis of the Crude Product from Cis-isomer 158a

The crude oil (135 mg) from the repeated reaction with $AgNO_3$

was stirred (heterogeneous) in a mixture of DME (1 ml) and 5% aqueous HCl (3 ml) for 19 hr. The reaction was worked up as before p.124

The acidic fraction (10 mg) was treated with excess CH_2N_2/ether.

TLC (EtOAc-PE68, 25:75): 3 spots.

The neutral fraction (82 mg) was changed only slightly (GLPC, PMR). The more polar spot on TLC disappeared and an even more polar spot had appeared.

The reaction was repeated with the recovered neutral material (82 mg) but at reflux for 4 hr.

The acidic fraction (32 mg) was methylated as before.

TLC: 3 spots

The neutral fraction (30 mg) still showed the very polar spot on TLC. The acidic products were not identified.

Reaction of Trans-2-bromo-4-t-butylcyclohexanone Ethylene Ketal 158b with $AgNO_3$/MeOH-pyridine

The reaction was done as before (p.) with the crude axial bromo-isomer 158b (275 mg, 1.0 mmol) except that the precipitate of AgBr (106 mg, 58%) was removed after refluxing for 1 hr. The reaction was continued for 11.5 hr and gave more AgBr (40 mg, 22%). The reaction was worked up as before (p.122).

Removal of solvent gave a liquid (220 mg) whose TLC (benzene) showed that some ketal 158 remained but that it was predominantly the equatorial isomer 158a. TLC (EtOAc-PE68, 25:75) showed one major product 159 (R_f=0.35), which matched the less polar product of the cis isomer 158a, and two minor products, one of which matched the more polar product of the cis isomer 158a.

GLPC showed some starting material (6c:6d, 2.5:1) with one major less polar peak 159. The ir spectrum showed no -OH, no C=O but strong C-O stretch at 1100 cm^{-1}.

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 4.34-3.6 (m, $-OCH_2CH_2O-$), 3.52, 3.32 (d.d, J=12Hz,3Hz), 3.13 (s,$-OCH_3$), 2.17-1.0 (m,$-CH_2-$), 0.86 (s,t-butyl)

Precise Mass Determination. Calc'd: 228.17238

Found: 228.17142

This spectrum is very similar to that of the major product 137 from the reaction of 2-bromocyclohexanone ethylene ketal 136 with $AgNO_3$ in methanol-pyridine. The reaction of the trans isomer 158b was repeated on a larger scale (1.1 g) without modification and afforded the same pale yellow liquid 159 (890 mg, 95%).

Hydrolysis of the Crude Product 159 from Trans-isomer 158b

The crude oil 159 (220 mg) was stirred at room temperature in a mixture of DME (1 ml) and 5% aqueous HCl (3 ml) for 15.5 hr. The reaction was worked up as before.

No acidic material was recovered.

The neutral layer gave a colourless liquid 160 (165 mg) which crystallized on standing at room temperature. This oily solid was washed with cold PE68 to afford white crystals (58 mg), m.p. 88-96°. Re-crystallization from PE68 gave white rhombic crystals of 160, m.p. 95-98° (sublimes above 70°).

TLC (EtOAc-PE68, 25:75) of the crude showed a major polar spot (R_f=0.1), which matched the position of the crystals, plus four less polar spots.

IR spectrum: $\nu^{CCl_4}_{max}$ 3620, 3590, 3480 (-OH), 1110 (C-O)

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 4.34-3.1 (brd.m,-OCH_2CH_2O-, 2.0-1.1 (brd,m,-CH_2-) 0.86 (s,t-butyl)

Mass spectrum: m/e 214 (P^+, 100%), 196 (P^+-18), 115 (P^+-99)

Anal. Calc'd. for $C_{12}H_{22}O_3$ (MW214): C, 67.25; H, 10.28;

Found: C, 67.47; H, 10.31;

The reaction was repeated on a larger scale (400 mg) without modification to afford more of the oily solid 160 (335 mg) which was recrystallized from PE68 (112 mg, m.p. 95-98°). The mother liquor (200 mg) was chromatographed on two thick plates (SiO_2) using EtOAc-PE68, 25:75. The most polar band afforded a syrup (53 mg) which showed two spots on TLC, a polar one 160 as expected and a non-polar one 163 (R_f=0.75). The ir spectrum shows O-H and C-O as above.

Reaction of Trans-2-bromo-4-t-butylcyclohexanone Ethylene Ketal 158b with $AgNO_3/H_2O$-DME-pyridine

The crude crystals of 158b (260 mg) were dissolved in DME (2 ml) and added to a stirred solution of $AgNO_3$ (400 mg) in water (5 ml) containing pyridine (100 mg). The starting material oiled out. The suspension was stirred at reflux for 4 hr during which time a dark grey precipitate of AgBr (170 mg, 95%) formed. The reaction was worked up as before and gave a colourless syrup 160 and 163 (200 mg).

TLC (EtOAc-PE68, 25:75): 2 spots (R_f=0.18 and 0.78)

IR spectrum: $\nu^{CCl_4}_{max}$ 3620, 3590, 3470 (-OH), 3 minor C=O, strong C-O bands

This spectrum is similar to the previous one (p. 130) except for variations in the fingerprint region.

Reaction of Crystalline Hydrolysis Product 160 with Triphenylphosphine/CCl_4

The crystals of 160 (14 mg, 0.060 mmol) were dissolved in CCl_4 (0.5 ml) with triphenylphosphine (17 mg, 0.070 mmol) and refluxed for 26 hr. A white precipitate was formed. The solvent was evaporated and the residue was taken up in pentane and filtered. Examination of the residue showed no dehydration product; therefore, the investigation was not continued.

TLC (EtOAc-PE68, 25:75): 2 spots (major spot, R_f=0.5 and trace of hemiketal 160)

IR spectrum: $\nu_{max}^{CCl_4}$ 2960, 2870 (C-H), 1730 (C=O), 1130 (C-O)

Reaction of Crystalline Hydrolysis Product 160 with $POCl_3$/Pyridine

The crystals of 160 (22 mg, 0.10 mmol) were dissolved in pyridine (150 mg) and cooled to 0°. Phosphoryl trichloride (50 mg, 0.25 mmol) was added with stirring and a white precipitate was formed. The ice bath was removed and the reaction mixture was stirred at room temperature for 5 hr. Finally, the reaction was heated on a steam bath for 15 min. The reaction mixture was poured into water, extracted with pentane and dried ($MgSO_4$). Examination of the residue showed no dehydration product; therefore, the investigation was not continued.

TLC (EtOAc-PE68, 25:75): 1 spot (R_f=0.5)

This material matched the product of the triphenylphosphine reaction above both by TLC and ir spectrum.

Reaction of Crystalline Hydrolysis Product 160 with $BF_3 \cdot Et_2O$/HOAc

The crystals of 160 (40 mg) were dissolved in glacial acetic acid (3 ml) at room temperature and BF_3 etherate (4 drops) was added. The

reaction was stirred for 4 hr at room temperature during which time a pink colour developed. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with 5% $KHCO_3$ and dried ($MgSO_4$). Evaporation of the solvent gave a yellowish, oily enol ether 163 (35 mg, 96%).

TLC (EtOAc-PE68, 25:75): 1 spot (R_f=0.9)

IR spectrum: $\nu_{max}^{CCl_4}$ 3.9 (s,4H,-OCH_2CH_2O-), 2.18-1.75 (m,4H, allylic), 1.75-1.05 (m,3H,-CH_2-), 0.85 (s,9H,t-butyl)

A drop of this crude in CCl_4 decolorized Br_2/CCl_4 instantaneously with no apparent HBr production.

The reaction was repeated with 70 mg of crystals and after workup afforded 60 mg (94%) of liquid 163.

Ozonolysis of Enol Ether 160

The crude liquid 160 (60 mg) was dissolved in CCl_4 and an excess of O_3 was bubbled through the solution at 0°. When starch-iodide paper indicated that ozone was being absorbed no longer, the solvent was evaporated and the resulting syrup was dissolved in HOAc (2 ml). Zinc (75 mg) was added gradually to the HOAc solution causing effervescence and release of heat. The suspension was stirred for 2 hr and then poured into water and extracted with ether. The ether layer was washed with 5% $KHCO_3$ and dried ($MgSO_4$). Evaporation of the ether gave a syrupy oil, 164 (65 mg).

IR spectrum: $\nu_{max}^{CCl_4}$ 2960, 2870 (C-H), 1740 (strong C=O), 1712 (weak C=O)

The crude oil was dissolved in a mixture of 95% ethanol (1 ml) and 5% KOH (3 ml) and stirred at room temperature (16 hr). The reaction mixture was poured into water and extracted with ether. The aqueous layer was then

acidified to pH 2 and re-extracted with ether. The ether solutions were dried as before.

The neutral fraction gave a white solid (5 mg) which was not examined further.

The acidic fraction gave an amber syrup (43 mg) whose TLC (EtOAc-PE68-HOAc, 25:73:2) showed a major polar spot which corresponded to 3-t-butyladipic acid and two less polar impurities. Crystallization was induced by washing the crude syrup with PE68. This afforded a pale yellow solid 165 (30 mg), m.p. 75-107°. Two recrystallizations from PE68-EtOAc gave white crystals 165, m.p. 114-118°. A mixture-melting point with authentic 3-t-butyladipic acid, m.p. 115-117° showed no depression.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3400-2500 (-OH), 1710 (C=O) and 1200 (C-O).

The ir spectrum matched exactly that of authentic 3-t-butyladipic acid prepared as described in the next experiment.

Preparation of 3-t-Butyladipic Acid 165

4-t-Butylcyclohexanone (900 mg) was added (0.5 hr) to hot 50% HNO_3 (5 ml) which contained V_2O_5 (5 mg).[133] The reaction was vigorous and brown fumes were emitted. After complete addition, the reaction was held at steam bath temperature (0.5 hr). On cooling to ice temperature, crystals formed. The solid (750 mg, 65%) was filtered and washed thoroughly with water.

The solid was recrystallized twice from PE68-EtOAc and afforded white crystals of 165, m.p. 115-117° (lit.[134] m.p. 115°). The PMR spectrum showed a broad multiplet due to the α - and β -protons ($\delta_{TMS}^{CDCl_3}$ 2.5-2.1).

Preparation of Dicyclohexyl Ketone 210

Dicyclohexylcarbinol (30 g, 0.5 mol, K & K Laboratories, Inc.) in acetone (250 ml) was titrated at room temperature with Jones reagent.[135] Intermittent cooling was needed to maintain this temperature. During the reaction, a dark-green liquid separated. When the greenish-brown colour persisted, the reaction mixture was quenched with water (250 ml) and extracted with ether. The separated ether layer was washed, dried and filtered. Evaporation of the solvent afforded a pale yellowish oil 210 (29.8 g, 0.150 mol, 100%) (lit.[52] b.p. 159°, 20 Torr).

IR spectrum: $\nu_{max}^{CCl_4}$ 2930, 2860 (C-H), 1706 (C=O)

Mass spectrum: m/e 194 (P^+), 111 (P^+-83), 83 (P^+-111)

Preparation of Chlorodicyclohexylketone 167

Sulfuryl chloride (21.6 g, 0.160 mol) was added dropwise (1 hr) to the crude dicyclohexylketone 210 (29.8 g, 0.150 mol) at 0°. After complete addition, the reaction mixture was stirred at room temperature (4 hr) and then was heated on the steam bath (15 min). The crude material was dissolved in ether and washed with dilute bicarbonate solution. Evaporation of the solvent afforded a yellowish oil (30.5 g, 0.133 mol, 90%). GLPC showed one major peak.

IR spectrum: $\nu_{max}^{CCl_4}$ 2930, 2860 (C-H) and 1712 (C=O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 3.0 (m, α'-proton) and 2.1-1.2 (m, $-CH_2-$)

A portion of the crude oil (400 mg) was chromatographed on four thick layer plates (silica gel) with ether - PE68 (5:95). The major band was collected and distilled bulb to bulb under vacuum. This treatment afforded

a colourless oil 167 which crystallized on standing m.p. 41.5-42.5° (lit.[46] m.p. 40°).

Mass spectrum (M-66): m/e 111 (P^+-117.5) and 83 (P^+-145.5,100%)

Mass spectrum (AEI,MS-12): m/e 228, 230 (P^+)

Preparation of 2-Bromodicyclohexylketone 167b

To a solution of dicyclohexyl ketone 210 (1.0 g, 5.0 mmol) in HOAc (10 ml) was added dropwise a solution of Br_2 (0.85 g, B.D.H.) in HOAc (5 ml). The amber colour faded rapidly and, after complete addition of bromine, the reaction mixture was poured into water and extracted with ether. The ether layer was washed with $NaHCO_3$ solution and dried ($MgSO_4$).

Evaporation of the ether gave a yellow oil (1.03 g) which solidified on cooling, m.p. 38-61°. The crude solid was recrystallized from ethanol-water to give white crystals 167b (0.7 g), m.p. 64.5-66.5° (lit.[156] m.p. 66°).

IR spectrum: $\nu_{max}^{CCl_4}$ 2935, 2860 (C-H) and 1708 (C=O)

Mass spectrum: m/e 272, 274 (P^+), 111 (P^+-161,163)

Preparation of Chlorodiisopropylketone 176

The method of preparation was the same as that used to prepare chlorodicyclohexylketone 167 except that after complete addition of SO_2Cl_2 (26.2 g, 0.23 mol) to diisopropylketone (25.2 g, 0.22 mol, Aldrich) the reaction mixture was held at room temperature overnight. GLPC of the crude oil showed that 10% of ketone remained.

The crude oil was distilled through a Vigreux column and the fraction with b.p. 141-143° at 750 Torr (lit.[137] b.p. 143-145° at 760 Torr) was collected.

IR spectrum: $\nu_{max}^{CCl_4}$ 2990, 2935, 2875 (C-H) and 1715 (C=O)

PMR spectrum: δ_{TMS}^{neat} 3.45 (m, J=6.5Hz, 1H)
1.66 (s, 6H), 1.14 (d, 6H, J=6.5Hz)

Favorskii Reaction of Chlorodicyclohexylketone 167

Chlorodicyclohexylketone 167 (4.6 g, 20 mmol) in dioxane (6 ml) was added dropwise (0.5hr) to a stirred suspension of powdered KOH (5.6 g, 100 mmol) in refluxing dioxane (30 ml). After the reaction mixture was refluxed for 9 hr, the suspension was cooled to room temperature and worked up in the manner outlined in the general experimental section.

The neutral fraction (1.25 g) was an orange oil which contained one volatile material according to GLPC. This fraction was not examined further.

The acidic fraction (2.89 g, 69%) was a strong smelling, dark brown oil which crystallized at room temperature. Recrystallization (H_2O-EtOH) gave a white, flaky compound 168 m.p. 117-120°.

A portion of the crude acidic material (770 mg) was chromatographed on a column of silica gel (20 g) with PE68. In this way, white crystalline 1-cyclohexylcyclohexanecarboxylic acid 168 (600 mg) was obtained, m.p. 123-125° (lit.[46] m.p. 119-120°).

IR spectrum: $\nu_{max}^{CCl_4}$ 3300-2400 (CO_2-H) and 1695 (C=O)

Mass spectrum: , m/e 210 (P^+), 128 (P^+-82, 100%)

TLC (PE68-EtOAc, 90:10): single spot (R_f=0.55)

Favorskii Reaction of Chlorodiisopropylketone 176

Chlorodiisopropylketone 176 (3.7 g, 25 mmol) in dioxane (5 ml) was allowed to react under the conditions outlined for chlorodicyclohexyl

ketone above except the total reaction time was longer (70 hr).

The neutral fraction (2.31 g) was a pale yellow liquid whose GLPC showed one major peak. This fraction was not examined further.

The acidic fraction (1.16 g, 36%) was a dark brown liquid which defied any attempt at crystallization. Bulb to bulb distillation under vacuum removed colored impurities and gave a colorless oil, 2,2,3-trimethylbutyric acid 177, which was crystalline only at ice temperature (lit.[136] m.p. 48-50°).

IR spectrum: $\nu_{max}^{CCl_4}$ 1700 (C=O)

PMR spectrum: δ_{TMS}^{neat} 9.52 (brd.s,1H), 2.1 (m,J=6.8Hz,1H), 1.17 (s,6H), 0.95 (d,J=6.8Hz,6H)

Mass spectrum: m/e 88 (P^+-42,100%), 70 (P^+-60)

The crude oil was eluted on a column of silica gel (30 g) with PE68. The combined fractions afforded a pale yellow oil (830 mg) which crystallized only at ice temperature.

Favorskii Rearrangement of 2-Chlorodicyclohexyl Ketone 167 and 2-Chlorodiisopropyl Ketone 176 under Various Conditions

See Table III and IV.

Reaction of 2-Chlorodicyclohexyl Ketone 167 with NaCN/MeOH

A solution of 2-chlorodicyclohexyl ketone 167 (0.50 g, 2.5 mmol) and NaCN (0.78 g, 16 mmol) in methanol (7 ml) was maintained at reflux for 1.5 hr. A white precipitate formed during the reflux period. The reaction was worked up by pouring into water and extracting with ether. Evaporation of the solvent afforded a colourless liquid 179 (0.4 g).

TLC: (EtOAc-PE68, 40:60): 1 spot (no chloroketone 167)

TABLE III

Favorskii Rearrangements of Chlorodicyclohexyl Ketone 167 and Bromodicyclohexyl Ketone 167b

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
167	2.3 g (10 mmol) in 5 ml MeOH	2.8 g KOH (50 mmol) 15 ml MeOH 5 hr reflux	349 mg oily crystals 168 (17%)	1.59 g liquid GLPC: 2 peaks (minor is 167)
167	2.0 g (9 mmol) in 4 ml dioxane + 1 ml MeOH	2.8 g KOH (50 mmol) 12 ml dioxane plus 3 ml MeOH 4 hr reflux	1.23 g oily crystals 168 (68%)	
167	1.0 g (4.5 mmol) in 1 ml t-BuOH	0.30 sodium (0.013 g. atom) 11 ml t-BuOH plus 2 ml 30% H_2O_2 2 hr room temp.	none	900 mg liquid GLPC: 1 peak TLC: 1 spot 167
167	900 mg (4.00 mmol) t-BuOH	300 mg sodium (0.013 g. atom) 11 ml t-BuOH 2 ml 30% H_2O_2 (2x) 1 hr reflux	none	830 mg liquid GLPC: 1 peak TLC: 1 spot 167

TABLE III (Cont'd)

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
167	800 mg (3.50 mmol) in 3 ml t-BuOH	300 mg sodium (0.013 g. atom) 10 ml t-BuOH 0.3 ml H_2O 5 hr reflux	260 mg off-white crystals 168 (36%)	220 mg syrup TLC: 1 spot (not 167)
167	500 mg (2.25 mmol) in 2 ml MeOH	0.80 g NaCN (16 mmol) 5 ml (MeOH) 2 hr reflux	See detailed experimental (p.	
167	6.0 g (26 mmol)	4.0 g NaOH (100 mmol) 40 ml H_2O 10 ml EtOH 36 hr reflux	1.5 g solid 168 (27%)	3.5 g yellow oil TLC (EtOAc-PE36, 5:95): 3 spots (one major 201, one minor and a trace of chloroketone 167) IR: $\nu_{max}^{CCl_4}$ 3460 (brd., O-H) 1690 (C=O)
167	150 mg (0.67mmol) 5 ml MeOH	350 mg $AgNO_3$ (2.11 mmol) 24 hr reflux	none	90 mg oil TLC: 2 spots (chloroketone 167 and enone 178
167	100 mg (0.45 mmol) 10 ml t-BuOH	190 mg NaOH (4.5 mmol) 2 ml H_2O	none	80 mg oil TLC: 3 spots

TABLE III (Cont'd)

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
167		2 ml H_2O_2 (2x) 4 hr reflux		(chloroketone 167 plus two trace polar compounds which were not examined)
167	90 mg (0.41 mmol) 5 ml EtOH	200 mg KOH (4.0 mmol) 1.5 ml H_2O saturated with H_2S 12 hr reflux	8 mg oil crystals 168 (recrystallized from PE 58, m.p. 116-118°)	75 mg syrup TLC: 2 spots (major spot is enone 178, no chloroketone 167) PMR: $\delta^{CCl_4}_{TMS}$ 6.65 (m)
167b	100 mg (0.35 mmol) 5 ml EtOH	200 mg KOH (4.0 mmol) 1.5 ml H_2O saturated with H_2S 19 hr reflux	5 mg oily crystals 168 (50%)	64 mg oil TLC: 4 spots (major spot is enone 178, no bromoketone 167b)
167b	100 mg (0.35 mmol) 10 ml t-BuOH	290 mg KOH (5.0 mmol) 2 ml H_2O 1 ml H_2O_2 (3x) 2 hr reflux	none	72 mg oil TLC: 3 spots (bromoketone 167b, enone 178 and a more polar compound which was not examined)

TABLE IV

Favorskii Rearrangements of Chlorodiisopropyl Ketone 176

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
176	1.9 g (13 mmol) in 5 ml MeOH	2.8 g KOH 15 ml (50 mmol) 5 hr reflux	247 mg oil 177 (15%)	1.0 g liquid GLPC: 2 peaks (no 176) PMR[32]: δ^{neat}_{TMS} 4.2* (brd.s,OH), 3.73 (s,-OMe)
176	1.9 g in 4 ml (13 mmol) dioxane plus	2.8 g KOH 12 ml dioxane plus 3 ml MeOH 4 hr reflux	635 mg oil 177 (38%)	not examined
176	2.0 g (14 mmol)	3.0 g KOH (53 mmol) 10 ml H_2O 13 hr 25° well stirred	25 mg brown oil 177 (1.5%)	1.3 g colourless liquid GLPC (80°): 3 peaks (hydroxyketone 176b plus two minor compounds) PMR[32]: δ^{neat}_{TMS} 4.22 (brd.m,1H,O-H) 3.35 (m,J=7.0Hz,1H) 1.35 (s,6H) 1.07 (d,J=7.0Hz,6H)

TABLE IV (Cont'd)

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
176	2.0 g (14 mmol)	3.0 g KOH (53 mmol) 10 ml H_2O 13 hr reflux	60 mg brown oil 177 (4%)	1.1 g amber oil GLPC (80°): 3 peaks (hydroxy-ketone 176b with overlapping peak and minor peak) PMR: as above plus many other peaks
176	2.0 g (14 mmol) in 1 ml DMSO	3.5 g KOH (powder) (53 mmol) 10 ml DMSO 2 hr 25°	256 mg amber liquid 177 (14%)	906 mg amber liquid 176b PMR: as above
176	2.0 g (14 mmol)	0.50 g sodium (0.022 g. atom) 30 ml t-BuOH 3.5 hr 25°	180 mg yellow oil 177 (10%)	1 g yellow liquid IR: $\nu_{max}^{CCl_4}$ 1712 (C=O), 1155, 1135 (C-O) GLPC (80°): 4 peaks (1 major peak, 3 minor ones) PMR: δ_{TMS}^{neat} 1.84 (m, J=5.5Hz) 1.42 (s, -Me) 1.02 (s, t-butyl) 0.85 (d, isopropyl-Me, J=5.5Hz)
	2.0 g 14 mmol in dioxane	3.0 g KOH (53 mmol) 3 ml MeOH + 9 ml	200 mg oil 177 (11%)	650 mg liquid GLPC (80°): 1 major peak 176b

TABLE IV (Cont'd)

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
		dioxane		plus trace impurities
176		3 ml 30% H_2O_2 (2x)		PMR: as below
		6 hr reflux		
	2.0 g (14 mmol)	3.0 g KOH (53 mmol)	210 mg yellow oil	600 mg liquid
	in 5 ml	10 ml dioxane +	177 (11%)	TLC (EtOAc-PE68,10:90): 1 spot
176	dioxane	2 ml H_2O		GLPC (80°): 2 peaks
		2 ml 30% H_2O_2 (2x)		(2-hydroxydiisopropylketone 176b
		2 hr reflux		plus trace of starting material 176)
				PMR[32]: δ^{neat}_{TMS} 4.15 (brd.s,-OH)
				3.35 (m,J=7.0Hz)
				1.35 (s,-Me)
				1.08 (d,isopropyl-Me J=7.0Hz)
	2.0 g (14 mmol)	3 g KOH (53 mmol)	110 mg pale	920 mg pale yellow liquid
		(powder)	yellow liquid	GLPC (80°): 1 peak hydroxyketone
176		10 ml t-BuOH	177 (6%)	176b
		2 ml H_2O_2		IR[32]: $\nu^{CCl_4}_{max}$ 3610,3480 (-OH)
		1 hr 25°		1710 (C=O)
				PMR: as above

TABLE IV (Cont'd)

Substrate	Concentration	Reaction Conditions	Acidic	Neutral
176	2.0 g (14 mmol)	3 g KOH (53 mmol) (powder) 12 ml t-BuOH 2.5 hr 25°	240 mg amber oil 177 (13%)	900 mg amber liquid GLPC (80°): 2 peaks (major peak is hydroxyketone 176b) PMR: as above
176	2.0 g (14 mmol)	3 g KOH (53 mmol) (powder) 12 ml t-BuOH 2.5 hr reflux	300 mg amber oil 177 (17%)	1 g yellow oil GLPC (80°): 4 peaks hydroxyketone 176b, an overlapping peak plus two minor peaks)
176	2.0 g	600 mg sodium (0.025 g. atom) 30 ml benzyl alcohol 12 hr 25°	100 mg yellow oil 177 (5%)	heavily contaminated with benzyl alcohol
176	1.5 g	2.0 g NaCN (40 mmol) 10 ml MeOH 9 hr reflux	See detailed experiment, p.	

IR spectrum: $\nu_{max}^{CCl_4}$ 2960, 2880 (C-H) and 2260 (C≡N)

Basic Hydrolyis of Epoxynitrile 179[95]

The crude epoxynitrile 179 (0.2 g, 9 mmol) was stirred vigorously (4 hr) in a refluxing solution of KOH (200 mg) in 3 ml of water and 3 ml of ethanol. The reaction was cooled to room temperature, quenched by pouring into water and extracted with pentane.

Evaporation of the solvent gave a white solid 180 (136 mg), m.p. 148-154° (sublimes above 110°). The crude solid was sublimed under vacuum and, then, recrystallized from ether-pentane, m.p. 154.5-155.5°.

IR spectrum: $\nu_{max}^{CCl_4}$ 3100 ($-NH_2$); 2925, 2860 (C-H); 1685 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 6.25 (brd.d, $-NH_2$), 2.2-1.1 (m, $-CH_2-$)

Mass spectrum: m/e 237 (P^+, 100%), 155 (P^+-82)

Anal. Calc'd. for $C_{14}H_{23}NO_2$(237): C, 70.90; H, 9.77; N, 5.91

Found: C, 70.84; H, 9.66; N, 5.85

Reaction of 2-Chlorodiisopropyl Ketone 176 with NaCN/MeOH

A solution of 2-chlorodiisopropyl ketone 176 (1.5 g, 10 mmol) and NaCN (2 g, 0.04 mol) in methanol (10 ml) was maintained at reflux (9 hr). The reaction mixture was worked up as before, p. 137 . Evaporation of the solvent gave a yellow liquid (830 mg).

GLPC: 2 peaks (1 major and 1 minor at shorter retention time)

TLC (ether-PE36, 30:70: 2 spots (major spot, R_f=0.5 and minor, polar spot)

IR spectrum: $\nu_{max}^{CCl_4}$ 2980, 2940, 2885 (C-H) and 2240 (C≡N)

PMR spectrum[138]: $\delta^{CCl_4}_{TMS}$ 1.55, 1.36 (s,Me-); 1.15 (overlapping d.d, J=6.5Hz, isopropyl)

benzene added: 1.45, 1.2 (s,Me-); 1.14 (d, J-6.5Hz); 1.0 (d,J-6.5Hz)

more benzene added: 1.35, 1.04 (s,Me-); 1.09 (d,J=6.5Hz); 0.91 (d,J=6.5Hz)

benzene alone: 1.30, 0.95 (s,Me-); 1.05 (d,J=6.5Hz); 0.84 (d,J=6.5Hz)

A portion of this crude liquid was injected onto a preparative GLC column (5% DEGS, 80°) and the glycidonitrile 259 collected in a cold trap (-80°), (lit.[95] b.p. 83-84°, 27 Torr).

TLC (EtOAc-benzene, 10:90): 1 spot

GLPC (135°): 1 peak

IR spectrum: unchanged

PMR spectrum: unchanged

Mass spectrum: m/e 124 (P^+-15, 100%)

Reaction of 2-Chlorodiisopropyl Ketone 176 with NaCN/CH_3CN

A suspension of NaCN (2 g, 0.04 mol) was stirred vigorously in a solution of 2-chlorodiisopropyl ketone 176 (1.5 g, 10 mmol) in acetonitrile (10 ml) at reflux (9 hr). The reaction was worked up as before (p. 137).

Evaporation of the solvent gave a pale yellow liquid (990 mg). Comparison of GLPC, TLC and ir and PMR spectra with those of epoxynitrile 179 from the previous experiment indicated that the product was the same except some chloroketone 176 still remained.

Basic Hydrolysis of Epoxynitrile 259

A suspension of crude epoxynitrile 259 (500 mg, 36 mmol) in a solution of NaOH (0.6 g) in water-ethanol (10 ml, 1:1) was maintained at reflux (2 hr). The reaction mixture was worked up according to the procedure on p.145.

The crude product was a white solid[95] (420 mg), m.p. 107-113°, which was recrystallized from ether-pentane to give colourless needles of 260, m.p. 105-107° (sublimes above 90°).

TLC (EtOAc-benzene, 10:90): 1 spot

IR spectrum: $\nu_{max}^{CCl_4}$ 3470, 3200 ($-NH_2$) and 1685 (C=O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 1.36 and 1.31 (s, Me-), 1.21 (d, isopropyl, J=6.5Hz) and 1.04 (d, isopropyl, J=6.5Hz)

Mass spectrum: m/e 157 (P^+), 142 (P^+-15, 100%)

Anal. Calc'd. for $C_8H_{14}NO_2$(157): C, 61.09; H, 9.62; N, 8.92

Found: C, 60.93; H, 9.79; N, 8.95

Acid Hydrolysis of Epoxynitrile 259

Crude epoxynitrile 259 (750 mg) was stirred in a mixture of concentrated HCl (1 ml), water (5 ml) and ethanol (5 ml) at room temperature for 1.5 hr. The reaction mixture was worked up as on p.137 and afforded a colourless liquid (700 mg).

GLPC (80°): 5 peaks (some epoxynitrile 259)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 5.18 (m, vinyl) and 2.0-0.8 (complexity of methyl peaks)

The crude liquid was developed on a silica gel (20 g) column with benzene - EtOAc, 95:5. The early fractions (300 mg) contained mainly

epoxynitrile 259 but, later, a white solid (190 mg) was eluted from the column and recrystallized from ether-pentane, m.p. 76-77°. The solid was tentatively assigned the structure 261.

IR spectrum: $\nu_{max}^{CCl_4}$ 3580, 3440 (brd.,-OH); 2960, 2890 (C-H) 1250, 700

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 2.06 (m,1H,J=6.5Hz), 1.54 and 1.34 (s,3H,-Me), 1.15 (dd,6H,J=6.5Hz) D_2O added, 4.7 (s,HOD)

Mass spectrum: m/e 130 (P^+-HCN), 100, 99, 70, 59 (α-cleavage, 100%)

Preparation of Methanol-O-d_1 [167]

A mixture of freshly distilled trimethyl orthoformate (400 g, 98.5-99°, Eastman Kodak) and deuterium oxide (55 ml, 99.8%, Stohler Isotope Chemicals) containing phosphorus pentoxide (0.5 g, Anachemia) was refluxed for 5 days. The reaction was protected from atmospheric moisture by connecting the condenser to a mercury bubbler.

The reaction mixture was distilled on the spinning band column and methanol-O-d_1, b.p. 64.8-65° at 755 Torr was collected.

Reaction of 2-Chlorodicyclohexyl Ketone 167 with NaOD/MeOD-dioxane

Freshly cut sodium metal (2.0 g) was dissolved in a refluxing solution of dioxane (25 ml), methanol-O-d_1 (6 ml) and deuterium oxide (2.5 g) to form a white, gelatinous suspension. To this vigorously stirred suspension was added (0.5 hr) 2-chlorodicyclohexyl ketone 167 (2.0 g) in dioxane (5 ml). The reaction mixture was maintained at

reflux for 11 hr. The workup procedure is outlined on p. 103.

The acidic fraction gave a yellow oil 168 (1.68 g, 90%) which crystallized on standing. The crude was purified by sublimation at reduced pressure, m.p. 120-122°. Deuterium analysis by comparison of the parent ion (m/e 210) in the mass spectrum with that from a non-deuterated sample gave 0.75 D per molecule.

Attempted Deuterium Exchange with 2-Chlorodicyclohexyl Ketone 167

A stream of deuterium chloride, prepared by addition of PCl_3 (19 g) to D_2O (4 g), was bubbled through a solution of 2-chlorodicyclohexyl ketone 167 (4 g) in $CDCl_3$ (4 ml) and acetic acid-d_4 (7 ml). The solution, then, was maintained at reflux for 48 hr. The solvent was evaporated and the yellow oil was distilled (2x) bulb to bulb at reduced pressure. Analysis by mass spectrometry showed very little deuterium incorporation.

Preparation of 2-Chlorodicyclohexyl Ketone-2-d_1 167

A suspension of dicyclohexyl ketone 5.5 g) was vigorously stirred (80 hr) in refluxing D_2O (6 ml) to which had been added thionyl chloride (0.3 ml). The reaction mixture was cooled to room temperature and extracted with ether.

The exchange procedure was repeated twice more and gave a slightly yellow oil (4.4 g). The crude oil was stirred at room temperature (2.5 hr) with sulphuryl chloride (3.5 g), and then the mixture was warmed on the steam bath (15 min). The residue was distilled under vacuum to afford 2-chlorodicyclohexyl ketone-2'-d_1 167 (4.1 g), b.p. 119-120° at 1.5 Torr, (lit.[94] b.p. 159-161° at 16 Torr).

GLC: 1 peak

TLC: 1 spot

Deuterium analysis by comparison of fragment ions (m/e 111, 83) in the mass spectrum with that from a non-deuterated sample gave 0.98 D per molecule.

Reaction of 2-Chlorodicyclohexyl Ketone-2'-d_1 167 with NaOH/MeOH-dioxane

2-Chlorodicyclohexyl ketone-2'-d_1 167 (1.0 g) in dioxane (3 ml) was added dropwise to a refluxing suspension of base prepared in the same manner as outlined on p. 148 except half quantities and non-deuterated materials were used. The reaction mixture was refluxed for 5 hr and then worked up as before, p. 103.

The acidic fraction gave a white solid (0.3 g, 32%) which was sublimed at reduced pressure and, then, recrystallized from pentane, m.p. 120-123°.

Deuterium analysis by comparison of the parent ion (m/e 210) and a fragment ion (m/e 165) in the mass spectrum with that from a non-deuterated specimen indicated 0.02D per molecule.

Preparation of 2-Chlorodiisopropyl Ketone-2'-d_1 176

A mixture of diisopropyl ketone (10 g), D_2O (7 g, 99.8%) and anhydrous K_2CO_3 (0.5 g) was refluxed for 24 hr. An aliquot was checked (PMR) and showed very little exchange so the mixture was refluxed for a further 30 hr. After cooling to room temperature, the mixture was extracted with ether and the ether layer dried ($MgSO_4$). The exchange reaction was repeated by refluxing the recovered ketone in a

suspension of D_2O (5 ml) containing $SOCl_2$ (0.3 ml) for 48 hr. This mixture was cooled and extracted with ether.

The diisopropyl ketone (4.85 g) recovered from the second exchange was stirred at room temperature (6 hr) with sulphuryl chloride (4.4 g) and then warmed on the steam bath (15 min). The residue was distilled on the micro spinning band column and the fraction 176, b.p. 134-140° was collected. Deuterium analysis by comparison of the fragment ion (m/e 43) with that from a non-deuterated sample in the mass spectrum gave 0.88 D per molecule.

Reaction of 2-Chlorodiisopropyl Ketone-2'-d_1 176 with NaOH in Dioxane-methanol

2-Chlorodiisopropyl ketone-2'-d_1 176 (1.25 g) in dioxane (2 ml) was added dropwise to a refluxing suspension of base prepared by dissolving sodium (1.25 g) in dioxane (20 ml) containing methanol (4 ml) and water (1 ml). The reaction was maintained at reflux (4.5 hr) with vigorous stirring and then worked up as on p. 103.

The acidic fraction was an amber oil (330 mg, 30%) which was distilled (3x) bulb to bulb under vacuum to remove the yellow colour. Deuterium analysis by comparison of fragment ions (m/e 43, 85) in the mass spectrum with those from a non-deuterated specimen showed 0.07 D per molecule.

Preparation of Isobutyl Bromide

Phosphorus tribromide (100 g, 0.37 mol) was added dropwise (5 hr) at room temperature to isobutyl alcohol (80 g, 1.1 mol). After complete addition, the mixture was stirred overnight (10 hr) and then heated on the steam bath (0.5 hr). The residue was distilled (2x) through Vigreux

column at atmospheric pressure and the fraction, b.p. 89-89.5° at 745 Torr (lit.[159] b.p. 88.5-90.5°, 728 Torr) was collected (87 g, 60%).

PMR spectrum: δ^{neat}_{Tms} 3.27 (d,2H,J=7Hz), 1.84 (m,1H) and 1.02 (d,6H,J=7Hz)

Preparation of Isobutyltriphenylphosphonium Bromide 185

A mixture of triphenylphosphine (25 g, 0.095 mol) and isobutyl bromide (14.3 g, 0.104 mol) in a sealed, heavy-walled, glass tube was heated in a wax bath at 110° (12 hr).* A white, crystalline precipitate 185 (31.4 g, 80%), m.p. 189-192°, (lit.[162] m.p. 196-197°) formed which was filtered and washed with benzene.

PMR spectrum[140]: $\delta^{CDCl_3}_{TMS}$ 7.76 (m,15H,phenyl), 3.72 (dd,2H,J=6.5Hz, 13.5Hz), 2.14 (m,1H), 1.08 (d,6H,J=6.5Hz)

Attempted Wittig Reaction of Acetone and Isobutyltriphenylphosphonium Bromide 185

A solution of "dimsyl" ion was prepared in the manner outlined in E.J. Corey's work[141] using NaH (0.43 g, 0.0[illegible]mol, 56.2% suspension) in dimethyl sulfoxide (55ml). When isobutyltriphenylphosphonium bromide 185 was added at 0° and shaken for 5-10 min, a red-amber suspension was formed. Acetone (1 ml, spec. grade, Fisher) was added

* If the sealed tube reaction is carried out at higher temperature (125-150°), a second phosphonium salt is formed which is probably t-butyltriphenylphosphonium bromide.
PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 1.70 (d,J=17.5Hz)

to the stirred suspension and the bright red colour faded rapidly to a dull amber-brown. The reaction mixture was warmed to room temperature (0.5 hr) and then poured into water (20 ml). Heat was released and a white precipitate formed.[142] The solid isobutyldiphenylphosphine oxide 186 (1.9 g, 75%), m.p. 136-138°, (lit.[143] m.p. 137.5-138) was filtered and washed with water and pentane.

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 8.0-7.3 (m, 10H, phenyl), 2.21 (dd, J=6.5Hz, 13Hz), 1.02 (d, 6H, J=6.5Hz)

The aqueous layer was extracted with pentane which was separated and dried ($MgSO_4$). Distillation of the pentane gave a liquid residue (900 mg) whose PMR spectrum (δ^{neat}_{TMS}) had an intense singlet at 7.28 (probably benzene), a very weak vinyl peak at 5.95 and a complexity of small, sharp peaks between 0.6 and 2.1. The high yield of isobutyldiphenylphosphine oxide 186 indicates that the phosphorane is not reacting with acetone or that it is only abstracting a proton.

The Wittig reaction outlined above was repeated except after addition of acetone the reaction mixture was maintained at 0° (1 hr) and then at room temperature (10 hr). When the reaction was quenched by pouring into water, isobutyldiphenylphosphine oxide 186 (70%), m.p. 138-139°, was formed.

The aqueous layer was extracted with pentane and the pentane layer dried ($MgSO_4$). Distillation of the pentane gave a residue whose PMR spectrum showed no vinyl peak but a sharp singlet due to benzene ($\delta^{CDCl_3}_{TMS}$ 7.35).

Attempted Wittig Reaction of Acetone and Phosphonium Bromide 185 in Ether

n-Butyllithium (25 mmol, 21.4 wt.% in hexane, Alfa Inorganics) was

added to a suspension of isobutyltriphenylphosphonium bromide 185 (10 g) in ether (300 ml) under N_2. The reaction mixture was stirred (2 hr) at room temperature during which time an orange-brown colour developed. Addition of an excess of acetone (spec. grade, Fisher) caused the colour to fade immediately to a light orange. The reaction was stirred (6 hr) at room temperature and then maintained at reflux (10 hr). The precipitate was removed by filtration and distillation of the ether left a residue whose PMR spectrum showed no vinyl peaks.

Wittig Reaction of Phosphonium Bromide 185 with Benzaldehyde

n-Butyllithium (6.5 ml) was added to a suspension of isobutyltriphenylphosphonium bromide 185 in ether (120 ml) under N_2. The reaction mixture was stirred (2 hr) at room temperature during which time an intense orange colour developed. Benzaldehyde (1.5 excess) in ether (5 ml) was added and, within a few minutes, the orange colour had faded. The reaction was stirred (10 hr) at room temperature and then filtered. The ether layer was washed with water (2x), saturated NaCl and dried ($MgSO_4$).

Evaporation of the ether gave a yellow liquid, a mixture of cis-trans double bond isomers of 1-phenyl-3-methylbut-1-ene, which was distilled bulb to bulb (70° at 6 Torr).[163]

GLPC (80°): 2 peaks (75:25)

PMR spectrum: $\delta^{\text{neat}}_{\text{TMS}}$ 7.2 (s, phenyl), 6.25 (m), 5.42 (dd), 2.85 (brd.m), 0.95 (d, J=6.5Hz, -Me)

Preparation of Hexahydrobenzyl Bromide

Cyclohexylcarbinol (15 g, 0.13 mol, Eastman) was treated with PBr_3 (11.8 g, 0.043 mol) as outlined on p. 151. The crude material was

distilled and the fraction (13.1 g, 60%), b.p. 89-90° (40 (lit.[160] b.p. 76-77° at 26 Torr) was collected.

GLPC (5% carbowax 4000, 100°): 1 peak

PMR spectrum: δ^{neat}_{TMS} 3.24 (d, $-CH_2Br$), 2.0-1.0 (brd.m, cyclohexyl)

Preparation of Hexahydrobenzyltriphenylphosphonium Bromide 187

A mixture of hexahydrobenzyl bromide (5.0 g, 28 mmol) and triphenylphosphine (7.4 g, 28 mmol) was heated at 125° in a sealed, glass tube (48 hr) as outlined on p. 152 . The product was a white solid 187 (8.8g, 70%) m.p. 230-233° (lit.[144] m.p. 225-228°).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 7.79 (brd.s, 15H, phenyl), 3.68 (dd,2H), 1.9-1.0 (brd.m,11H)

Attempted Wittig Reaction with Cyclohexanone and Phosphonium Bromide 187

This reaction was carried out following the procedure outlined for the Wittig reaction with benzaldehyde, p. 154 . Hexahydrobenzyltriphenylphosphonium bromide 187 (8.8 g, 20 mmol) and freshly distilled cyclohexanone (2.5 g, 25 mmol) were used.

The product was an oily residue whose PMR spectrum showed a broad multiplet indicative of allylic protons but essentially no vinylic adsorption.

Preparation of Isopropyltriphenylphosphonium Bromide 188

Isopropyl bromide (1.5 g, 12 mmol) and triphenylphosphine (3.2 g, 12 mmol) were heated together in a sealed, glass tube at 150° (19 hr) as outlined on p. 152 . The product was a white solid (4.2 g, 90%), m.p. 200-230° (dec) (lit.[145] m.p. 239-240°).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 8.2-7.6 (m, 15H, phenyl), 5.28 (m,1H)
1.38 (dd,6H,J=7Hz,19Hz)

Wittig Reaction of Isobutyraldehyde and Phosphonium Bromide 188

The ylide of isopropyltriphenylphosphonium bromide 188 (3.8 g, 10 mmol) was prepared by the same procedure as outlined on p. 152. Isobutyraldehyde (0.80 g, 11 mmol) was added at room temperature and then the reaction mixture was stirred overnight (10 hr). When the reaction was quenched by the addition of water an unidentified precipitate formed (3.4 g). The solid was filtered and recrystallized from $CHCl_3$-benzene, m.p. 249-254°.

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 8.0-7.5 (m, 15h, phenyl), 5.0 (m,1H)
2.86 (s,3H), 1.46 (dd,6H,J=7Hz,19Hz)

D_2O added: singlet (2.86 disappears)

The melting point and PMR spectrum suggest that the solid is the hydrated phosphonium salt but this point was not pursued.

The aqueous layer was extracted with pentane which was separated and dried ($MgSO_4$). Distillation of the solvent gave a liquid residue whose PMR spectrum (neat) showed only weak vinylic adsorption at 4.83 δ.

Preparation of Cyclohexyltriphenylphosphonium Bromide 189

Cyclohexyl bromide (2 g, Aldrich) and triphenylphosphine (3.2 g) in benzene (1 ml) were heated in a sealed, glass tube at 150° (19 hr).

The product is a white solid 189 (1.5 g, 30%), m.p. 250-255° (lit.[144] m.p. 255-259°).

Wittig Reaction of Cyclohexanecarboxaldehyde and Phosphonium Bromide 189

The deep red solution of cyclohexyltriphenylphosphorane was prepared by adding n-butyllithium (1.9 ml, 2.1M) to cyclohexyltriphenylphosphonium bromide 189 (1.5 g, 3.5 mmol) in DMSO (10 ml) under N_2. The reaction mixture was maintained at room temperature (10 min) and then cyclohexanecarboxaldehyde (0.33 g, 2.9 mmol, Aldrich) was added. The reaction was stirred at room temperature for 6 hr and then extracted with pentane. The pentane layer was washed with water and dried ($MgSO_4$).

Evaporation of the pentane gave an oil 190 (90 mg, 15%).

TLC: (EtOAc:PE36, 10:90): 1 spot (R_f=0.9)

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 4.85 (brd.d, vinyl), 2.2-1.8 (brd.m, allylic) 1.8-0.9 (brd.m, methylene)

The DMSO solution was poured into 5% aqueous HCl and extracted with ether. The ether was washed with water and dried ($MgSO_4$). Evaporation of the ether gave an oily solid (530 mg).

TLC: 4-5 spots (no spot at R_f=0.9 as found in the pentane layer, major spot is very polar and fluoresces under u.v.)

This oily solid was washed with pentane to yield a white powder (300 mg), m.p. 155-158° (sublimes ~145°), tentatively identified as a mixture of triphenylphosphine oxide and diphenylcyclohexylphosphine oxide.

Mass spectrum[161]: m/e 284 (P^+) 283 (P^+-1) 278 (P^+) 277 (P^+-1) almost equal intensity

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 8.0-7.2 (phenyl) and 2.1-1.2 (cyclohexyl)

Preparation of 2,4-Dimethylpentan-2-ol 191

A Grignard reagent was prepared by adding isobutyl bromide (14 g) to magnesium turnings (2.4 g) in dry ether (45 ml). When the reaction with magnesium subsided, acetone (6 g) in ether (10 ml) was added. After complete addition of acetone, the reaction was maintained at reflux (3.5 hr) and then poured into cold 10% aqueous HCl (70 ml). The ether layer was separated and dried ($MgSO_4$).

Evaporation of the ether by Rotavap left a liquid (6 g) which on distillation gave a fraction 191 (3 g), b.p. 130-131° at 760 Torr (lit.[146] b.p. 130-132° at 760 Torr).

IR spectrum: $\nu_{max}^{CHCl_3}$ 3600, 3450 (-OH) and 2955, 2870 (C-H)

PMR spectrum: δ_{TMS}^{neat} 3.72 (s,-OH), 2.1-1.6 (brd.m), 1.22 (s,-Me), 0.96 (d, isopropyl)

Dehydration of 2,4-Dimethypentan-2-ol 191

A mixture of pentanol 191 (3 g) and iodine (20 mg) was distilled on a steam bath through a 10 cm Vigreux column. The distillate (2 g, 80%) was a colourless liquid, primarily 192, (lit.[146] b.p. 83-84° at 760 Torr) which was dried in CH_2Cl_2 ($MgSO_4$).

PMR spectrum: δ_{TMS}^{neat} 4.95 (brd.d), 4.68 (m), vinyl protons

Epoxidation of 2,4-Dimethylpent-2-ene 192

The crude distillate from above was stirred in CH_2Cl_2 (80 ml) with a suspension of m-chloroperbenzoic acid (4.5 g, Aldrich) at 25° for 24 hr. The solid was removed by filtration and the solvent layer washed with 5% NaOH and dried ($MgSO_4$).

Evaporation of the solvent gave a liquid residue which was distilled

bulb to bulb at atmospheric pressure, (lit.[146] b.p. 110-110.5° at 760 Torr).

GLPC (5% Carbowax 4000, 70°): 2 peaks (less polar is major)

IR spectrum: $\nu_{max}^{CCl_4}$ 3040 (C-H of terminal epoxide), 2960, 2870 (C-H), 1265, 1120, 900 (epoxide C-O)

PMR spectrum: δ_{TMS}^{neat} 2.45 (s), 2.28 (d), no vinyl protons

The mixture of epoxides was separated by preparative GLPC (10% carbowax 6000, 80°) and the individual compounds were collected at -80°.

The major, less polar compound 262 was a liquid.

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 2.36 (d,1H,J=8.5Hz), 1.55 (m,1H), 1.29 (d,6Hz), 1.0 (dd,6H, isopropyl, J=6.5Hz)

The minor, more polar compound 263 was a liquid.

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 2.59 (s,2H), 1.75 (m,3H), 1.3 (s,3H), 0.93 (dd,6H, isopropyl, J=6.5Hz)

Preparation of 2-Chlorodiisopropyl Ketone 176 from Epoxide 262

Acetonitrile (7 mol) was saturated with HCl gas (Matheson) at -78°. Epoxide 262 (1 g) in acetonitrile (2 ml) was added dropwise to this solution and then the reaction mixture was maintained at -78° for 1.5 hr. The reaction was warmed to room temperature and poured into pentane (50 ml) containing anhydrous Na_2CO_3. The pentane was washed with water and dried ($MgSO_4$).

Evaporation of the pentane afforded a colourless liquid (600 mg).

GLPC (80°): 2 peaks (epoxide 262 and a major product)

The crude liquid in acetone (6 mol) was treated with Jones reagent

until the brown colour was constant. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$).

Evaporation of the ether gave a slightly yellow liquid, primarily 176 (400 mg) by comparison with an authentic sample.

GLPC (80°): 4 peaks (major peak matches 2-chlorodiisopropyl ketone 176)

PMR spectrum: $\delta^{neat.}_{TMS}$ 3.41 (m), 1.66 (s), 1.1 (d, J=6.5Hz)
(compare with PMR spectrum, p. 136)

Preparation of 2-Chloro-cyclohexylacetonitrile 197

When cyclohexanecarboxaldehyde (11.2 g, 0.10 mol) was stirred into a solution of $NaHSO_3$ (11 g) in water (35 ml) a thick white paste formed rapidly. The solid was cooled to 25°, broken up and vigorously shaken with a solution of KCN (14 g) in water (50 ml). An oil separated which was extracted with ether. The ether layer was washed with water and dried ($MgSO_4$).

Evaporation of the ether gave the cyanohydrin 196 as a murky oil (12.3 g, 90%).[147]

GLPC (120°): 1 peak

TLC (EtOAc-PE36,15:88): 1 spot (no aldehyde)

IR spectrum: $\nu^{CHCl_3}_{max}$ 3635, 3470 (OH), 2270 (C≡N), no C=O

A portion of the cyclohexanecarboxaldehyde cyanohydrin 196 (1.4 g, 0.010 mol) and triphenylphosphine (2.6 g, 0.010 mol) were dissolved in CCl_4 (20 ml). The solution was maintained at reflux for 2.5 hr during which time a small amount of white precipitate formed.[148]

Evaporation of the solvent by Rotavap afforded an oily solid which

was stirred with cold ether. The white solid triphenylphosphine oxide (2.3 g, 83%) was removed by filtration and then evaporation of the ether gave an oil (1.7 g). Bulb to bulb distillation of the crude oil gave a colourless liquid 197 b.p. 54-55° at 0.6 Torr (lit.[166] b.p. 102-104° at 8 Torr).

IR spectrum: $\nu_{max}^{CCl_4}$ 2935, 2860 (C-H), no OH, no C=O

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 4.35 (brd.d)

Base Condensation of Cyclohexanone with 2-Chloro-cyclohexyl-acetonitrile 197

A solution of potassium t-butoxide (0.12 g potassium, 0.0020 g atom) in t-butanol (3.5 ml) was added dropwise to a stirred solution of cyclohexanone (0.32 g, 3 mmol) and 2-chloro-cyclohexylacetonitrile 197 (0.51 g, 3.0 mmol) in t-butanol (1 ml) at 25°.[100] After complete addition of base, the reaction was maintained at 25° for 12 hr. The reaction mixture was poured into water and extracted with pentane. The pentane was washed with water and dried ($MgSO_4$).

Evaporation of the solvent afforded a colourless oil (585 mg) which partially solidified on standing.

TLC (EtOAc-PE36, 15:85): 4 spots (major spot coincides with epoxynitrile 179, p. 137)

IR spectrum: $\nu_{max}^{CHCl_3}$ 2240 (C≡N) (spectrum coincides with that of epoxynitrile 179, p. 145, plus N-H and C=O peaks indicative of amide 180, p. 145)

This reaction was repeated on a larger scale using a slight excess of potassium t-butoxide. The crude product was developed on column chromatography (silica gel) with EtOAc-PE68 (5:95) to yield pure liquid

epoxynitrile 179 in 85% yield, identical with a sample from p. 137.

Reaction of Epoxynitrile 179 with HCl/Ether

The procedure outlined here is that used successfully by Stork et al.[100]. A solution of epoxynitrile 179 (0.5 g) in anhydrous ether (8 ml) was cooled to 0° and then flushed with HCl gas (Matheson) for 15 min. The ether was evaporated and the residue dissolved in pentane (20 ml). The pentane solution was vigorously shaken with 5% aqueous KOH solution (20 ml) for 1-2 min and then separated. The pentane layer was washed with water and dried ($MgSO_4$).

Evaporation of the pentane gave a yellow oil (330 mg) which partially solidified on standing.

TLC (EtOAc-PE36, 10:90): 2 spots (major product 178 flouresces under u.v. light, minor amount of chloroketone 167)

IR spectrum: $\nu_{max}^{CHCl_3}$ 2935, 2855 (C-H); 1655 (C=O), 1635 (C=C)

The solid was recrystallized from ether-PE68 to afford white needles, m.p. 127-133°, which were not examined further.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3510, 3400 (N-H); 1685 (C=O), 1572

Reaction of Epoxynitrile 179 with Various Epoxide Ring Opening Reagents

See Table V.

Attempted Acid Catalysed Hydrolysis of Glycidamide 180

A solution of glycidamide 180 (100 mg) in dioxane (1.5 ml) and 5% aqueous HCl (3 ml) was maintained at reflux for 3 hr. The reaction mixture was cooled to room temperature and extracted with ether. The

TABLE V

Attempted Ring Opening of Epoxynitrile 179

179	Reagent	Conditions		Result
500 mg	375 mg $ZnCl_2$ 7 ml ether saturated with HCl gas --- 10 ml 5% aqueous KOH	24 hr — 2 min	25° 25°	TLC: 2 spots (major spot 178)
200 mg	5 ml ether, saturated with HCl gas --- 10 ml 5% aqueous KOH	15 min 2 min8	-70° 25°	160 mg oil TLC: 1 spot (epoxynitrile 179)
250 mg	5 ml ether saturated with HCl gas --- 10 ml 5% aqueous KOH	1,2 hr	-55°	200 mg oil TLC: 2 spots (major spot 178) IR: $\nu_{max}^{CHCl_3}$ 1655 (C=O), 1635 (C=C) PMR: $\delta_{TMS}^{CDCl_3}$ 6.86 (m, vinyl) 2.98 (m) 2.35-2.05 (m, allylic) 1.95-1.05 (m, $-CH_2-$) GLPC (150°): 3 peaks (1 major, 2 minor)
300 mg	6 ml CH_3CN saturated with HCl gas	10 min	0°	320 mg orange-brown oil TLC: 3 spots IR: $\nu_{max}^{CHCl_3}$ 2210 (s, C≡N) 1655 (weak C=O)

TABLE V (Cont'd)

179	Reagent	Conditions		Result
200 mg	4 ml CH_3CN saturated with HCl gas --- 5 ml 10% K_2CO_3 solution	45 min 2 min	-40° 25°	130 mg yellow oil IR: $\nu_{max}^{CHCl_3}$ 2210 (s, C≡N) TLC: 2 spots (epoxynitrile 179 and enone 178)
250 mg	2 ml CH_3CN saturated with $Et_4N^+Cl^-$	2.5 hr	25°	TLC: 1 spot (epoxynitrile 179)
250 mg	2 ml CH_3CN saturated with $Et_4N^+Cl^-$	16 hr/	reflux	147 mg brown oil TLC: 2 spots (no chloroketone 167), epoxynitrile 179 and cyanohydrin of enone 178) IR: $\nu_{max}^{CHCl_3}$ 3570 (O-H) 2235, 2215 (C≡N) no C=O PMR: $\delta_{TMS}^{CDCl_3}$ 6.1 (m, vinyl) 2.86 (brd.s, OH, disappears with D_2O addition)
500 mg	10 ml CH_3CN saturated with HCl gas and $Et_4N^+Cl^-$ --- 400 mg NaOH 5 ml EtOH 2 ml H_2O	3 hr 15 min	-60° 25°	425 mg pale yellow oil TLC: 2 spots (no chloroketone 167 epoxynitrile 179 and cyanohydrin of enone 178) IR: $\nu_{max}^{CHCl_3}$ 3575 (O-H) 2235, 2215 (C≡N) 310 mg liquid TLC: 2 spots (enone 178 and a trace

TABLE V (Cont'd)

179	Reagent	Conditions		Result
				of epoxynitrile 179)
				IR: $\nu_{max}^{CHCl_3}$ 1655 (C=O)
				1635 (C=C)
	10 ml $CHCl_3$	18 hr	25°	
1.0 g	saturated with HCl gas[149]			
	10 ml 5% aqueous KOH	2 min	25°	GLPC (160°): 2 peaks (enone 178: epoxynitrile 179, 1:2)
				PMR: $\delta_{TMS}^{CHCl_3}$ 6,86 (m, vinyl)
	5 ml CCl_4	20 hr	25°	
500 mg	saturated with HCl gas			
	10 ml 5% aqueous KOH	2 min	25°	0.5 g oil GLPC (160°): 2 peaks (enone 178 and epoxynitrile 179)
	5 ml HOAc	1.5 hr	25°	
500 mg	saturated with HCl gas			460 mg oil
	10 ml 5% aqueous KOH	2 min	25°	GLPC (160°): 5 peaks (major peak, enone 178)
				IR: $\nu_{max}^{CCl_4}$ 1655 (C=O)
				1635 (C=C)
				PMR: $\delta_{TMS}^{CCl_4}$ 6.9 (m, vinyl

TABLE V (Cont'd)

179	Reagent	Conditions		Result
500 mg	5 ml HOAc saturated with $Et_4N^+Cl^-$	20 hr	85°	400 mg oil; distilled bulb to bulb, 85-90° at 0.1 Torr (lit.[94] b.p. 152-153° at 14 Torr) GLPC (160°): 1 peak (enone 178) IR: $\nu_{max}^{CCl_4}$ 1660 (C=O) 1635 (C=C) PMR: $\delta_{TMS}^{CDCl_3}$ 6.9 (m,1H), 3.0 (m,1H), 2.22 (m,4H), 2.0-1.2 (m,14H) (Fig. 2, p.) UV: λ_{max}^{EtOH} 235 nm (ϵ =8,000)

ether layer was washed and dried ($MgSO_4$).

Evaporation of the ether afforded a yellowish liquid (112 mg).

TLC (EtOAc - pentane, 20:80): 2 spots (perhaps amide plus a more polar spot)

IR spectrum: $\nu_{max}^{CHCl_3}$ 3500, 3400 (N-H); 1737 (C=O), 1665 (C=C)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 5,8 (m), 4.5 (dd, J=11Hz), no low field -COOH proton. D_2O added, no change.

Since there was no evidence of simple hydrolysis, this experiment was not pursued.

Attempted Diazotization of Glycidamide 180 With Aqueous HOAc-$NaNO_2$ Solution

A suspension of glycidamide 180 (500 mg) in acetic acid (5 ml) and 20% aqueous $NaNO_2$ solution (5 ml) was stirred at room temperature (13 hr) in a stoppered flask. The mixture was poured into water and extracted with ether. The ether layer was washed with water, $NaHCO_3$ solution and then dried ($MgSO_4$). The HCO_3^- solution was acidified (pH2) but no precipitate formed.

Evaporation of the ether gave a white solid (350 mg), m.p. 153-155°. TLC and ir spectrum ($CHCl_3$) indicated that this was recovered glycidamide 180.

Attempted Diazotization of Glycidamide 180 with 55% Aqueous HOAc-$NaNO_2$ Solution

Sodium nitrite (1.3 g) was added in parts to a stirred solution of glycidamide 180 (100 mg) in acetic acid (3 ml) and water (1 ml). Brown fumes evolved when the flask was unstoppered. The solution was stirred

at room temperature for 5 hr and then poured into water and extracted with ether. The ether was washed with water and dried ($MgSO_4$).

Evaporation of the ether gave a yellow oil (85 mg) which crystallized on standing, m.p. 154-156°. The solid was insoluble in 5% aqueous KOH and consisted only of recovered glycidamide 180.

Attempted Reaction of Glycidamide 180 with $NaNO_2$/HOAc

Sodium nitrite (1 g) was added quickly with stirring to a solution of glycidamide 180 (200 mg) in acetic acid (10 ml). The reaction was stirred until brown fumes ceased to evolve (15 min) and then the mixture was poured into water and extracted with ether. The ether layer was washed with water, 5% aqueous KOH and dried ($MgSO_4$).

Evaporation of the ether gave a white solid (130 mg). Both the TLC and ir spectrum indicated only recovered glycidamide 180.

Reaction of Glycidamide 180 with NOCl[104]

(a) in $CHCl_3$

Nitrosyl chloride (Matheson) was bubbled through a solution of glycidamide 180 (120 mg) in chloroform (1.5 ml) for 1 min at room temperature. The solution rapidly turned brown.

The reaction was maintained at 25° for 30 min and then the solvent was evaporated. The residue was a bright green oil (160 mg) which was insoluble in 5% aqueous KOH.

TLC (EtOAc - pentane, 20:80): 4 spots (trace of glycidamide 180 with major spot, R_f=0.6 which fluoresces under u.v. light)

(b) in MeOH

Nitrosyl chloride was bubbled through a solution of glycidamide 180 (500 mg) in methanol (10 ml) containing triethylamine (1 ml) for 1.5 hr at 25°. The reaction was maintained at room temperature for 6 hr and then poured into water. The aqueous mixture was extracted with ether. The ether layer was washed and dried ($MgSO_4$).

Evaporation of the ether gave a pale green oil (312 mg).

TLC (EtOAc - pentane, 20:80): 8 spots (major spot is non-polar, R_f=0.8)

IR spectrum: $\nu_{max}^{CCl_4}$ 2935, 2855 (C-H) and 1710 (C=O)

The crude product was chromatographed on a column of silica gel (12 g) with EtOAc-PE68, 5:95. The fractions (5 ml) were checked by TLC and two of the early fractions were combined to give a colourless oil (120 [redacted]

TLC (EtOAc-PE68, 5:95): 4 spots (1 major spot, R_f=0.6)

IR spectrum: $\nu_{max}^{CCl_4}$ 2935, 2855 (C-H) and 1710 (C=O)

PMR spectrum: $\delta_{TMS}^{CCl_4}$ 4.9, 4.75, 4.55 (m); 4.3-3.8 (m), 2.5-1.0 (m, $-CH_2-$)

Both the TLC and ir spectrum were consistent with those of 2-chlorodicyclohexyl ketone 167 but the PMR spectrum (see p. 134) was vastly different. It is possible that the lower field peaks are impurities, but this possibility was not pursued.

(c) in EtOH

Nitrosyl chloride was bubbled (1.25 hr) through a solution of glycidamide 180 (530 mg) in ethanol (10 ml) containing triethylamine (1 ml) at 0°. The reaction was maintained at ice temperature for 4 hr

and then worked up as in previous experiment.

Evaporation of the ether afforded an orange oil (625 mg).

TLC (EtOAc-pentane, 5:95): 10 spots (some glycidamide 180 unreacted)

Since hydrolysis could not be attained, the experiments with NOCl were discontinued.

Attempted Hofmann Degradation of Glycidamide 180

In a modification of the procedure used by Stevens et al.[105] chlorine was bubbled (5 min) through an ice cold solution of NaOH (50 mg) in water (1.2 ml). After addition of powdered glycidamide 180 (150 mg), the suspension was warmed to room temperature and stirred for 48 hr. The reaction mixture was then extracted with ether.

Evaporation of the ether extract gave a colourless syrup (55 mg) whose TLC (EtOAc-pentane, 10.90) showed starting material 180 plus a single, minor, less polar spot which was not chloroketone 167.

The reaction was repeated on a larger scale using one gram of glycidamide 180. Even after stirring for 110 hr, the ir spectrum of the recovered material (0.8 g) showed predominantly starting material 180.

Reaction of Glycidamide 180 with Br_2 in MeO⁻/MeOH

Glycidamide 180 (500 mg, 2.1 mmol) was dissolved in an ice cold solution of NaOMe (250 mg Na, 11 g atom) in methanol (9 ml). Bromine (350 [redacted] 2.2 mmol) was added dropwise to this stirred solution and was immediately decolorized. After complete addition of bromine, the solution was warmed to room temperature and stirred for 11 hr. The

solution was then poured into water which was extracted with ether.

Evaporation of the ether gave a viscous syrup (500 mg) which crystallized on standing.

TLC (EtOAc-PE68, 30:70): 3 spots (major is starting material 180 . no bromoketone 167b)

IR spectrum: $\nu_{max}^{CHCl_3}$ 3515, 3398 (N-H); 2930, 2855 (C-H); 1756, 1680 (C=O); 1568

In CCl_4 the C=O (1756) shifts to 1785 cm^{-1}.

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 6.32 (brd.m,N-H), 3.5 (s,-OMe), 2.1-1.1 (m,$-CH_2-$)

A portion of the crude (250 mg) was chromatographed on thick layer plates (SiO_2) with EtOAc-PE68, 30:70. Besides starting material 180 (150 mg), a second solid (50 mg) was isolated, m.p. 172-174°. This material does not decolorize $Br_2/CHCl_3$ nor does it form a 2,4 DNP derivative.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3425, 3260 (N-H, O-H); 2940, 2860 (C-H); 1720, 1712 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 7.1 (brd.m,N-H and OH), 2.0-1.4 (m,$-CH_2-$)

Mass spectrum (M-66): m/e (no P^+) 223, 207, 195, 99 (100%), 98

NIH { CI: m/e 252 (P^+-1?), 208
EI: m/e 252, 223, 209, 195, 184, 179, 110, 99 (100%), 98

Anal. Calc'd. for $C_{14}H_{23}NO_3$(253): C, 66.4; H, 9.1; O, 18.96; N, 5.54

Found: C, 66.04; H, 7.85; O, [illegible]8; N, 5.74

Changing the concentration of any of the reactants did not improve the yield nor did the presence or absence of O_2 and raising the temperature

actually reduced it. On occasion, the reaction was irreproducible, and after it was observed (p. 177) that α-hydroxyketone 201 could not be converted to α-chloroketone 167, this route was not investigated further. The isolated solid was tentatively assigned the structure 200.

When t-BuO⁻/t-butanol was used in the Hofmann degradation, α-hydroxyketone 201 (15%) was isolated after chromatography on thick layer plates (SiO_2). The structure was proved by exact comparison of its ir spectrum with that of α-hydroxyketone 201 (p. 176).

Preparation of 2-Hydroxycyclohexylacetic Acid 264

Freshly prepared cyclohexanecarboxaldehyde cyanohydrin 196 (12 g) p. 160 , was stirred vigorously in refluxing 50% aqueous HCl (40 ml) for 6 hr. The reaction mixture was cooled to 25° and extracted with ether. The ether was extracted with 10% aqueous NaOH solution and then the basic aqueous layer was acidified (pH2) with concentrated HCl. A white solid was precipitated. The resulting precipitate was removed by extracting with ether. The ether layer was washed and dried ($MgSO_4$).

Evaporation of the solvent gave a white solid 264 (12.5 g, 90%), m.p. 135.5-137.0° (lit.[150] m.p. 135°).

Mass spectrum: m/e 113 (P^+-CO_2), 95, 83, 76 (McLafferty, 100%)
no parent ion

Esterification of 2-Hydroxycyclohexylacetic Acid 264

A portion of the crude acid 264 (6.5 g) was dissolved in a mixture of methanol (30 ml) and benzene (70 ml) which contained concentrated H_2SO_4 (2 ml). The solution was maintained at reflux for 17 hr and then cooled to room temperature. An excess of anhydrous K_2CO_3 was added and

then the bulk of the solvent was distilled off. The residue was taken up in ether which, in turn, was washed and dried ($MgSO_4$).

Evaporation of the solvent gave a pale yellow liquid 265 (5.9 g, 84%).

TLC (EtOAc-pentane, 10:90): 1 spot

IR spectrum: $\nu_{max}^{CHCl_3}$ 3540 (O-H), 2935, 2855 (C-H), 1730 (C=O)

PMR spectrum: δ_{TMS}^{neat} 3.67 (s, $-OCH_3$), 3.52 (d, J=7Hz), 1.9-1.0 (brd.m, $-CH_2-$).

Preparation of Methyl 2-Chlorocyclohexylacetate 202

The crude ester 265 (5.9 g, 34 mmol) and triphenylphosphine (9.0 g, 34 mmol) were dissolved in carbon tetrachloride (73 ml, spectral grade, Fisher). The solution was maintained at reflux for 25 hr, during which time a white precipitate formed. The solvent was removed by Rotavap and then the oily solid was stirred with cold pentane. The pentane suspension was filtered to remove the precipitated triphenylphosphine oxide (9.5 g, 100%); m.p. 150-153° (lit.[143] m.p. 156°).

Evaporation of the pentane gave a yellow oil (5.9 g, 90%). The crude oil was distilled under vacuum to afford a colourless liquid 202 (4.4 g), b.p. 67-68.5° at 0.7 Torr.

GLPC (110°): 1 peak

TLC (EtOAc-pentane, 10:90): 2 spots (major ester 202 and minor ester 265)

IR spectrum: $\nu_{max}^{CHCl_3}$ 3540 (weak O-H) and 1740 (C=O)

PMR spectrum: δ_{TMS}^{neat} 4.07 (d, J=7Hz), 3.71 (s, $-OCH_3$), 2.1-1.1 (brd.m, $-CH_2-$).

Mass spectrum: m/e 155 (P^+-Cl), 133, 131 (P^+-CO_2CH_3), 110, 108 (McLafferty, 100%), no parent ion

Attempted Darzen's Condensation of Cyclohexanone and Ester 202

A solution of potassium t-butoxide (0.72 g potassium, 0.18 g atom) in t-butanol (20 ml) was added dropwise (1 hr) to a stirred mixture of cyclohexanone (1.55 g, 16 mmol) and chloroester 202 (3.5 g, 18 mmol) in t-butanol (2 ml) at 0°. After complete addition of base, the reaction mixture was warmed to room temperature and stirred for 60 hr. Then, the mixture was poured into water (100 ml) and extracted with pentane. The pentane layer was washed and dried ($MgSO_4$).

Evaporation of the solvent gave a yellow liquid (2.8 g).

TLC (EtOAc-pentane, 10:90): 3 spots

The crude liquid was chromatographed on a column of silica gel (90 g) with EtOAc-pentane (5:95). The first few fractions (920 mg) gave a mixture of esters, probably 202 and its t-butyl analog.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1735 (C=O) no -OH

PMR spectrum: δ_{TMS}^{neat} 4.1 (d, J=7Hz), 3.88 (d, J=7Hz), 3.7 (s, $-OCH_3$), 1.47 (s, t-butyl)

These were soon followed by fractions containing the major compound (700 mg) tentatively assigned the structure 204.[167]

IR spectrum: $\nu_{max}^{CHCl_3}$ 1705 (C=O), no -OH

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 5.41 (m, vinyl), 1.48 (s, t-butyl)

There was no evidence of any Darzen's product 203.

Reaction of Triphenylphosphine and Methyl 2-Chlorocyclohexylacetate 202

A solution of chloroester 202 (500 mg, 2.6 mmol) and triphenylphosphine (870 mg, 3.3 mmol) in benzene (5 ml) was heated in a sealed glass tube at 150° for 24 hr. The reaction mixture was cooled to room temperature and filtered to remove the white solid 207 (565 mg, 70%), m.p. 222-223° (lit.[143] m.p. 212-213°), which had formed during heating.

IR spectrum: $\nu_{max}^{CHCl_3}$ no C=O

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 7.8 (m,15H, phenyl), 3.31 (d,3H,J=14Hz)

The TLC (EtOAc-PE36, 5:95) of the filtered benzene solution showed 8-10 spots. Although one of these appeared to be major, the material was not examined further.

A portion of the white solid 207 (20 mg) was dissolved in water and mixed with 2-3 drops of aqueous 5% $AgNO_3$ solution. A white precipitate formed immediately (AgCl).

A second portion of the solid 207 (100 mg) was dissolved in water (1 ml) and mixed with a solution of NaOH (0.5 g) in water (2 ml). The white precipitate, which formed immediately, was extracted with ether. ether layer was washed and dried ($MgSO_4$).

Evaporation of the solvent gave a white solid, methyl diphenylphosphine oxide, (56 mg, 83%), m.p. 112-114° (lit.[143] m.p. 111-112°).

IR spectrum: $\nu_{max}^{CHCl_3}$ no C=O

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 7.83, 7.55 (m,10H, phenyl);
1.98 (d,3H,J=13Hz)

Preparation of Ethyl 2-Chlorocyclohexylacetate 266

The ester was prepared as outlined on p. 172 except absolute ethanol was used in place of methanol during the esterification of 2-hydroxycyclohexylacetic acid 264. The crude chloroester 266 was distilled under vacuum and the fraction, b.p. 79-80.5° (1.3 Torr), was collected.

Mass spectrum: 169 (P^+-Cl), 124, 122 (McLafferty, 100%); no parent ion

Reaction of Triphenylphosphine with Ethyl 2-Chlorocyclohexylacetate 266

The reaction was carried out as outlined on p. 152 but, even after heating for 46 hr, no precipitate was observed.

The reaction was repeated using double the concentration of triphenylphosphine but, again, after 45 hr, no precipitate was observed.

Preparation of α-Hydroxydicyclohexyl Ketone 201

Chloroketone 167 (6.0 g) was stirred vigorously in a refluxing solution of NaOH (3.5 g) in H_2O-ethanol, 4:1 (50 ml) for 36 hr. The neutral products were isolated by ether extraction of the aqueous suspension.

Evaporation of the ether gave a yellow oil (3.5 g, 64%) which was chromatographed on a column of SiO_2 with EtOAc-PE68, 5:95. The fractions were checked on TLC and, when the same, were combined to yield a slightly oily, crystalline solid 201 (2.5 g), m.p. 30-39° (lit.[151] m.p. 37-37.5°). The material proved difficult to re-crystallize and was used as isolated.

TLC (EtOAc-PE68, 20:80): 1 spot

GLPC (150°, 5% DEGS): 1 peak

IR spectrum: $\nu_{max}^{CHCl_3}$ 3460 (O-H), 2925, 2855 (C-H), 1692 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 3.8 (brd.s, O-H), 2.9 (brd.m, H)

2.0-1.0 (m, $-CH_2-$)

Attempted Conversion of Hydroxyketone 201 to Chloroketone 167

A solution of hydroxyketone 201 (100 mg) and $SOCl_2$ (100 mg) in DME (2 ml) was refluxed for 20 hr. Aliquots checked on TLC after 1 hr and after 3 hr showed starting material 201 plus a less polar spot. The reaction was worked up by pouring into water and extracting with ether.

Evaporation of the ether gave a yellow oil (80 mg). Examination of the oil by TLC (EtOAc-PE68, 5:95) and PMR spectroscopy showed a mixture of hydroxyketone 201 and enone 178 but no chloroketone 167.

TABLE VI

Attempted Conversion of Hydroxyketone 201 to Chloroketone 167

Substrate 201	Reactants	Results
94 mg	HCl gas (15 min)[149] $CHCl_3$ (2 ml) r.t. 48 hr	TLC (EtOAc-PE68, 10:90) 1 spot 201
110 mg	$SOCl_2$ (200 mg) reflux 5 min	TLC: 3 spots (201, 178 and minor)
100 mg	triphenylphosphine (125 mg) CCl_4 (1.5 ml) reflux 4 hr	TLC: 2 spots (201 and 178)

Preparation of 4-Hydroxycyclohexanone 208

The procedure was that used by Fetizon et al.[108] A suspension of celite-Ag_2CO_3 (64 g) and 1,4-cyclohexanediol (3.25 g, Aldrich) in benzene (550 ml) was maintained at reflux (15 hr). The suspension was cooled to 25° and filtered. The excess solvent (500 ml) was removed by distillation and the remainder, upon standing at 25°, deposited white crystals (0.5 g) of 1,4-cyclohexanediol, m.p. 96-100°. After the crystals were filtered off, the remaining solvent was removed by Rotavap.

The crude oil (2.5 g) was purified by column chromatography (silica gel, 130 g) using $CHCl_3$-ether, 98:2 as elutant. Evaporation of the solvent gave a colourless liquid 208 (1.5 g, 60%).

IR spectrum[108]: $\nu_{max}^{CHCl_3}$ 3620, 3400 (-OH) and 1720 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 4.15 (m,1H), 3.91 (s,1H-OH), 2.9-1.9 (m,8H,$-CH_2-$)

Preparation of 4-Hydroxycyclohexanone Thioketal 209b

Freshly distilled BF_3 etherate (1 ml) was added to a solution of 4-hydroxycyclohexanone 208 (0.5 g) and 1,2-ethanedithiol (1 ml) in acetic acid (8 ml). The reaction was stirred at 25° (12 hr) and then poured into water and extracted with chloroform. The chloroform was washed with 5% KOH and dried ($MgSO_4$).

Evaporation of solvent gave a foul smelling oil (0.7 g).

TLC (EtOAc-PE36, 25): 2 spots (no ketone 208)

The crude oil was chromatographed on a column (SiO_2) with EtOAc-PE36, 10:90. The excess 1,2-ethanedithiol was eluted first followed by a colourless oil 209a (0.5 g).

IR spectrum: $\nu_{max}^{CHCl_3}$ 2950 (C-H), 1728 (C=O), no OH

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 4.8 (m), 3.27 (s, $-SCH_2-$), 2.0 (s, -OAc), 2.2-1.6 (m, $-CH_2-$)

Continued elution of the column with a steadily increasing concentration of EtOAc gave a white solid 209b (0.1 g), m.p. 83-86°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3600, 3440 (-OH), no C=O

Mass spectrum: m/e 190 (P^+) 132, 131 (P^+-58,59)

Precise Mass Determination Calc'd: 190.04858

Found: 190.04600

Hydrolysis of 4-Acetoxycyclohexanone Thioketal 209a

The acetoxythioketal 209a (130 mg) was dissolved in a solution of NaOH (100 mg) in ethanol -H_2O, 4:1 (5 ml). The solution was maintained between 50-60° for 1 hr and then the ethanol was evaporated. After water was added to the residue, the suspension was extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$), filtered and evaporated.

The residue 209b (110 mg) was a pale yellow solid whose TLC and ir spectrum corresponded to those of the more polar 4-hydroxycyclohexanone thioketal from the column.

Preparation of Deuterated Ra-Ni

Ni-Al alloy (30 g) was added slowly (1 hr) to a warm (70-80°) solution of NaOD (22.5 g sodium) in D_2O (150 ml). The suspension was cooled to room temperature and then the liquid was decanted. The metal precipitate was washed with D_2O (15 ml, 3x) and then with ethanol-O-d_1.

Preparation of Cyclohexanone-4,4-d_2

The Ra-Ni prepared above was vigorously stirred in a refluxing solution of acetoxythioketal 209a (3 g) in ethanol-O-d_1 (150 ml) for 1.5 hr. An aliquot checked by TLC showed the reaction was complete. The suspension was filtered and the excess ethanol was removed by distillation through a Vigreux column. The residue was mixed with NaCl solution and extracted with ether. The ether layer was dried ($MgSO_4$) and filtered.

Distillation of the ether left a residue which was dissolved in acetone (30 ml). Jones reagent was added until the orange colour persisted at room temperature; then, the excess acetone was distilled off. The residue was mixed with NaCl solution and extracted with ether (3x). The combined ether layers were dried ($MgSO_4$) and filtered.

Distillation of the ether gave a light brown liquid (1.2 g). The remaining ether was not removed by Rotavap since losses of cyclohexanone would have been incurred.

Preparation of Deuterated Epoxynitrile 179(d)

The reaction procedure is outlined on p. 161 except that with the crude cyclohexanone-4,4-d_2 from above a 5% mole excess of chloronitrile 197 and a 10% mole excess of t-butoxide were used. An aliquot checked on TLC showed the reaction was complete within 19 hr. The reaction mixture was poured into water (50 ml) and extracted with pentane. The pentane layer was separated and dried ($MgSO_4$).

Evaporation of the pentane gave an amber oil (2.55 g) with a strong odour of chloronitrile 197. This crude oil was chromatographed on a column (SiO_2) to remove chloronitrile 197 but the recovered epoxynitrile

179(d) (2.1 g) still contained this contaminant (GLC,~10%).

Preparation of Deuterated Unsaturated Ketone 178(d)

The crude epoxynitrile 179(d) (2.1 g) was dissolved in CH_3CN (20 ml) which was saturated with $Et_4N^+Cl^-$ (10 g, Baker). The solution was refluxed for 18 hr after which GLC showed only a trace of starting material 179(d) and TLC showed a single, major spot 178(d). The solution was refluxed for 4 hr more and then poured into 5% KOH (60 ml). The aqueous mixture was extracted with pentane (2x) which was separated and dried ($MgSO_4$).

Evaporation of the pentane gave a yellow oil, 1-cyclohexenyl cyclohexyl ketone-4,4-d_2, 178(d), (2.0 g).

Preparation of Chlorodicyclohexyl Ketone-4,4-d_2 167(d) via Li/NH_3 Reduction of Unsaturated Ketone 178(d)

Lithium metal (100 mg, 14.3 g. atom) was dissolved in liquid NH_3 (40 ml, redistilled from potassium metal + cat. $FeCl_3$) at -78°. A portion of the crude unsaturated ketone 178(d) (1.0 g, 5.2 mmol) in ether (5 ml) was added to the deep blue solution with stirring. After 1.5 hr, the blue colour had faded. The ammonia was distilled off and a portion of ether (20 ml) was added. The grey slurry was added to a stirred solution of acetic anhydride (2.5 g, 25 mmol) in ether (20 ml) at 0°.

Evaporation of the ether left a residue which was taken up in cold, dry formic acid (2 ml). This solution was added dropwise to an ice-cold solution of Cl_2 (5% excess determined by addition of an aliquot to fresh KI solution and back titration with 0.1N $Na_2S_2O_3$) in formic acid (5 ml). After stirring for 0.5 hr, the reaction was

poured into water and extracted with ether. The ether layer was separated, washed to neutrality with $KHCO_3$ solution and dried ($MgSO_4$).

Evaporation of the ether gave a crude oil (1.06 g) with a slight ester-like smell.

TLC (EtOAc-Hex, 10:90): 3 spots (chloroketone 167(d), ketone 210(d) and an unidentified more polar spot)

GLPC (150°, 5% DEGS): 2 major peaks (chloroketone 167(d): ketone 210(d), 45:55)

The crude oil was chromatographed on a column (SiO_2) with CCl_4. Like fractions were combined to yield chlorodicyclohexyl ketone-4,4-d_2 167(d) (112 mg) and dicyclohexyl ketone-4,4-d_2 210(d).

Deuterium analysis of the ketone 210(d) by mass spectroscopy by comparison of the parent ion (m/e 194) with that of an undeuterated specimen gave the following percentage distribution:

3.9 (d_0) 24.8 (d_1) 55.5 (d_2) 10.5 (d_3) 4.2 (d_4) 1.1 (d_5).

Likewise, deuterium analysis of the chloroketone 167(d) gave a similar distribution within ± 3%. Examination of the fragment ion, m/e 111, of the chloroketone 167(d) indicated no equilibration of the two rings during preparation.

Favorskii Reaction of 2-Chlorodicyclohexyl Ketone-4,4-d_2 167(d)

Chloroketone-d_2 167(d) (33 mg) in dioxane (0.3 ml) was added dropwise to a solution of sodium hydroxide (43 mg sodium) in dioxane-MeOH-H_2O, 0.5:0.15:0.07 (0.72 ml) at reflux. The reaction mixture was vigorously stirred (7 hr) since two phases developed during addition of starting material. The reaction was worked up as before (p. 101).

Evaporation of the solvent gave an oil (22 mg, 72%) which crystallized at room temperature. Sublimation (85° at 0.2 Torr) gave

colourless 1-cyclohexylcyclohexane carboxylic acid-d_2 I68(d), m.p. 117-120°C. Deuterium analysis by comparison of the McLafferty fragment ion (m/e 128) in the mass spectrum with that of a non-deuterated sample gave the following percentage distribution: 51 (d_0) 13.9 (d_1) 27.4 (d_2) 6.9 (d_3) 2.3 (d_4) 0.6 (d_5). This indicated complete equilibration of the two rings. Furthermore, the spectrum of the ketone 210(d) fragment (m/e 111) is practically superimposable on that of the McLafferty fragment (m/e 128) (Fig. 3, p. 77).

Preparation of Dicyclopropyl Ketone 220

The procedure was that outlined in Organic Synthesis.[152] The product was a colourless liquid 220, b.p. 55-56° at 11 Torr (lit.[152] b.p. 72-74° at 33 Torr).

IR spectrum: $\nu_{max}^{CCl_4}$ 3110, 3025 (C-H) and 1680 (C=O)

PMR spectrum: δ_{TMS}^{neat} 2.07 (m,2H), 0.87 (m,8H)

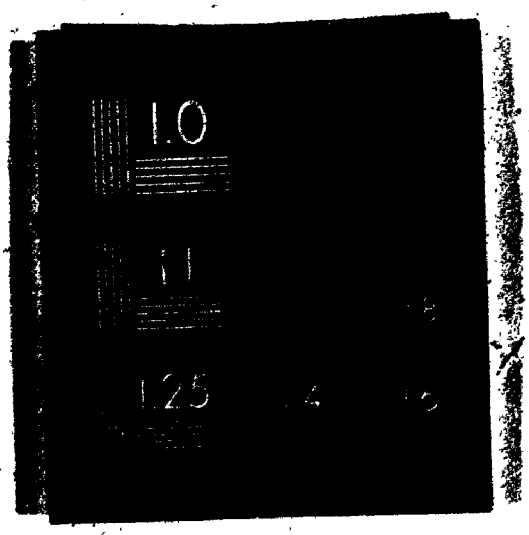
Reaction of Dicyclopropyl Ketone 220 with Br_2/HOAc

A solution of dicyclopropyl ketone 220 (2.00 g, 18.2 mmol), Br_2 (3.00 g, 18.8 mmol) and 48% HBr (150 mg) in glacial HOAc (20 ml) was stirred at room temperature for 3 hr. During this time, the colour gradually faded. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with aqueous 5% $KHCO_3$ and then dried ($MgSO_4$).

Evaporation of the ether gave a light yellow liquid (5.0 g). Integration of the PMR spectrum showed the ratio of single ring cleavage to double ring cleavage to be 86:14. The crude material was distilled under vacuum and the fraction, b.p. 78-80° at 0.08 Torr 221 was

3 3

OF/DE



collected.

IR spectrum: $\nu_{max}^{CCl_4}$ 3030, 2970 (C-H) and 1705 (C=O)

PMR spectrum: δ_{TMS}^{neat} 4.76 (d.d,1H,J=6.5,7.0Hz), 3.58 (t,2h,J=6.5Hz), 2.65-2.05 (m,3H), 1.04(m,4H)

Preparation of α-Bromodicyclopropyl Ketone 223

A suspension of dibromoketone 221 (1.0 g, 3.7 mmol) was stirred vigorously in a refluxing solution of NaOH (1.0 g, 25 mmol) in H_2O (2 ml) for 30 min. The reaction mixture was cooled to room temperature and extracted with ether. The ether layer was washed with aqueous 5% HCl and dried ($MgSO_4$).

Evaporation of the ether gave a light brown liquid 223 (567 mg, 81%).

GLPC (90%, 5% DEGS): 1 peak

IR spectrum: $\nu_{max}^{CCl_4}$ 3015 (C-H) and 1685 (C=O)

PMR spectrum: δ_{TMS}^{neat} 2.62 (q,1H,J=6.0Hz), 1.62, 1.40 (d.m,4H)
(Fig.4, p. 81) 0.93 (d,4H,J=6.0Hz)

A sample whose spectral properties remained unchanged was purified by preparative GLPC.

Mass spectrum: m/e 188, 190 (P^+) 187, 189 (P^+-1) 147, 149 (P^+-41) 69 (P^+-119,121,100%)

Precise Mass Determination. Calc'd: 187.98358 (Br^{79})

Found: 187.98196

The above reaction was repeated on a larger scale and the α-bromodicyclopropyl ketone 223 purified by distillation (b.p. 72-73° at 10 Torr).

Reaction of Methyl Cyclopropyl Ketone 224 with Br_2/CH_2Cl_2

Hydrogen bromide (Matheson) was bubbled through an ice cold solution of methyl cyclopropyl ketone 224 (10.0 g, 0.19 mol) and Br_2 (19.6 g, 0.122 mol) in CH_2Cl_2 (80 ml) until the colour had completely faded (30 min). The solution was flushed with dry N_2 to remove excess HBr, warmed to room temperature and then washed with aqueous 2% Na_2CO_3 (50 ml). The CH_2Cl_2 layer was separated and dried ($MgSO_4$).

Evaporation of the solvent gave a colourless liquid, 3,5-dibromopentan-2-one, 225 (29.5 g, 100%).

PMR spectrum: $\delta^{\text{neat}}_{CH_2Cl_2}$ 4.5 (d.d, J=7.0, 6.5Hz), 3.45 (t, J=6.5Hz) 2.6-2.2 (m) 2.26 (s, -Me)

Attempted Preparation of α-Bromocyclopropyl Methyl Ketone 229

See Table VII.

Preparation of α-Bromocyclopropyl Methyl Ketone 229

Crude dibromide 225 (22 g, 0.09 mol) in DMSO (120 ml) was added dropwise (3 hr) to a stirred solution of DABN (21 g, 0.15 mol, Aldrich) in DMSO (50 ml) maintained at +15°. After addition was complete, the reaction mixture was maintained at +15° for a further 12 hr. Prior to aqueous workup in 5% HCl (150 ml), the volume of the reaction mixture was reduced to 50 ml by distillation under vacuum. The aqueous mixture was extracted with ether. The ether layer was separated and dried ($MgSO_4$).

Evaporation of the solvent gave a pale yellow liquid 229 (7.16 g, 48.5%).

GLPC (120°, 10% DEGS): 1 peak

TABLE VII

Attempted Preparation of α-Bromocyclopropyl Methyl Ketone 229

Substrate 225	Conditions	Result	Yield
320 mg	1g KOH 2 ml H_2O 70° 30 min	Neutral fraction (20 mg) contained bromoketone 229 (PMR)	5%
1.4 g	5 ml triethylamine (Baker) reflux 6 hr	Neutral fraction (200 mg) contained starting material 225 and bromoketone 229 (PMR), 1:4	17%
1.2 g	150 mg sodium 12 ml MeOH 0° 1 hr	No starting material 225 or bromoketone 229 (PMR)	0%
500 mg	4 ml diisopropylethylamine (Aldrich) 90° 24 hr	Neutral fraction (60 mg) showed some bromoketone 229 (PMR)	10%
500 mg	2 ml diisopropylethylamine 4 ml CH_3CN reflux 24 hr	Neutral fraction (80 mg) was bromoketone 229 (PMR)	24%
500 mg	500 mg 1,8-Bis (dimethylamino) napthalene[153] 4 ml CH_3CN reflux 21 hr	no bromoketone 229 (PMR)	0%
500 mg	2 ml DABN 2 ml CH_3CN r.t. 15 min	Neutral fraction (100 mg) is bromoketone 229 (PMR)	30%

TABLE VII (Cont'd)

Substrate 225	Conditions	Neutral	Yield
1 g 7 ml CH_3CN	1 g DABN 8 ml CH_3CN reflux 4 hr	Neutral fraction (145 mg) is bromoketone 229 (PMR)	22%
1 g 10 ml DMSO	1 g DABN 5 ml DMSO r.t. 2.5 hr	Neutral fraction (300 mg) is bromoketone 229 (PMR)	45%
1 g 10 ml DMSO	1 g DUBN 5 ml DMSO r.t. 6 hr	Neutral fraction (240 mg) is bromoketone 229 (PMR)	36%
1 g 10 ml $HCONH_2$	1 g DABN 5 ml $HCONH_2$ 0° 2 hr	Neutral fraction (400 mg) is predominantly starting material 225	minor

IR spectrum: $\nu_{max}^{CHCl_3}$ 3015 (C-H) and 1698 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 2.4 (s,-Me), 1.64, 1.40 (d.m,AA'BB;)

(Fig. 4, p. 81)

A portion of the crude was distilled bulb to bulb (~60° at 30 Torr) to yield a colourless sample.

Mass spectrum: 162, 164 (P^+) 161, 163 (P^+-1) 147, 149 (P^+-15) 43 (P^+-119, 121, 100%)

Precise Mass Determination. Calc'd: 163.96594 (Br^{81})

Found: 163.96506

Reaction of Cyclopropyl Phenyl Ketone 230 with $Br_2/CHCl_3$

A solution of cyclopropyl phenyl ketone 230 92.0 g, 13.7 mmol, Aldrich) and Br_2 (2.19 g, 13.7 mmol) in $CHCl_3$ (16 ml) at 0° was treated with HBr gas (Matheson). Within seconds, the solution had decolorized.

Evaporation of the solvent by Rotavap gave a yellow syrupy oil 231 (4.2 g, 100%).

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 8.1-7.9 (m,phenyl), 7.6-7.3 (m,phenyl), 5.44 (t,J=6.5Hz), 3.55 (t,J=6.5Hz), 2.56 (q,J=6.5Hz)

Preparation of α-Bromocyclopropyl Phenyl Ketone 232

The crude oil from above (4.2 g) in DMSO (10 ml) was added dropwise to a stirred solution of DABN (2.7 g, 1.5 excess) in DMSO (10 ml) at room temperature. The reaction mixture was stirred for 11 hr and then poured into aqueous 5% HCl. The aqueous mixture was extracted with ether. The ether layer was separated and dried ($MgSO_4$).

Evaporation of the solvent gave an amber liquid 232 (2.27 g, 74%).

GLPC (16%, 10% DEGS): 1 peak

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 8.15-7.90 (m,2H,phenyl), 7.55-7.25 (m,3H,phenyl)
(Fig. II, p. 81) 1.7-1.3 (d.m,4H,AA'BB')

A portion of the crude was distilled bulb to bulb (65-70° at 0.1 Torr) to yield a colourless liquid 232.

Mass spectrum: 224, 226 (P^+) 105 (P^+-149,151,100%)

Precise Mass Determination. Calc'd: 225.98158 (Br^{81})

Found: 225.97744

Reaction of Bromodicyclopropyl Ketone 223 with EtO^-/EtOH

Bromoketone 223 (2.0 g, 10.6 mmol) in EtOH (4 ml) was added to a stirred refluxing solution of NaOEt (1.5 g sodium, 65 g. atom) in EtOH (20 ml) under argon. A precipitate gradually formed during the reaction period (9 hr). The reaction mixture was poured into water and extracted with ether. The separated aqueous layer was acidified (pH=2) and re-extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$) and filtered, and evaporated by Rotavap.

The neutral fraction was a brown oil (1.2 g).

TLC ($CHCl_3$-ether, 98:2): 7 spots (no bromoketone 223)

PMR spectrum: $\delta^{CCl_4}_{TMS}$ no vinyl protons, 6 complex multiplets between 4.0-0.0

IR spectrum: $\nu^{CCl_4}_{max}$ 3600 (OH), 3100, 3030 (C-H), no C=O

Because of its complex nature, it was not examined further. The acidic fraction was a pale yellow liquid (830 mg).

TLC (EtOAc-PE68, 25:75): 4 spots (least polar spot is major)

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 9.8 ($-CO_2H$), 5.48, 5.05 (m, vinyl), 4 complex multiplets between 2.6-0.0

A portion of the crude was reacted with CH_2N_2 in ether at room temperature.

TLC ($CHCl_3$-ether, 98:2): 6 spots (least polar is major)

GLPC (120°, 10% DEGS): 3 peaks (2 major peaks are overlapping, 1:1)

After evaporation of the solvent, the ester mixture was chromatographed on a column (SiO_2) with $CHCl_3$-ether, 98:2. In this way, a pure fraction (170 mg) of the least polar material was obtained.

TLC ($CHCl_3$-ether, 98:2): 1 spot

GLPC (120°, 10% DEGS): 2 peaks (overlapping, 1:1)

IR spectrum: $\nu^{CCl_4}_{max}$ 3090, 3020, 2990, 2960 (C-H) and 1735 (C=O)

PMR spectrum: $\delta^{CCl_4}_{TMS}$ 5.40, 5.08 (m, vinyl); 3.66, 3.64 (2s, -OMe); 4 complex multiplets between 2.6-0.0

Mass spectrum: m/e 168 (highest mass unit), 153, 139, 109

The reaction was repeated on a larger scale and further material was isolated in the same way.

A portion of the purified ester mixture (350 mg) was dissolved in CH_2Cl_2 (6 ml) and reacted with O_3 at ice temperature (6 hr). An aliquot was checked by GLPC which showed that both peaks had disappeared. The solvent was evaporated and the residue treated with Zn dust (450 mg) in HOAc (5 ml) followed by an aqueous workup. The aqueous mixture was extracted with ether which was then separated and dried ($MgSO_4$).

Evaporation of the solvent gave a colourless liquid (270 mg).

PMR spectrum: $\delta^{CCl_4}_{benzene}$ 9.7 (d, -CHO, J=2.0Hz) 3.68 (s, -OMe) plus other complex parts

There was evidently no Favorskii acid present, since it would have been stable under the reaction conditions; therefore, the reaction was not pursued further.

Attempted Favorskii Reaction of Bromodicyclopropyl Ketone 223

See Table VIII.

Reaction of Bromodicyclopropyl Ketone 223 with Aqueous 30% NaOH at Reflux

A suspension of bromodicyclopropyl ketone 223 (1.0 g, 11% ketone 220 by GLPC) in aqueous 30% NaOH (10 g NaOH, 20 ml H_2O) was vigorously stirred at reflux for 13.5 hr. The reaction mixture was cooled to room temperature and extracted with ether. The aqueous layer was cooled to 0°, acidified (pH=2) and extracted again with ether. The ether layers were dried ($MgSO_4$) and filtered.

The neutral fraction gave a yellow liquid (50 mg) after evaporation of solvent. The PMR spectrum is that of dicyclopropyl ketone 220.

The acidic fraction, after evaporation of solvent, gave a tan oil (278 mg, 36%) which crystallized on standing, m.p. 55-88°. The crude acid was found to sublime readily (60° at 0.1 Torr) to yield white crystals 234, m.p. 92-93.5°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3540 (OH), 3100, 3030, 2995, 2960, 2900 (C-H) and 1706 (C=O)

PMR spectrum: $\delta_{CH_2Cl_2}^{CDCl_3}$ 7.0 (brd.m,O-H), 1.95 (m,2H), 1.05 (m,4H), 0.52 (m,4H)

Analysis: Calc'd for $C_7H_{12}O_3$, MW 144: C, 58.30; H, 8.33

Found: C, 58.55; H, 8.34

TABLE VIII

Attempted Favorskii Reactions of Bromodicyclopropyl Ketone 223

Substrate 223	Conditions	Results
1.0 g	2.0 g NaCN 12 ml MeOH reflux 2 hr	no reaction
1.0 g	0.5 g NaCN 10 ml $CH_3OCH_2CH_2OH$ reflux (124°) 7 hr	no reaction
0.5 g	450 mg $AgNO_3$ 7 ml MeOH 210 mg pyridine reflux 4 hr	no reaction
0.5 g	675 mg $AgNO_3$ 9 ml H_2O 230 mg pyridine reflux 4.5 hr	no reaction
0.5 g	700 mg NaOH 7 ml MeOH reflux 20 hr	Neutral fraction - mainly bromoketone 223. Acid fraction (67 mg), complex mixture, not examined further
0.5 g 1 ml MeOH	370 mg sodium 6 ml MeOH reflux 7.5 hr	Neutral fraction (250 mg) - TLC shows bromoketone 223 plus 6 other spots which match exactly the neutral fraction from the EtO^-/EtOH reaction. Acidic fraction (130 mg) - TLC shows 5 spots of approximately equal intensity, not examined further.

TABLE VIII

Attempted Favorskii Reactions of Bromodicyclopropyl Ketone 223.

Substrate 223	Conditions	Results
0.5 g	1.5 g NaOH 10 ml THF 25° 24 hr	no reaction
0.5 g	1.5 g NaOH 10 ml THF reflux 42 hr	Neutral fraction - mainly bromoketone 223 Acidic fraction - TLC shows a major spot and PMR spectrum matches that of hydroxy acid 234 formed in refluxing aqueous 30% NaOH (p.191)
0.5 g 1 ml t-BuOH	370 mg sodium 10 ml t-BuOH reflux 1.5 hr	Both fractions were complex mixtures (TLC) and were not examined further.
0.5 g 6 ml t-BuOH	765 mg NaOH 15 ml H_2O 10 ml H_2O_2 (70%) 25° 2 hr	no reaction
0.5 g	650 mg NaOH 5 ml H_2O reflux 5 hr	Neutral fraction - bromoketone 223 (GLPC, TLC) Acidic fraction (32 mg) - 4 spots of equal intensity (TLC)
1.0 g	10 g NaOH 20 ml H_2O reflux 13.5 hr	See detailed experimental.

Mass spectrum: m/e 125 (P^+-29), 99 (P^+-45), no parent ion

HA-100 spectrum: $\delta^{CH_2Cl_2}_{CDCl_3}$ 7.2 (brd.m,OH), 1.87 (overlapping quartets,2H,J=7.5 Hz), 1.18 (m,1H), 0.96 (t,3H,J=7.5Hz), 0.45 (m,4H)

Decoupling experiments show the quartets are coupled only to the triplet and the proton at 1.18 δ is coupled only to the cyclopropyl protons at 0.45 δ (Fig. 5, p.86).

A portion of the crude acid was methylated with CH_2N_2 in ether at room temperature to yield the methyl ester 234b.

GLPC (125°, 10% DEGS): 1 peak

TLC ($CHCl_3$): 4 spots (1 major spot plus 3 trace spots)

IR spectrum: $\nu^{CHCl_3}_{max}$ 3535 (OH), 3100, 3000, 2965, 2935, 2880 (C-H) and 1726 (C=O)

PMR spectrum: $\delta^{CDCl_3}_{benzene}$ 3.75 (s,3H,-OMe), 2.85 (brd.s,1H,OH), 1.84 (m,2H,$-CH_2-$), 1.1 (m,1H, -proton), 0.86 (m,3H,$-CH_3$), 0.35 (m,4H,cyclopropyl) D_2O added, singlet (2.85) disappears

Mass spectrum: m/e 129 (P^+-29), 99 (P^+-59), 69, 57, no parent ion

Reaction of Hydroxy Acid 234 with $Pb(OAc)_4$

After the manner of Kochi,[154] $Pb(OAc)_4$ (200 mg, 0.45 mmol) was added to a solution of hydroxy acid 234 (65 mg, 0.45 mmol) in benzene (2 ml) containing pyridine (1 drop) at room temperature. Immediate effervescence was observed and a powdery white precipitate replaced the initial crystals of $Pb(OAc)_4$. The mixture was refluxed for 5 min and then filtered. The solution was washed with aqueous 5% HCl and

aqueous 5% Na_2CO_3 and then dried ($MgSO_4$).

PMR spectrum: $\delta^{\text{benzene}}_{\text{benzene}}$ 2.3 (q, J=7.5Hz) 1.55 (m)
1.1 (t, J=7.5Hz) 0.62 (m)

Decoupling experiments show that the signal at 1.55 δ is coupled only to the signal at 0.62 δ.

IR spectrum: $\nu^{\text{benzene}}_{\text{max}}$ 1694 (C=O)

The volume of the benzene solution was reduced to 0.5 ml by distillation and then the remaining solution was diluted with aqueous 90% EtOH (2 ml). This solution was mixed with freshly prepared 2,4-dinitrophenylhydrazine reagent (2 ml). A dark orange precipitate formed immediately. The suspension was filtered and the orange crystals (19 mg, 20%), m.p. 159-164°, were collected. These crystals were sublimed (140°, 0.2 Torr) to yield reddish-orange crystals (16.5 mg), m.p. 166-167.5° (lit.[118] m.p. 161-162°).

TLC (benzene-EtOAc, 95:5): 1 spot

PMR spectrum: $\delta^{CDCl_3}_{\text{dioxane}}$ 11.63, 11.15 (brd.s, NH); 9.1, 8.28, 7.88 (m, phenyl); 2.31 (brd.m, $-CH_2-$), 1.9-0.7 (m)

HA-100 spectrum: shows overlapping phenyl pattern at low field (Fig. 9, p. 196) and overlapping quartets and triplets at high field

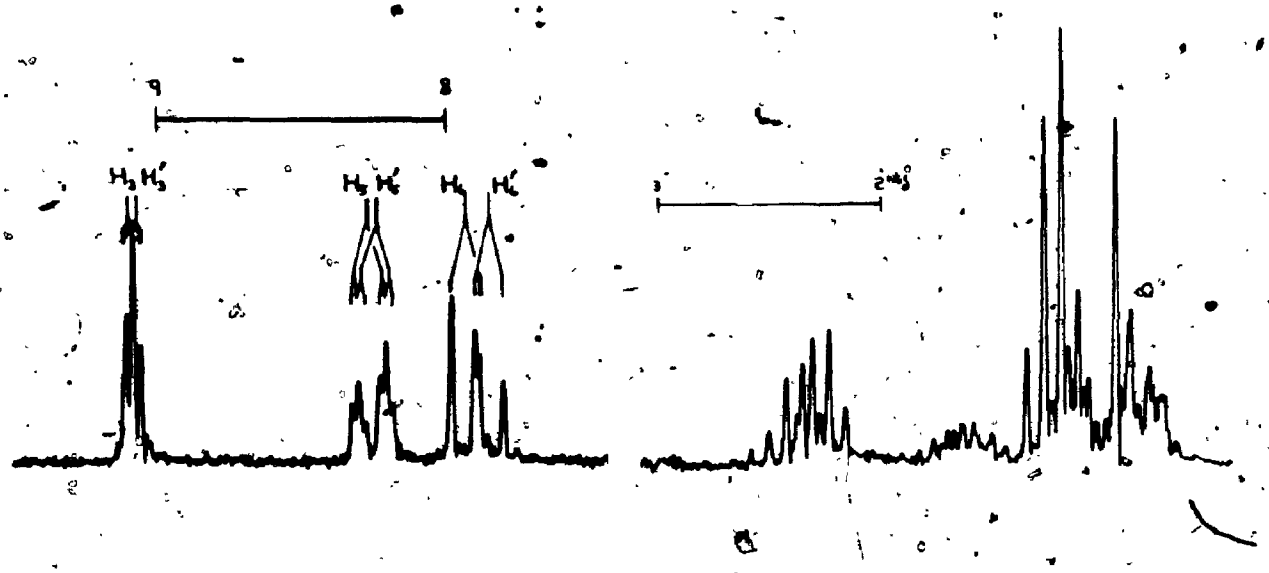
Mass spectrum: m/e 278 (P^+)

Analysis: Calc'd for $C_{12}H_{14}N_4O_4$ (MW 278): C, 51.85; H, 5.04
Found: C, 52.16; H, 5.12

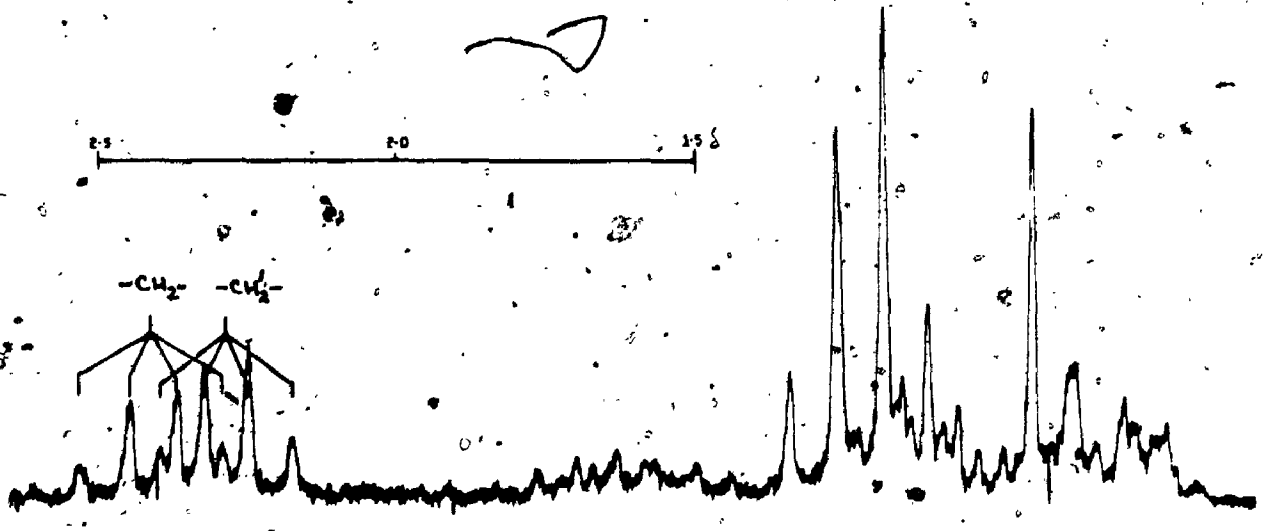
A temperature coalescence study was attempted by PMR spectroscopy; however, it was abandoned due to decomposition of the sample above 150°. No coalescence of the overlapping signals was observed up to that

Fig. 9

100 MHz Spectrum of the 2,4-DNP Derivative of Ethyl Cyclopropyl Ketone



(high field region expanded)



temperature.

Reaction of Bromodicyclopropyl Ketone 223 with 30% NaOD/D_2O at Reflux

A suspension of bromodicyclopropyl ketone 223 (506 mg, 11% ketone by GLPC) in a refluxing solution of NaOD (2.5 g sodium) in D_2O (12.2 ml) was vigorously stirred for 6.5 hr. The reaction mixture was cooled to room temperature, poured into H_2O (20 ml) and extracted with ether. The aqueous layer was cooled to 0°, acidified (pH2) with concentrated HCl, and extracted with ether. The separated ether layer was extracted with aqueous 5% Na_2CO_3 (15 ml). The separated aqueous carbonate layer was acidified and extracted with ether. The ether layer was dried ($MgSO_4$) and filtered. In this way, the O-D content in the acidic fraction was minimized.

The acidic fraction, after evaporation of solvent, gave an amber syrup (132 mg) which crystallized on standing. The crude gave white crystals of 234(d) (75 mg, 21%) m.p. 90-92°, on sublimation (65° at 0.1 Torr).

PMR spectrum: $\delta^{CDCl_3}_{\text{dioxane}}$ 7.0 (brd.m) and 0.4 (m)

(Fig. 5, p. 36)

A portion of the sublimed acid was methylated with CH_2N_2/ether at room temperature to yield the methyl ester 234(d).

GLPC: 1 peak.

Mass spectrum: 130, 129 (P^+-29) 104, 105 (P^+-59) 70, 62, no parent ion

Deuterium analysis by mass spectroscopy (fragments, m/e 104, 105) showed the following percentage distribution: 28 (d_5) 72 (d_6). Furthermore, a similar analysis (fragments, m/e 129, 130) showed 22%

(d_0) and 78% (d_1). These results indicate complete exchange of the ethyl protons but only 75% (±3%) exchange of the α-cyclopropyl proton.

Reaction of Bromocyclopropyl Methyl Ketone 229 with Aqueous 30% NaOH at Reflux

Bromocyclopropyl methyl ketone 229 (1.6 g, 9.8 mmol) was added dropwise (4.3 hr) to a vigorously stirred, refluxing solution of NaOH (10 g) in H_2O (20 ml). The reaction period was extended 30 min and then the mixture was cooled to room temperature and worked up as before (p. 105).

No neutral fraction was observed but the acidic fraction was an amber oil (140 mg).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 9.2 (s,-CO_2H), 1.27 (s,-Me), 2.8-0.7 (complex multiplets)

The crude acid was chromatographed on a column (SiO_2) with $CHCl_3$ to give a liquid, 1-methylcyclopropane carboxylic acid, 236 (54 mg) which solidified on standing in the fridge, m.p. 25-32° (lit.[119] m.p. 32-33°).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 10.8 (brd.s,-CO_2H,1H), 1.29 (s,-Me,3H), 1.5-1.20 (m,AA',2H), 0.85-0.6 (m,BB',2H)

Mass spectrum: m/e 100 (P^+) 99 (P^+-1) 85 (P^+-15) 55 (P^+-45)

the ratio $P^+ : P^+-1 = 0.87$

A solution of the acid (44 mg) and p-bromophenacyl bromide (121 mg) in EtOH-triethylamine, 2:1 (1.5 ml) was refluxed for 1 hr. The solution was then evaporated to dryness and the residue was extracted with ether. Evaporation of the ether extract gave a dark brown liquid (93 mg) which partially solidified on standing. The crude material was

recrystallized from EtOH-H_2O to give tan coloured flakes (32 mg), m.p. 56-63° and then from pentane to give a feathery solid, m.p. 63-64° (lit.[119] m.p. 64-65°).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 7.7 (m,4H, phenyl AB), 5.23 (s,2H,-CH_2-) 1.36 (s,3H,-Me), 1.5-1.25 (m,2H,AA'), 0.9-0.62 (m,2H, BB')

The Favorskii rearrangement was repeated using the conditions above but varying the rate of addition. The yield of Favorskii acid never exceeded 15-20% although the amount of polymeric tar seemed reduced with longer addition times. After one such reaction, the crude acid fraction (100 mg) was distilled bulb to bulb (90° at 20 Torr) and the colourless distillate (44 mg) was examined by PMR spectroscopy. Although the spectrum was much cleaner than that of the crude material, there was no indication of a doublet around 2.17 δ (J=7.0Hz)[155] which would reveal the presence of the alternative Favorskii acid, cyclopropylacetic acid 252.

Reaction of Bromocyclopropyl Methyl Ketone 229 with MeO^-/MeOH at Reflux.

A solution of bromocyclopropyl methyl ketone 229 (800 mg) in MeOH (4 ml) was added dropwise (15 min) to a refluxing solution of NaOMe (800 mg sodium) in MeOH (15 ml). The reaction mixture was refluxed for 5 hr during which time a precipitate formed. The mixture was worked up as before (p. 103).

The neutral fraction was an amber liquid (340 mg) whose TLC and PMR spectrum showed bromoketone 229 plus several other compounds. This fraction was not examined further.

The acidic fraction was an amber liquid (112 mg) which solidified

on standing, m.p. 95-125°.

TLC (EtOAc-pentane-HOAc, 40:60:2): 3 spots (2 major spots, of which one is u.v. active).

Recrystallization of a portion of the crude acid from ether-pentane gave an off-white solid, m.p. 120-125° which was not examined further.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1755 and 1735 (C=O)

PMR spectrum: $\delta_{TMS}^{CDCl_3}$ 3.60 (s) 2.0 (s) 1.36 (m,AA') 0.85 (m,BB') integration, 1:1:2:2. D_2O added; 3.6 (s) disappears.

A portion of the crude acid was methylated with CH_2N_2/ether and examined by GLPC (10% DEGS). There is a single peak which corresponds to the methyl ester 234b but it represents a very minor percentage. The major peak is a very polar compound (r.t.=20 min at 150°).

Attempted Reaction of Bromocyclopropyl Methyl Ketone 229 with Ag^+

A suspension of the bromoketone 229 (500 mg) in refluxing solution of $AgNO_3$ (800 mg, 1.5 excess) in H_2O (10 ml) containing pyridine (260 mg) was stirred vigorously for 4.5 hr. The cooled mixture was extracted with ether. The aqueous layer was acidified (pH2) and re-extracted with ether.

The neutral fraction was recovered bromoketone 229 (310 mg) and the acidic fraction was a brown tar (15 mg) which was not examined further.

Reaction of Bromocyclopropyl Methyl Ketone 229 with 30% NaOD/D_2O at Reflux

A suspension of bromoketone 229 (512 mg) in a solution of NaOD

(2.1 g sodium) in D_2O (11.5 ml) was vigorously stirred at reflux for 1 hr. The reaction mixture was cooled to room temperature and worked up as before (p. 197).

The acidic fraction, after evaporation of ether, was an amber syrup (116 mg) which was chromatographed on a column (SiO_2) with $CHCl_3$ to give the Favorskii acid 234(d) (25 mg).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 10.3 (brd.s,-CO_2H), 1.4-1.15 (m,AA'),
(Fig. 6, p. 89) 0.85-0.55 (m,BB')

Mass spectrum: m/e 103 (P^+), 102 (P^+-1), 101 (P^+-2), 85, 58

The P^+-2 fragment is small but, since there is no corresponding fragment at m/e 100, it is not a d_1 species. It is either the P^+-1 fragment of a d_2 species or else the P^+-1 fragment is formed by two pathways: loss of a ring proton plus a small amount due to loss of a methyl proton. In either case the percentage of d_3 is very high.

Preparation of γ-Phenylbutyrolactone 237.

β-Benzoylpropionic acid was prepared as outlined in Org. Synthesis[156] except all quantities were divided by ten. After cleaning with Norite, the basic aqueous solution of the β-benzoylpropionic acid was treated with $NaBH_4$ (1.25 g) in small portions.[157] After addition of the $NaBH_4$, the reaction mixture was left stirring overnight. After 12 hr, the mixture was acidified carefully with concentrated HCl and extracted with ether. The ether was evaporated and the residue (10.5 g) was dissolved in benzene (50 ml) with p-toluenesulfonic acid (20 mg). Water (1 ml) was removed by continuous azeotropic distillation (20 hr). The benzene was then removed by Rotavap and the crude phenylbutyrolactone[237] purified by distillation, b.p. 120-121° at 0.4 Torr (lit.[157] b.p. 135-

140° at 2 Torr), m.p. 25-35° (lit.[157] m.p. 37-38°).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 7.23 (s, 5H, phenyl), 5.52-5.25 (m, 1H, benzyl), 2.75-1.8 (m, 4H)

IR spectrum: $\nu^{CCl_4}_{max}$ 3090, 3055, 3005, 2975 (C-H) and 1790 (C=O)

Reaction of Bromocyclopropyl Phenyl Ketone 232 with Aqueous 30% NaOH at Reflux

A suspension of bromoketone 232 (1.0 g) in a refluxing solution of NaOH (8 g) in H_2O (16 ml) was stirred vigorously for 21 hr. The reaction mixture was then worked up as before (p. 102).

The neutral fraction, after evaporation of solvent, gave an amber oil (57 mg) which was not examined further.

Evaporation of the acidic fraction gave a light green liquid (525 mg, 75%).

TLC ($CHCl_3$-HOAc, 35:1): 2 spots (one major spot)

A portion of the crude, acidic fraction (450 mg) was chromatographed on four preparative TLC plates (SiO_2) with $CHCl_3$-MeOH, 96:4 to give a slightly yellow liquid (350 mg). This liquid was distilled bulb to bulb (95° at 0.07 Torr) to yield a colourless liquid 237 which solidified on cooling, m.p. 28-35° (lit.[157] m.p. 37-38°).

TLC ($CHCl_3$-MeOH, 96:4): 1 spot (r.f.=0.8)

Mass spectrum: m/e 162 (P^+, 100%) 161 (P^+-1) (Fig. 8, p. 99)

IR spectrum: $\nu^{CCl_4}_{max}$ same as authentic γ-phenylbutyrolactone 237

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ same as authentic γ-phenylbutyrolactone 237

Reaction of Bromocyclopropyl Phenyl Ketone 232 with 30% NaOD/D_2O at Reflux

A suspension of bromoketone 232 (0.5 g) in a refluxing solution of NaOD (2.3 g sodium) in D_2O (10 ml) was stirred vigorously for 7 hr. The reaction mixture was then worked up as before (p. 103).

The acidic fraction, after evaporation of solvent, gave an amber syrup (265 mg, 75%). This material was chromatographed on two preparative TLC plates (SiO_2) with $CHCl_3$-MeOH, 96:4, to give a pale yellow liquid 237(d) (140 mg).

PMR spectrum: $\delta^{CDCl_3}_{TMS}$ 7.24 (s,5H,phenyl)

2.7-1.84 (brd.dd,1.7H,J=12.5Hz)

Mass spectrum: m/e 167, 166, 165 (P^+). The latter is the most (Fig. 8, p. 99) intense.

Deuterium analysis by mass spectroscopy (parent ion) showed the following percentage distribution: d_0, d_1, d_2 (0) d_3 (78) d_4(3) d_5 (19). The absence of any peak at m/e 163 indicates that the P^+-1 fragment is due to loss of hydrogen not deuterium.

HA-100 spectrum: $\delta^{CDCl_3}_{TMS}$ 7.54 (s,5H, phenyl) and

2.78-2.06 (brd.dd,1.5H,J=13.5Hz)

The use of a shift reagent (Europium) demonstrated that the remaining protons were the beta-methylene protons by comparison with the HA-100 spectrum of γ-phenyl butyrolactone 237 using approximately the same amount of shift reagent (Fig. 7, p. 98).

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