1971

Mechanistic Study Of A Favorskii Rearrangement

Yock-chai Toong

MECHANISTIC STUDY OF A FAVORSKII REARRANGEMENT

by

TOONG Yock-Chai
Department of Chemistry

Submitted in partial fulfillment of

the requirement for the degree of

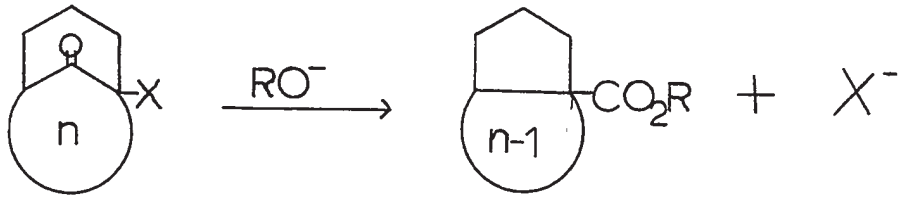
Doctor of Philosophy

Faculty of Graduate Studies
The University of Western Ontario
London, Ontario, Canada

July 1971

ABSTRACT

The skeletal rearrangement of an α-haloketone with a base to give a carboxylic acid derivative is called the Favorskii rearrangement. The mechanisms of the rearrangement in the bicyclic haloketones below have been studied by using deuterium incorporation, optical activity tests for symmetrization in the products, and kinetic isotope effects.



n = 6, 7, 8.

X = Br, Cl.

The mechanism of the rearrangement in the bicyclic system was found to be dependent on the acidity of the α'-hydrogen of the haloketones, the reactivity of the carbonyl group of the haloketones, the basicity and the nucleophilicity of the reagent, and the nature of the halogen. There is no observable solvent effect on the rearrangement mechanism and the stereochemistry of the product. Of all the possible mechanisms only the cyclopropanone and the semibenzilic mechanisms were found operating in the bicyclic system. There is no evidence for the

oxyallyl mechanism which is not favoured in this bicyclic system for structural reasons. It was found that the mechanism for the bicyclic haloketones changed gradually from the semibenzilic mechanism to the cyclopropanone mechanism in going from n = 6 to n = 8. The rate of the semibenzilic mechanism decreased from n = 6 to n = 8, but the reverse was true for the cyclopropanone mechanism.

For the semibenzilic mechanism the base adds, presumably reversibly, to the carbonyl group, and the ejection of halide followed in the slow step, but for the cyclopropanone mechanism a concerted 1,3-elimination was the rate determining step. The kinetic isotope effect, the rate ratio of the bromo- and chloroketones, the negative entropy of activation are all consistent with the concerted mechanism. Perhaps this is the first example of a 1,3-concerted elimination with double inversion which is different from the stepwise cyclopropanone mechanism so far found in Favorskii rearrangements. The postulated cyclopropanone intermediate was too unstable to be isolated from the reaction medium. Bases with different basicity and nucleophilicity such as alkoxides, hydroxide, hydrosulfide, cyanide, bicarbonate, and hydroperoxide were used for the rearrangement, and the cyanohydrin intermediate was isolated in the reaction medium. The stereochemistry of the products was determined by comparison with authentic samples obtained from unambiguous synthesis. Only cis fused products were obtained from the series of haloketones studied. The formation of only cis-product might suggest that the ring opening of cyclopropanone is stereospecifically cis.

The results of the present study showed that the mechanism of Favorskii rearrangement varies with the reaction conditions. With the newly found understanding of the factors that control the mechanism of the

rearrangement, it should be possible to predict the mechanism of rearrangement in other systems, particularly when both semibenzilic and cyclopropanone mechanisms are possible in the system. The use of alkaline hydroperoxide to induce semibenzilic rearrangement specifically might be of potential synthetic value where the isomeric α-haloketones will give different products.

ACKNOWLEDGEMENTS

The author would like to express his sincere gratitude to Dr. E. W. Warnhoff for advice, encouragement and guidance at all stages of the work. Thanks are also due to Dr. J. B. Stothers for the C-13 NMR spectrum.

Assistance from various members of the faculty as well as fellow students is also gratefully acknowledged.

The author is indebted to the National Research Council of Canada for funding this work.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF TABLES (contd.)

CHAPTER I

Introduction

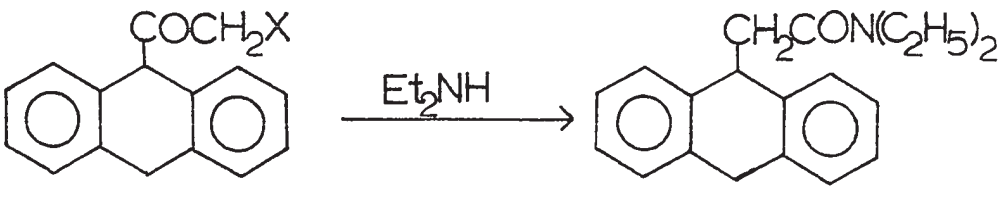
(A) The Definition and Scope of the Favorskii Rearrangement

The Favorskii rearrangement belongs to one of the important classes of organic reactions called molecular rearrangements. It was first observed by Demarcay in 1880 that the dibromoketo ester 1 reacted with base to give the rearranged unsaturated acid, mesaconic acid 2 (1). The reaction of halogenated ketones with base was independently studied by Favorskii in 1894 (2) and since then considerable work has

1 2

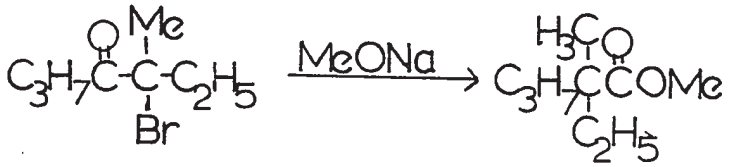
been done to show that rearrangement of halogenated ketones to acid derivatives is a general reaction. Therefore, the Favorskii rearrangement can be defined according to Kende as the skeletal rearrangement of α-halogenated ketones in the presence of bases, such as hydroxides, alkoxides, or amines, to give carboxylic acid salts, esters, or amides, respectively (1). α-Mono-halogenated ketones undergo reaction to give derivatives of saturated acids having the same number of carbon atoms. In the case of dihalogenated ketones, α, α-, α, α' - and α, β-dihaloketones give unsaturated carboxylic acids or esters. Similarly,

the trihalogenated ketones in the presence of base can give unsaturated haloacids. Furthermore, the Favorskii rearrangement is applicable to both acyclic and alicyclic halogenated ketones. The rearrangement of acyclic α-monohaloketones is particularly sensitive to both structural factors and reaction conditions. Substitution on the α and α′ position affect the yield of rearrangement product or prohibit the reaction. It was observed that increasing alkyl substitution at the α'-carbon decreases the yield of product. For example, in the series of ketones $(CH_3)_2CBrCOR$, the yield of rearrangement product where R is methyl, ethyl, or n-propyl ranges from 39% to 69%; where R is isopropyl the yield is at most 29%, while when R is t-butyl (no α'-hydrogen atom) rearrangement is not observed (3, 4). This observation could be rationalized if the presence of an α'-hydrogen is necessary for the rearrangement while increasing methyl substitution increases the difficulty for the α'-H to react. On the other hand, the substitution of aryl groups on the α'-carbon promotes the rearrangement. 1-Chloro-3-phenylacetone was converted into the corresponding 3-phenylpropionic ester in 80% yield. With the diaryl substituted halogenated ketones, the reaction is very fast, even diethylamine can serve as the reagent. The dihydroanthracene ketone 3 (x = Cl, Br) on treatment with diethylamine gives the diethylamide rearrangement product 4 in about 40% yield (5, 6).



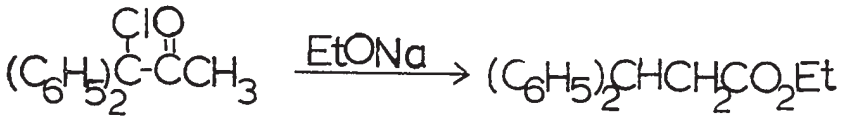
3 4

Alkyl substitution on the halogen-bearing carbon atom promotes the rearrangement. This is ascribed to steric hindrance toward competing bimolecular substitution and the higher reactivity of the secondary or tertiary halides than the primary halide (1). The reaction of 3-bromo-2-butanone with sodium methoxide gave only substitution product whereas the 3-bromo-3-methyl-4-heptanone afforded a good yield of rearrangement ester 5 under the same conditions (7).



5

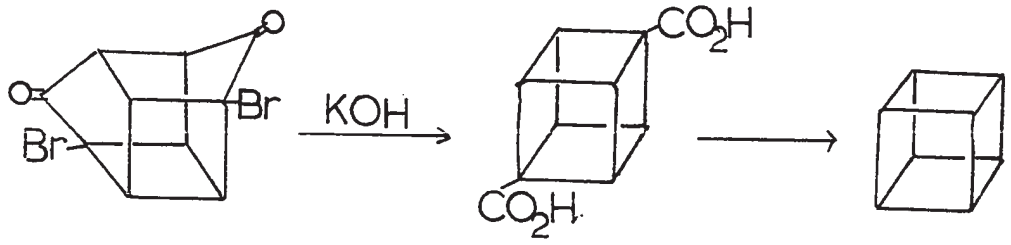
The substitution of aryl groups on the halogen-bearing carbon also has a favourable effect on the rearrangement. Thus, 1-chloro-1-phenylacetone reacts with methanolic methoxide to give rearrangement product in 69% yield, and the tertiary haloketone 6 rearranges to give ethyl-3,3-diphenylpropionate in 85% yield (8).



6

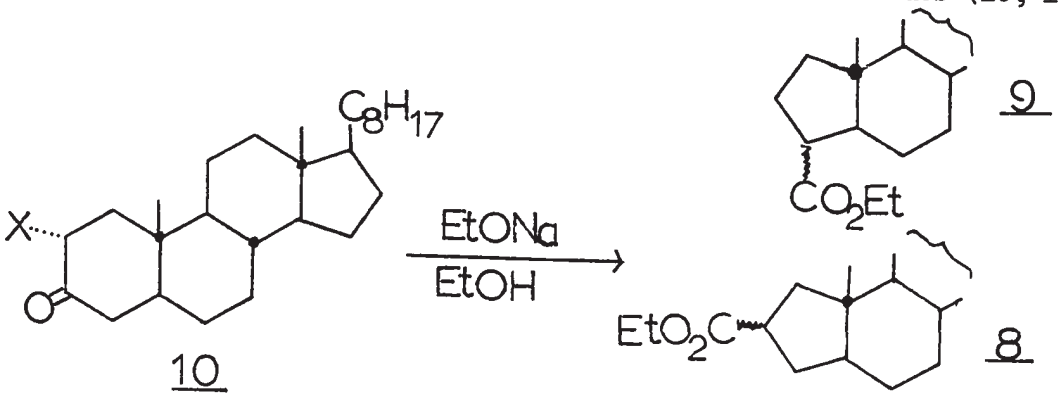
The Favorskii rearrangement of alicyclic monohaloketones provides a valuable synthetic route to alicyclic carboxylic acids. The reaction for α-halogenated cycloalkanones in rings from four to ten carbon atoms is quite general, yields ranging from 40% to 75%, except for 2-halocyclopentanone from which no rearrangement acid has been obtained. However, when the cyclopentane ring was fused in a strained system, normal rearrangement product was obtained. This ring contraction of

α-halocyclopentanone was one of the important steps in the synthesis of cubane 7 (9). In addition, the rearrangement has found synthetic



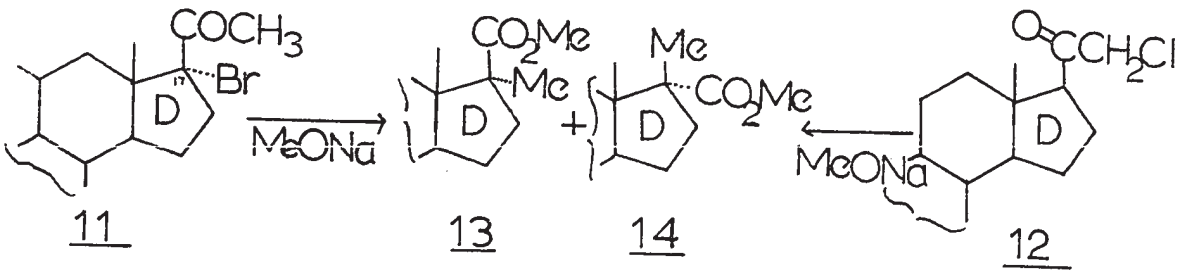
7

utility in steroid chemistry as a direct route to A-norsteroids and in transformations leading to 17-methyletianic acid derivatives. Two esters 8 and 9 were isolated with the former predominating when 2-halocholestanones 10 were allowed to react with alkoxides (10, 11).



10 9 8

The 17α-bromo-20-ketosteroids 11 and 21-chloro-ketosteroids 12 undergo rearrangement readily to high yields of 17-methyletianic esters. The 17α-methyl ester 13 is invariably the principle product along with a significant amount of the 17β-epimer 14 (34).



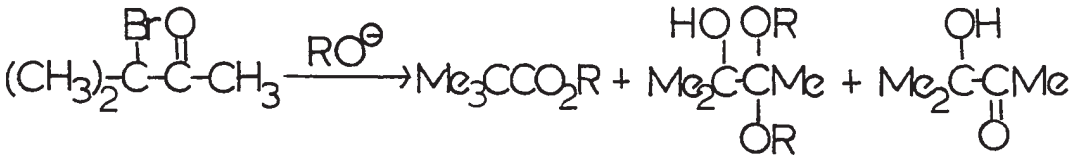
11 13 14 12

Bromo- and chloro-ketones are generally used for the rearrangement. The order of reactivity of halogenated compounds is iodo > bromo > chloro > fluoro. 2-Iodocholestanone and 21-fluoro-20-ketone steroid were found to give rearrangement esters 8, 9, 13 and 14 (12). The reactivity sequence was iodo > bromo > chloro in the 2α-halocholestanone series. Chloroketones are normally preferable to bromoketones as substrates in the Favorskii rearrangement. For example, chloromethyl cyclohexyl ketone reacts with sodium methoxide to give 30% of the Favorskii ester, whereas the corresponding bromoketone under these conditions gives exclusively side reaction product (13). 2-Bromocyclohexanone gave a lower yield of methyl cyclopentanecarboxylate than 2-chlorocyclohexanone (14).

There are a variety of bases and solvents used to bring about the rearrangement. The commonly used bases are metallic alkoxides, such as sodium methoxide, sodium ethoxide, sodium isopropoxide and potassium t-butoxide. Organic bases such as diethylamine and pyridine are also sometimes used. Inorganic bases like potassium hydroxide, barium carbonate and potassium bicarbonate in aqueous solution are also used, they frequently give more side products than the alkoxides. The choice of solvents ranges from polar solvents such as methanol, ethanol and aqueous solution, to non-polar solvents such as, dimethoxyethane, dioxane, ether and xylene. Silver nitrate in aqueous solution is not a typical reagent for Favorskii rearrangements, but sometimes can effect a rearrangement. For example, 1-bromo-1-benzoylcyclohexane does not give rearrangement products on treatment with sodium methoxide, but rearrangement products are obtained in low yield when treated with ethanolic silver nitrate or with the heterogeneous sodium hydroxide in

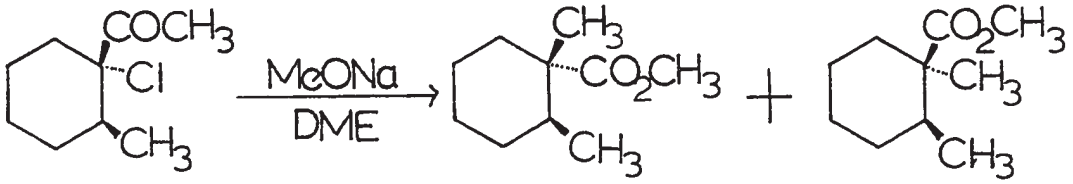
xylene (15).

The choice of optimum base and solvent for rearrangement varies with the structure of the individual haloketone. There is no single alkoxide-solvent combination suitable for all α-haloketones. The reaction of 3-bromo-4-methylbutan-2-one 15 with various bases in different solvents give different products as shown in Table I (1).



15 16 17 18

Besides the considerable effect solvents have on the yield of a Favorskii rearrangement, they also have a profound effect on the steric course of the reaction. For example, House found that the reaction of 19 with sodium methoxide in dimethoxyethane was highly stereospecific giving 94.5% of 20. The reaction became nonspecific when it was carried



19 20 21

out in methanol, giving about equal amounts of 20 and 21 (16).

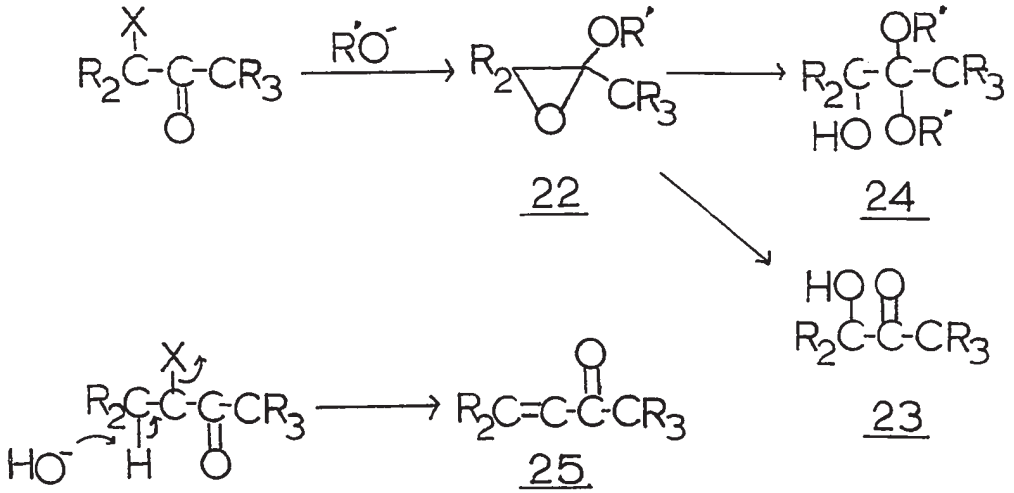
There are several side reactions which usually accompany the rearrangement. The principle side products formed at the expense of the rearrangement are the epoxy ether 22, the α-hydroxyl ketone 23 and the α-hydroxy ketal 24 having the same carbon skeleton as the

TABLE I

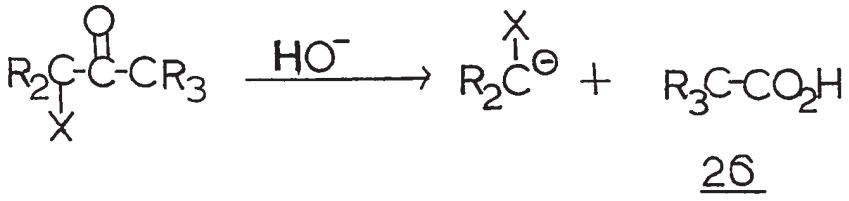
Reaction of $(CH_3)_2-\underset{\underset{Br}{|}}{C}-\overset{\overset{O}{||}}{C}-CH_3$ 15 Under Conditions of the Favorskii Reaction

Base	Solvent	Products (%) 16	Products (%) by Products	
Sodium isopropoxide	Diethyl ether	64	0	
Sodium ethoxide	Diethyl ether	61	0	
Sodium methoxide	Diethyl ether	39	20	17
Sodium isopropoxide	Isopropyl alcohol	20	8	17
Sodium ethoxide	Ethanol	14	32	17
Sodium methoxide	Methanol	0	77	17
Barium carbonate	Water	3	-	
Potassium hydroxide	Water	0	76	18

original haloketone. If there is a β-H in the haloketone, dehydrohalogenation can occur to give the unsaturated ketone 25. Furthermore,

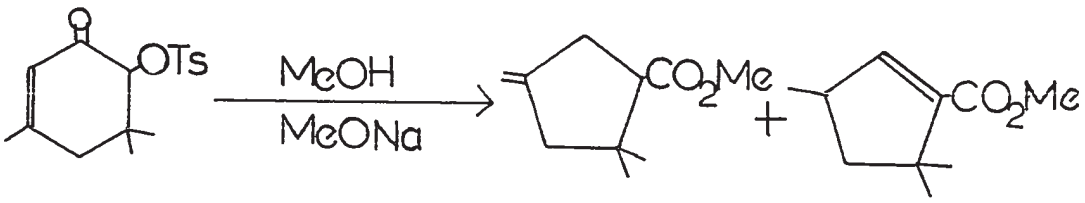


the carbonyl group can be cleaved by base to give the acid 26. The extent to which the above side reactions interfere with the main rearrangement must depend on relative rate ratios. The ratios are a function of several factors, primarily the structure of the haloketone,

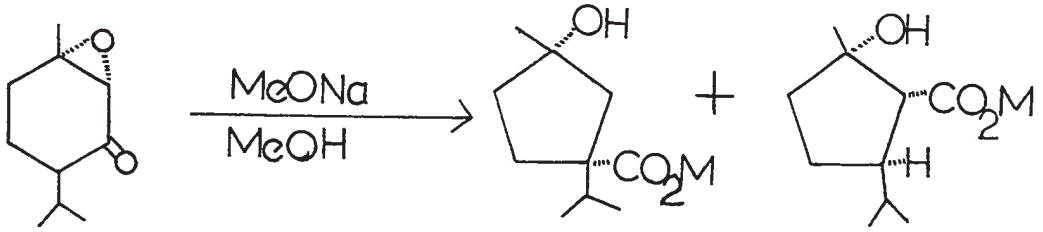


the nature of the halogens, the polarity of the solvents and the nature of the nucleophiles.

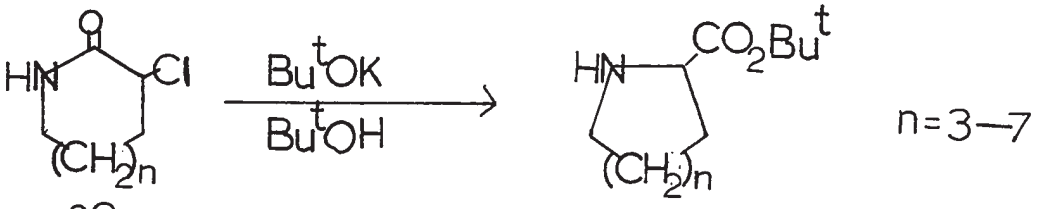
Recent studies have shown that certain carbonyl compounds other than α-haloketones also give rearrangement under suitable conditions. For example, α-tosyloxyketone 27 (17), epoxy ketone 28 (18), α-halolactams 29 (19), α-haloamide 30 (20) and haloketone 31 (21) gave Favorskii products when treated with base. The amino ketone 32 when deaminated in nitrous acid gives acid 33 (22). Therefore, the definition of the Favorskii rearrangement can be extended to α-substituted



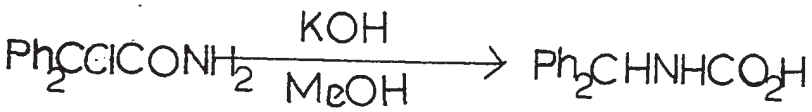
27



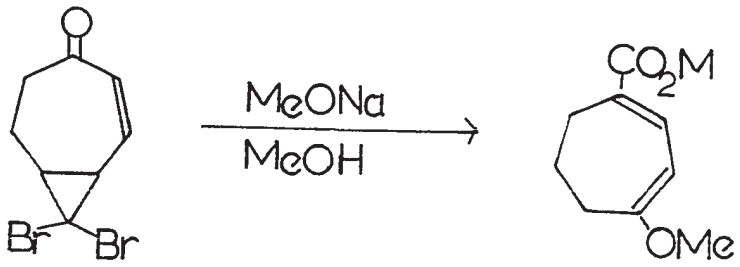
28



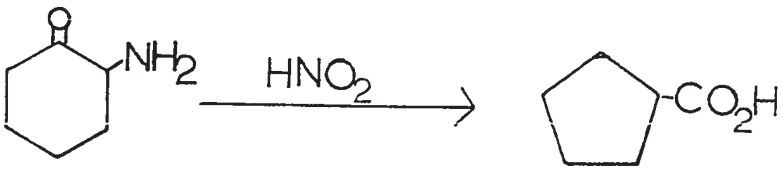
29



30



31



32

carbonyl compounds which give carboxylic derivatives in the presence of base, silver nitrate or other suitable reagents.

(B) The Mechanism of the Favorskii Rearrangement

Several mechanisms have been advanced to account for the rearrangement. The mechanisms can be divided into two categories, namely "unsymmetrical" and "symmetrical" mechanisms. The "unsymmetrical" mechanisms (no symmetrical intermediate is involved) can be subdivided into the epoxy ether, ketene and semibenzilic pathways. The "symmetrical" mechanisms involve a symmetrical intermediate which collapses to the Favorskii product. The symmetrical mechanism can be subdivided into cyclopropanone, oxyallyl and carbonium ion mechanism. Each mechanism will be discussed below with immediate reference to the action of alkoxides on α-monohaloketones, but its extension to other bases or polyhaloketones will be evident.

(1) Unsymmetrical Mechanisms

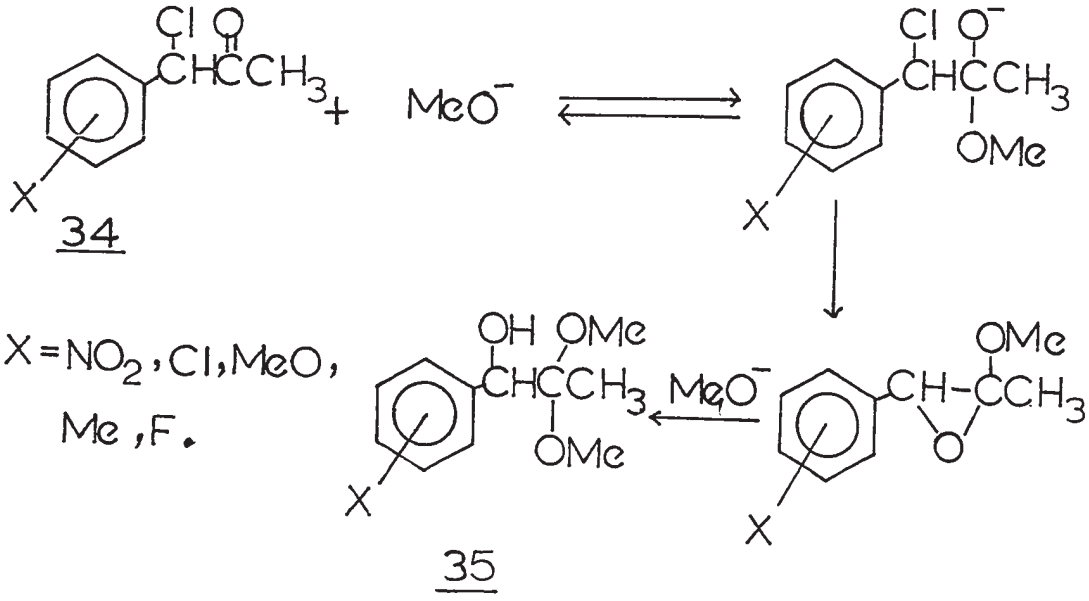
(i) Epoxy Ether Mechanism

The rearrangement was considered by Favorskii (23) to proceed by addition of alkoxide to the carbonyl carbon, with concomitant ejection of halide ion, to produce epoxy ether 22 followed by rearrangement to product. Aston and Greenburg (3) studied the reaction of alkoxide with α-haloketones and favoured the epoxy ether as a common

intermediate for the rearrangement product and the by-product. Since then pure epoxy ethers have been obtained by the action of ethereal alkoxides on α-halopropiophenones and α-halocyclohexyl phenyl ketone. These epoxy ethers reacted rapidly with methanol or methanolic methoxide to form α-hydroxy ketals, and with aqueous acid or base to give α-hydroxy ketones, but no rearrangement to esters was observed (24). The formation of α-hydroxy ketals from epoxy ethers was studied by Bordwell (25) on the chloroketone 34. It was shown that the formation of hydroxy ketal 35 (X=H) was dependent upon base concentration, the lower the base concentration, the higher the yield of hydroxyketal. The amount of hydroxyketal 35 was also related to the variation of substituents on the aryl group. Electron donating groups favour the Favorskii rearrangement and electron withdrawing groups promote the hydroxy ketal formation. Thus the epoxy ether intermediate is not involved in the rearrangement, but plays a central role in the formation of by-products.

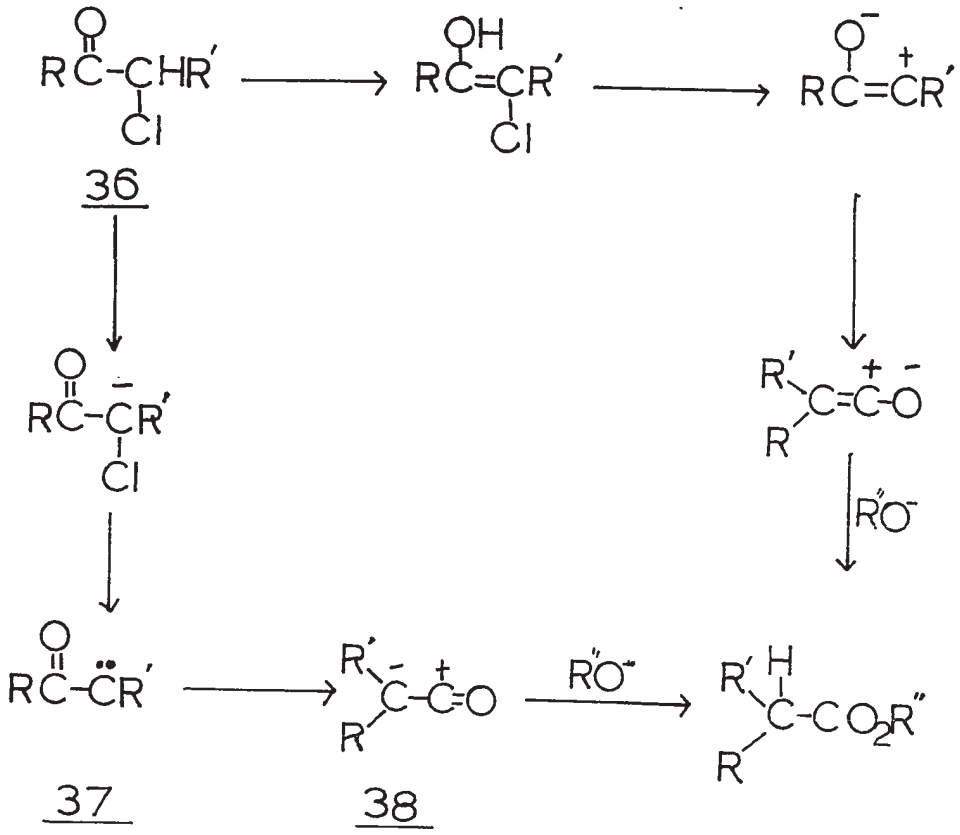
(ii) Ketene Mechanism

Richard suggested the intermediate formation of a ketene by the elimination of hydrogen chloride from the enol of 36 or by 1,1-elimination of hydrogen chloride from 36 to form a ketocarbene, an unknown species at that time, 37, which rearranges to give ketene 38 (26). The ketene finally reacts with base to give ester. There is no evidence for the ketene intermediate and it fails to accommodate those numerous examples of rearrangement that produce esters of the trialkylacetic type which cannot arise from a ketene precursor.


Cl O
CHCCH3+
X
MeO⁻
Cl O⁻
CHCCH3
OMe
X
OH OMe
CHCCH3
OMe
X
MeO⁻
OMe
CH-CCH3
O
X
X=NO2, Cl, MeO, Me, F.

34

35


O
RC-CHR'
Cl
OH
RC=CR'
Cl
O⁻
RC=CR'
R'
C=C-O
R
R''O⁻
O
RC-CR'
Cl
O
RC-CR'
R'
C-C=O
R
R''O⁻
R'
H
C-CO2R''
R

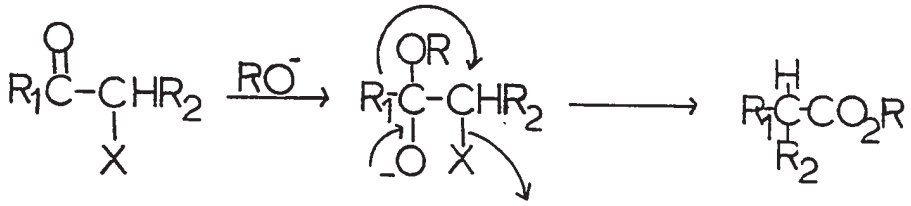
36

37

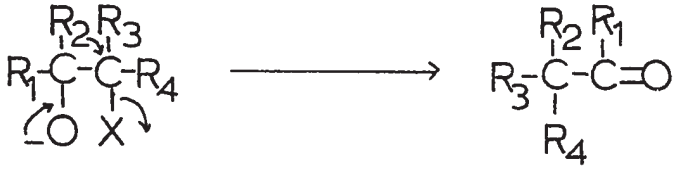
38

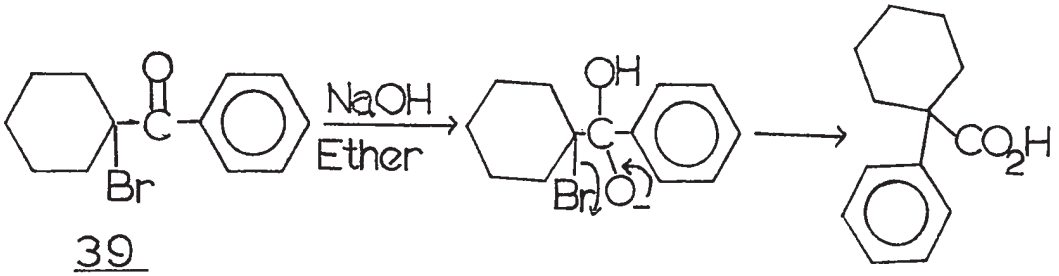
(iii) Semibenzilic Mechanism

The semibenzilic mechanism features addition of alkoxide to the carbonyl carbon atom of the haloketone, followed by a concerted displacement of halide ion by 1,2-migration of an alkyl group with its electron pair. This mechanism has received considerable support for



its close analogy to the well established course of the benzilic acid rearrangement and also to rearrangement of 1,2-halohydrins to ketones. This mechanism was first suggested by Tchoubar and Sackur for the rearrangement of 1-bromocyclohexyl phenyl ketone 39 with powdered

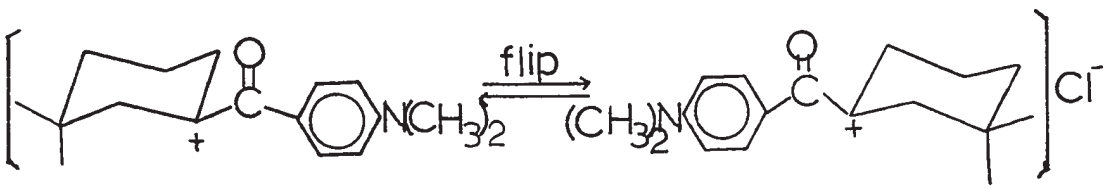




39

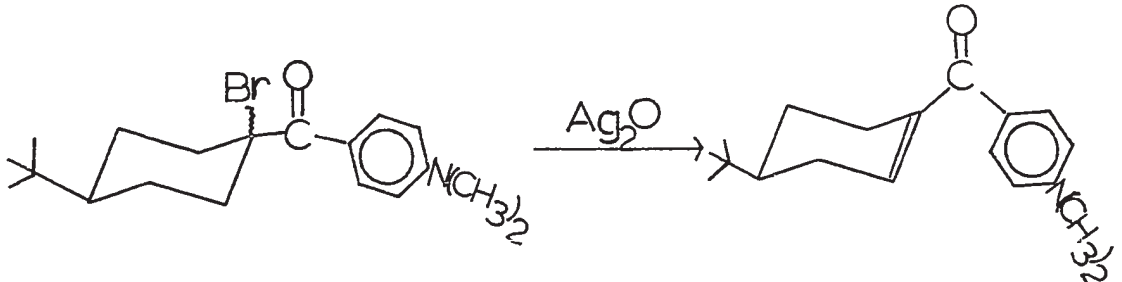
sodium hydroxide in ether (27). This rearrangement of an α-haloketone without an α'-H to give Favorskii acid has often been called the quasi-Favorskii rearrangement. Being essentially an S_N2 displacement, the semibenzilic mechanism requires inversion of the configuration of the halogen-bearing carbon atom.

Inversion during the rearrangement of the chlorocyclohexyl aryl ketones was recently confirmed unambiguously in a rigid system (28). The rearrangement was stereospecific; the cis-bromoketones (40a, 40b) gave only trans-acid (41a, 41b) and vice versa for the trans-bromoketones (42a, 42b). But studies on the related optically active chloroketones 43 and 44 by Smissman in refluxing xylene with powdered sodium hydroxide to give racemic Favorskii products 45 and 46 contradict the stereochemical requirement for an S_N2 type displacement in the rearrangement (29, 30). The result was rationalized by postulating first ionization of the α-haloketones at the catalyst surface with assistance from the adjacent benzoyl π-orbital system to give a solvent separated ion pair 47, a racemized keto carbonium ion, from which racemic acid was obtained. The carbonium ion 47 gained support when more work was done on the bromoketones 40 and 42 with silver oxide in

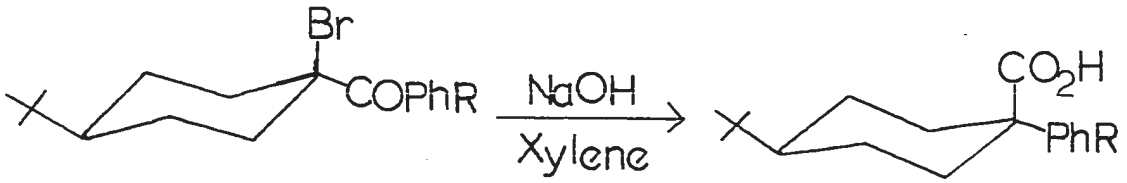


47

dioxane. It was found that the unsubstituted 40a and 40b gave rearrangement acids as major products, but with electron donating substituents on the aryl group gave only elimination products which had not been isolated before (31). It is conceivable that the



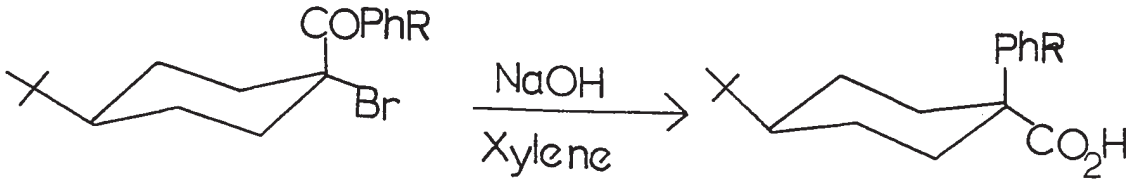
40 or 42



40 41

a. R = H

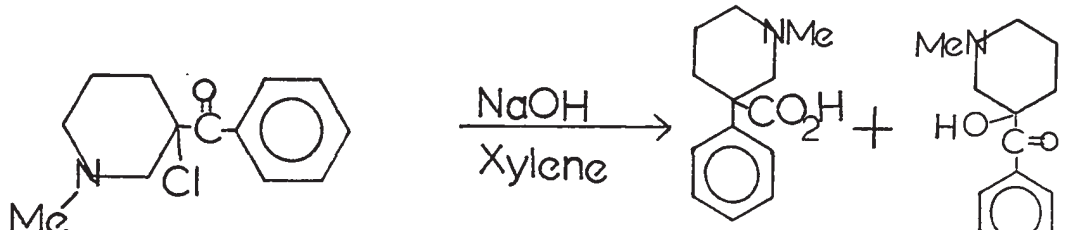
b. R = NMe_2



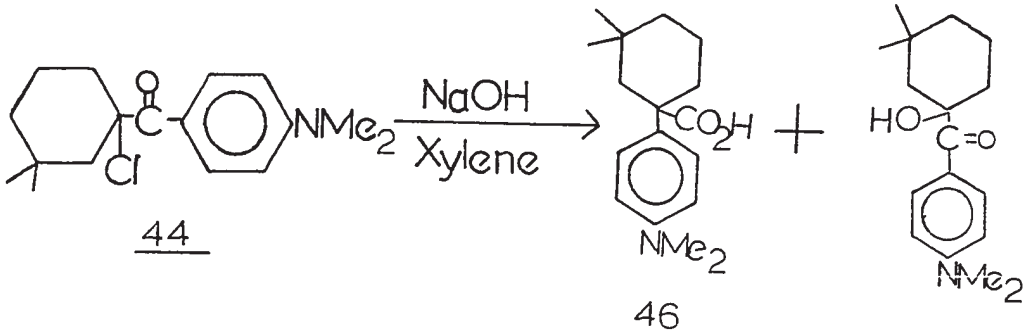
42

a. R = H

b. R = NMe_2

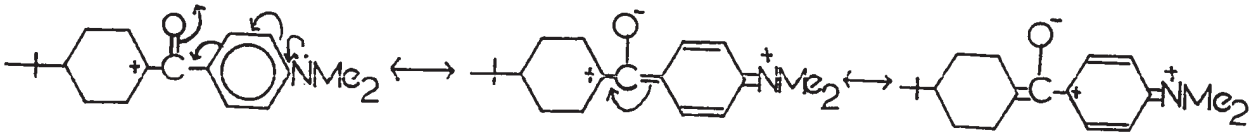


43 45



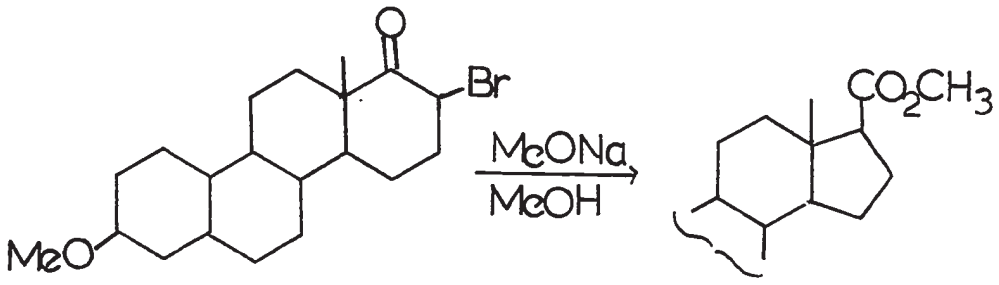
44 46

carbonium ion 47A was formed with the participation of the electron donating group. It is probably the amino substituent that makes the reaction give an "abnormal" result. The semibenzilic mechanism

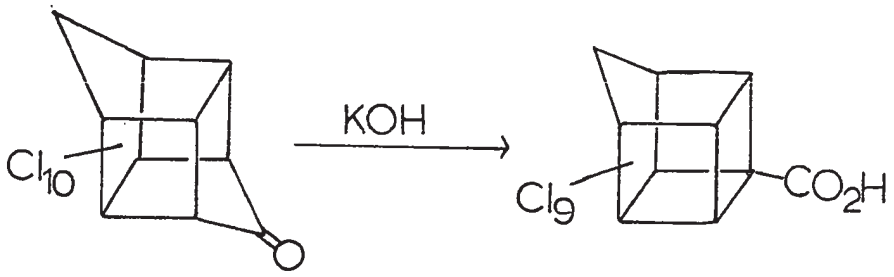


47A

explains nicely those rearrangements occurring in haloketones lacking an α'-hydrogen such as 48 and 49 (32, 33) where it is the only likely mechanism.



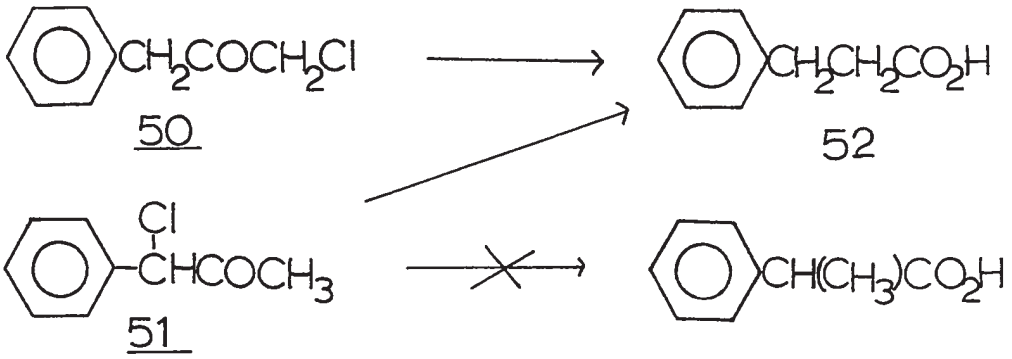
48



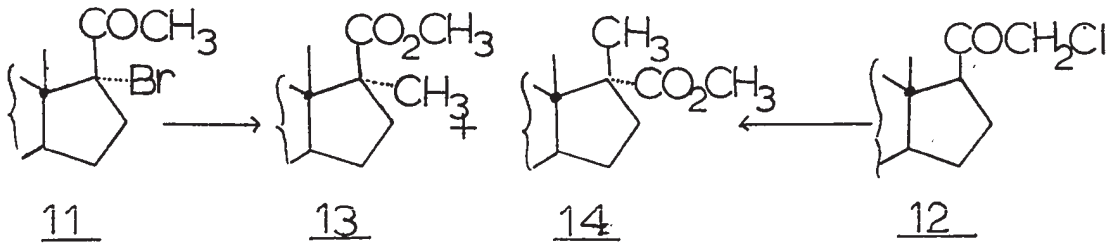
49

(2) Symmetrical Mechanisms

A common feature of each of the unsymmetrical mechanisms is their prediction that the rearrangement product of a given α-haloketone would be different from that derived from its α'-halogenated isomer. For example, 1-chloro-3-phenylacetone 50 should, according to the unsymmetrical mechanisms give rise to 3-phenylpropionic acid, while 1-chloro-1-phenylacetone 51 should rearrange exclusively to 2-phenylpropionic acid. It is found, however, that both haloketones 50 and 51 yield the same acid 52 (8b). The 17α-bromo- and 21-chloro-ketosteroids, 11 and 12 gave a mixture of 17α-and 17β-methyletianic esters



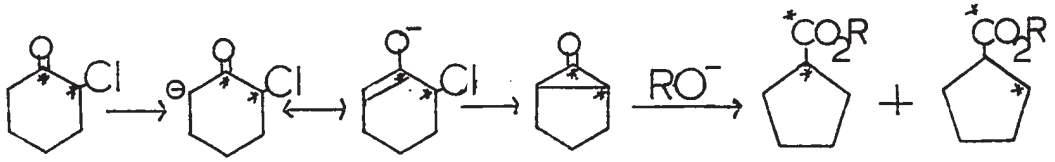
13 and 14 when treated with base (34). Evidently, the unsymmetrical



mechanisms do not fit these results which require the formation of a common symmetrical intermediate from either haloketones. Hence, the symmetrical mechanisms are called for.

(i) Cyclopropanone Mechanism

Loftfield (14) proposed a cyclopropanone as an intermediate in the rearrangement of α-haloketones containing an enolizable α'-hydrogen. The rearrangement involves initial removal of the α'-hydrogen followed by the intermediate formation of a cyclopropanone which is cleaved by base to give rearranged product. The mechanism was studied with the rearrangement of ^{14}C-labeled 2-chlorocyclohexanone, a structure which did not preclude the operation of any of the above



mechanisms. The rearrangement of this chloroketone in dilute ethanolic sodium ethoxide was shown to follow essentially first order kinetics with respect to both haloketone and alkoxide. When 2-chlorocyclohexanone-1,2-^{14}C in which the isotope was equally distributed between carbon atoms 1 and 2, was treated with less than one equivalent of sodium isoamyloxide in isoamyl alcohol, the product was isoamyl cyclopentanecarboxylate accompanied by recovered chloroketone. Careful degradation of both the ester and the haloketone established that the recovered chloroketone had the same isotope distribution as the starting material, and that the radioactive carbon in the ester fraction was distributed 50% on the carbonyl carbon atom, 25% on the ring α-carbon atom, and 25% on the two ring β-carbon atoms. The findings clearly excluded any reversible halogen migration from to α' before rearrangement, and necessarily ruled out significant participation by any of the

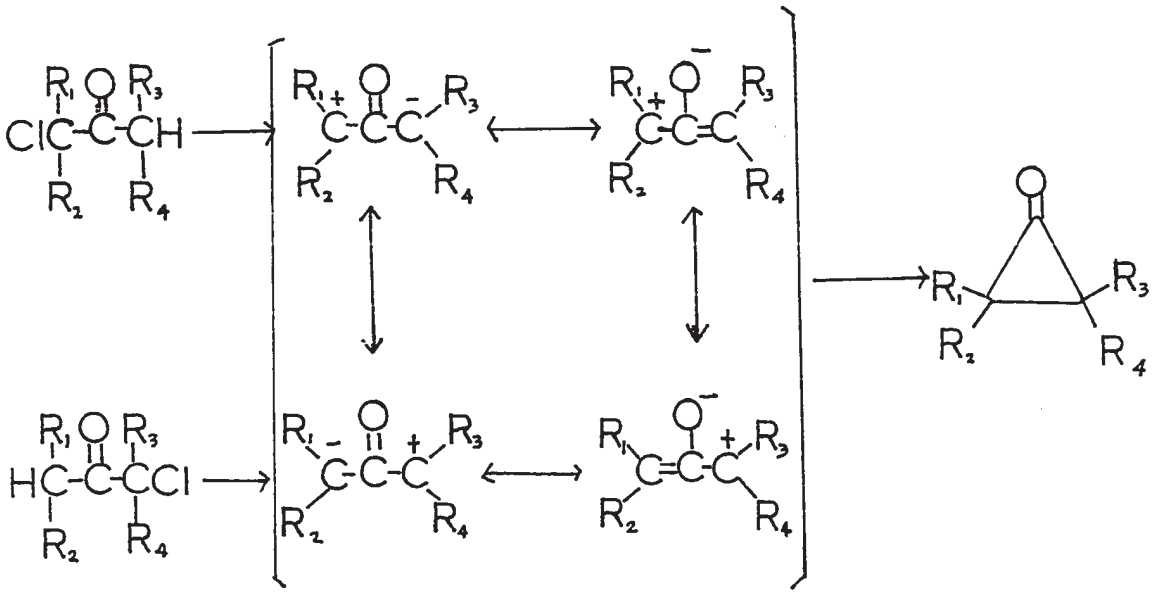
unsymmetrical mechanisms. The data are compatible, however, with an intermediate in which, by reason of symmetry, the α-and α'-carbon atoms of the cyclohexanone are formally equivalent. This criterion is satisfied by a mechanism that involves a cyclopropanone or its equivalent.

(ii) Oxyallyl Mechanism

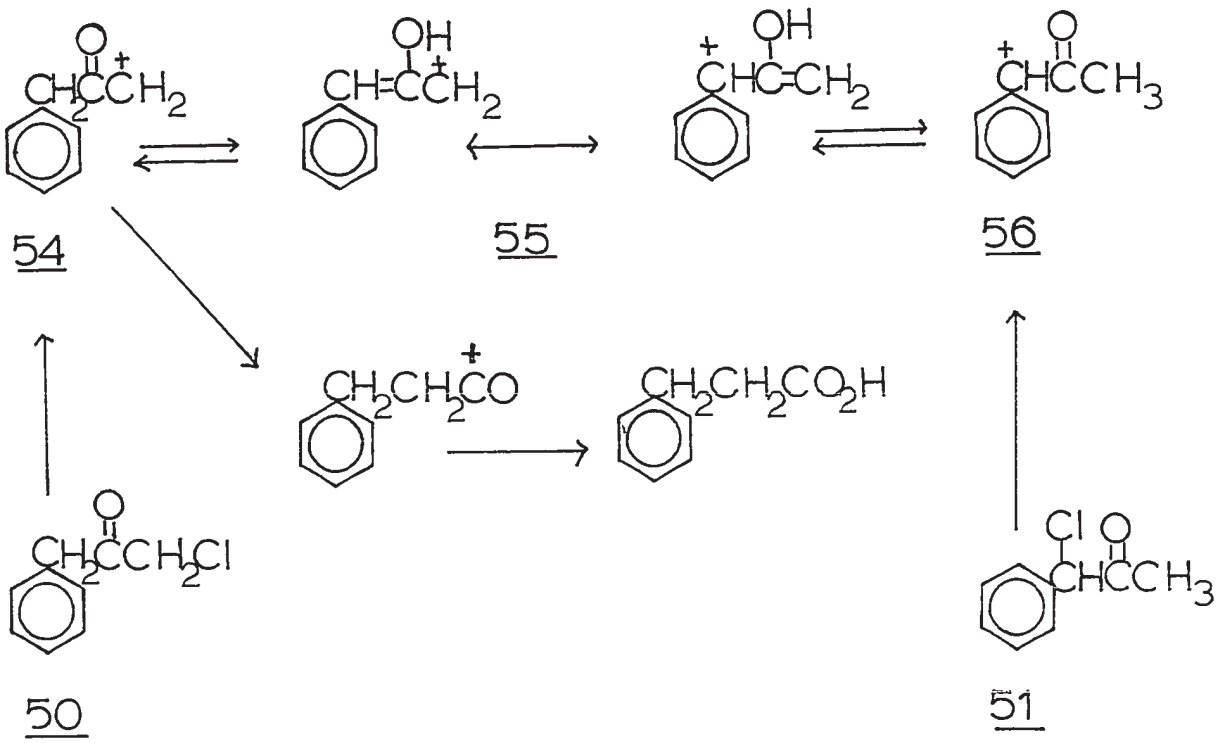
In order to explain the formation of the same rearrangement product from two isomeric α-haloketones, Aston (35) had earlier postulated a common delocalized intermediate 53 which was formed by abstraction of the α'-hydrogen and followed by ionization of the halide ion. The intermediates were stabilized by resonance. The delocalized intermediate, zwitterion or oxyallyl, then cyclized to the cyclopropanone from which the Favorskii product was obtained. The oxyallyl mechanism is entirely in harmony with the experimental findings of Loftfield.

(iii) Carbonium Ion Mechanism

MePhee and Klingsburg (8) suggested a carbonium ion mechanism to explain the rearrangement of 1-chloro-phenylacetone 51 and 1-chloro-3-phenyl acetone 50 to 3-phenylpropionic acid. The haloketone undergoes unimolecular dissociation to a carbonium ion 54 which can tautomerize through an enol allylic carbonium ion 55 to the isomeric carbonium ion 56. The delocalized enol allylic carbonium ion 55 is responsible for rearrangement of isomeric haloketones to same acid. The carbonium ion mechanism lacked analogy at that time and had the drawback that no key role was assigned to the base which is a normal requisite of the



53



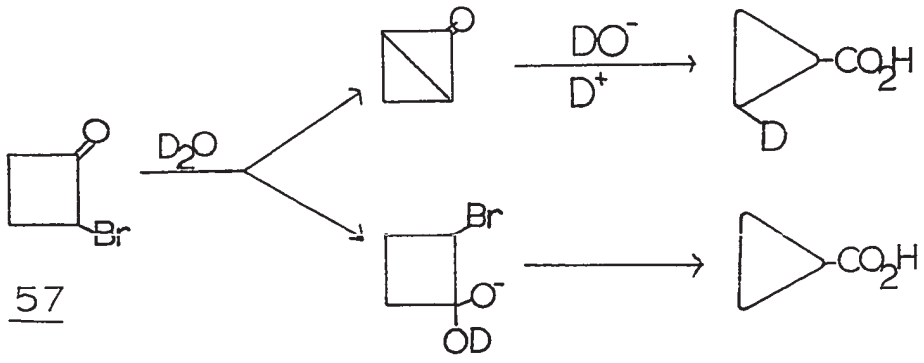
54 55 56

50 51

Favorskii rearrangement. The enol allylic ion 55 mechanism gained support from Bordwell's systematic studies on the 1-chlorophenylacetone 51 and 1-chloro-3-phenylacetone 50 (36). The enol allylic ion was formed first by abstraction of the α'-hydrogen followed by ionization of the halide. It has turned out that the enol allylic ion is the intermediate for alkoxy ketone formation and not for the rearrangement product. Further details of the enol allylic ion will be discussed in a later section.

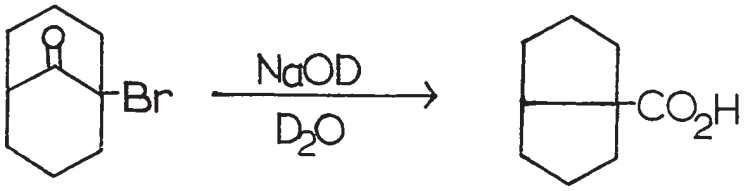
(3) Evidence for the Mechanisms

Of all the mechanisms discussed above only the semibenzilic, cyclopropanone and oxyallyl mechanisms have received experimental support. For haloketones without an α'-hydrogen the semibenzilic mechanism is the only reasonable pathway for the rearrangement. The evidence for the semibenzilic mechanism was the stereochemical result on the 4-t-butyl-1-bromocyclohexyl phenyl ketones 40 and 42. The contradictory result from 43 and 44 was clarified by the recent work on 40 and 42 (31). Other experimental support for the semibenzilic mechanism comes from the rearrangement of the α-bromocyclobutanone 57 in deuterium oxide or silver nitrate in deuterium oxide to give non-deuterated product. In this case the semibenzilic and cyclopropanone mechanisms are possible a priori. The result is consistent with



57

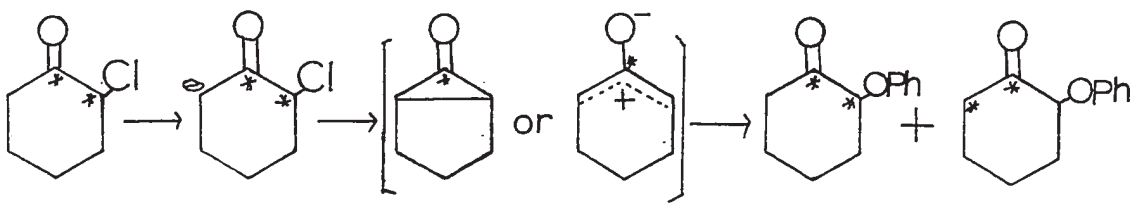
the semibenzilic mechanism, for the cyclopropanone mechanism would give monodeuterated product provided that there is no deuterium exchange before rearrangement (37). Recently, Warnhoff, Wong and Tai studied the rearrangement of the bicyclic haloketone 58 in deuterated solvents. Little or no deuterium was incorporated in the product 59 when sodium deuteroxide and potassium t-butoxide were used as base. The result



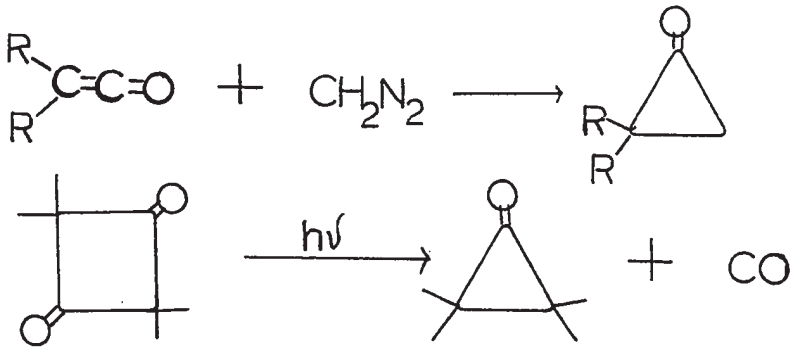
58 59

demonstrated that the semibenzilic mechanism was in operation; the lack of acidity of the α'-hydrogen at the bridgehead of the haloketone favoured the semibenzilic mechanism (38).

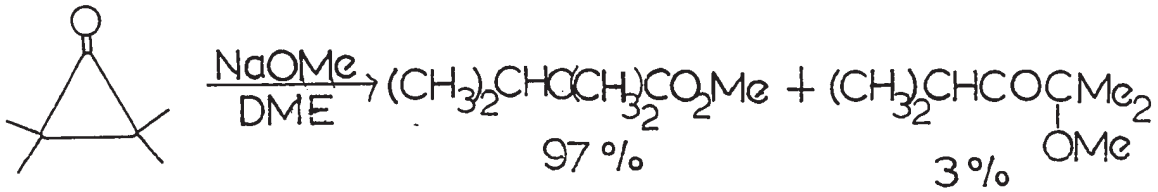
The first piece of experimental evidence supporting the cyclopropanone mechanism was the ^{14}C-label work on 2-chlorocyclohexanone by Loftfield. In the related study by Smith and Gonzalez (39) on 2-chlorocyclohexanone-1,2-^{14}C with sodium phenoxide only substitution product was isolated. The result showed that a symmetrical intermediate was involved for the formation of the substitution product. The C-1 contains 50% of the initial activity, C-2 and C-6 each contains 25%

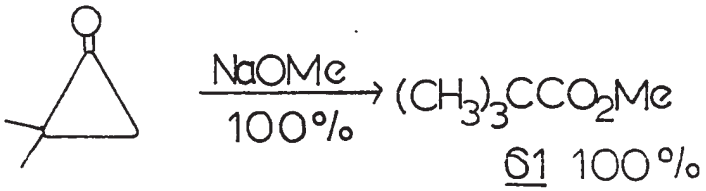


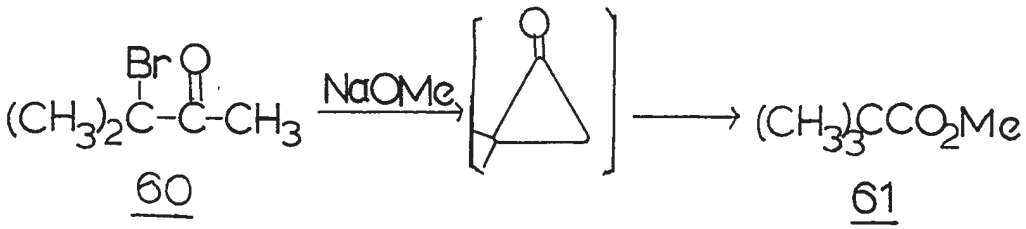
of the activity as required by a symmetrical intermediate. Furthermore, the 2-chloro-6,6-dimethylcyclohexanone fails to react with sodium phenoxide as required by the cyclopropanone mechanism. Recently cyclopropanones have been obtained at low temperature and their structures have been established by spectroscopic methods. The cyclopropanones are readily prepared by reaction of a diazo compound with a ketene (40) or the photoelimination of carbon monoxide from cyclobutanediones (41). It is noteworthy that cyclopropanone has a rather short C=O bond length (1.18 Å) and long C_2C_3 bond length (1.58 Å) (42).



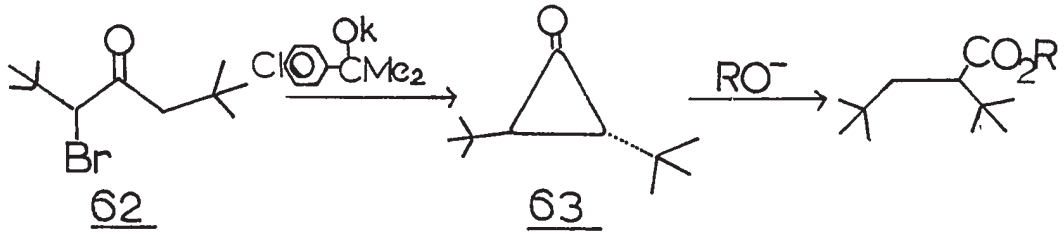
The strained carbonyl group and the weak C_2C_3 bond of cyclopropanone imply high reactivity of the compound. The chemistry of cyclopropanone has been well studied by Turro (43) and will not be discussed here. The reaction of alkoxides with cyclopropanones gives the expected Favorskii rearrangement products in high yields (44). Strong indication of a cyclopropanone intermediate in the rearrangement of 3-bromo-3-methyl-2-butanone 60 with sodium methoxide come from the exclusive formation of methyl trimethylacetate 61 which is also found exclusively from the reaction of 2,2-dimethylcyclopropanone with the same base. More recently a stable substituted cyclopropanone was isolated under Favorskii conditions (45). The reaction of α-bromodineopentyl ketone 62 with the potassium salt of p-chlorophenyl

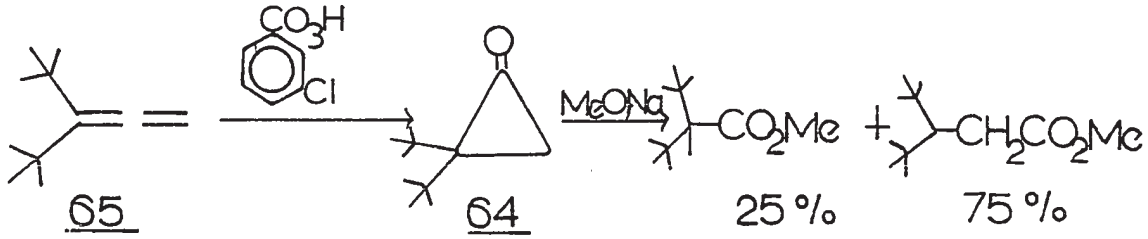






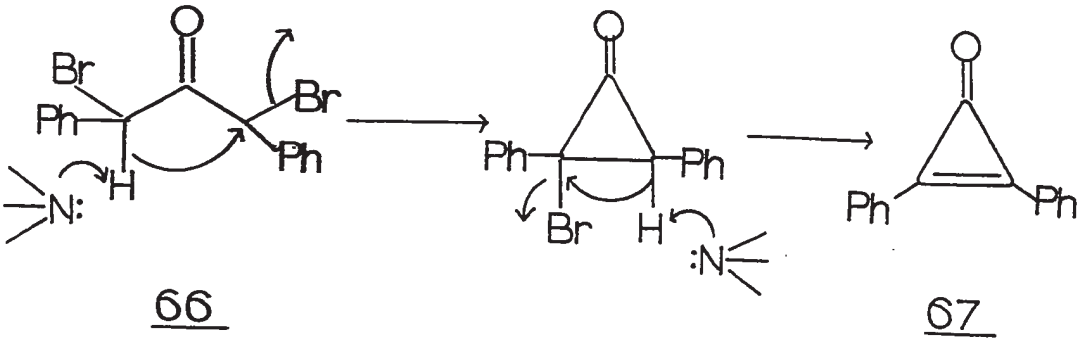
dimethylcarbinol gave trans-2,3-di-t-butylcyclopropanone 63, mp. 24-26°. Further treatment of 63 with the alkoxide formed the Favorskii product (46). Another stable substituted cyclopropanone 64 was isolated from expoxidation of the allene 65, it is so stable that it required two days refluxing in methanolic sodium methoxide to complete



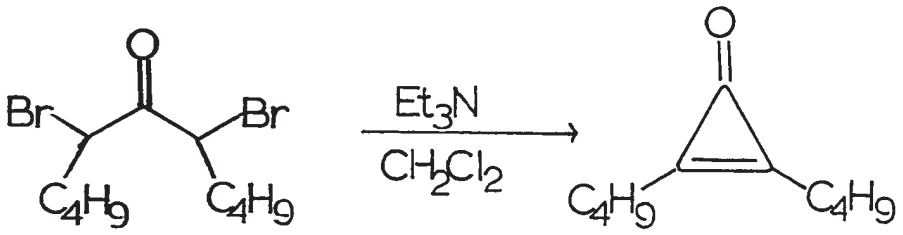


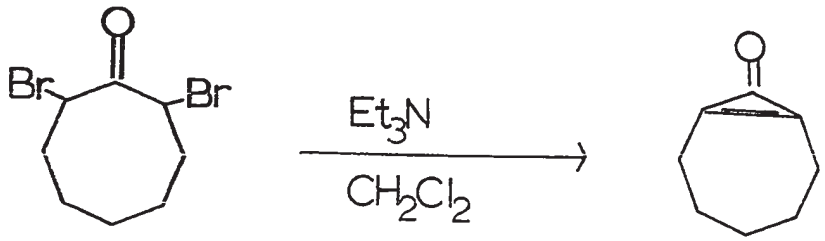
the Favorskii rearrangement (47)! Some more evidence of a cyclopropanone intermediate in the Favorskii rearrangement is found in what amounts to an interception of such a species, and its conversion to an isolable product without destruction of the three-membered ring.

Breslow and co-workers treated a mixture of α,α'-dibromodibenzyl ketone 66 with triethylamine in methylene chloride at 25°, and obtained diphenylcyclopropenone 67 as the product. Similar reactions were carried out with aliphatic and cyclic dibromoketones (48). These reactions unequivocally demonstrate that the cyclopropanone can be an intermediate in the Favorskii rearrangement.

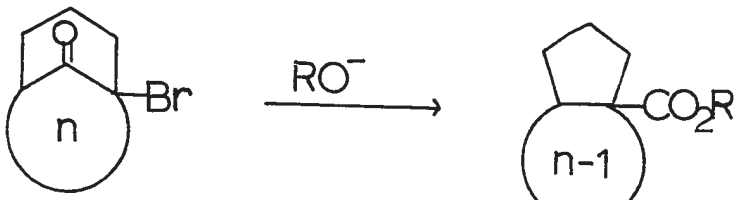


66 67





Warnhoff, Wong and Tai (38) shed further light on the factors that control the mechanism of the rearrangement. They considered that as haloketones with an enolizable α'-hydrogen become less acidic there will be a change in mechanism from cyclopropanone to semibenzilic mechanism. The acidity of the α'-hydrogen is increased by increasing the ring size of the bicyclic bromoketone 58(n). The mechanisms are



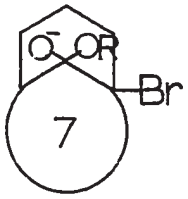
58(n)

59(n)

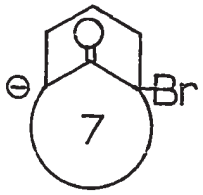
n = 6,7,8.

differentiated by deuterium incorporation studies and optical activity tests for symmetrization during rearrangement. A semibenzilic mechanism requires retention of optical activity and no deuterium incorporation in the product 59(n). The cyclopropanone mechanism requires both deuterium incorporation in the product 59(n) and racemization of optically active acid. The rearrangement of 58(7) with deuterated sodium hydroxide proceeds through the semibenzilic path but with potassium t-butoxide a cyclopropanone path is followed. The rearrangement of the optically active bromoketone 58(8) with deuterated sodium hydroxide occurs with 96% racemization of the product and 0.90 deuterium atom per molecule incorporation. The result is consistent with the cyclopropanone mechanism. It is noteworthy that the change in mechanism in 58(7) with potassium t-butoxide may be due to a steric

effect in the attack of the carbonyl by the nucleophiles in the semi-benzilic process. The anion 58A may not exist in high enough concentration



58A

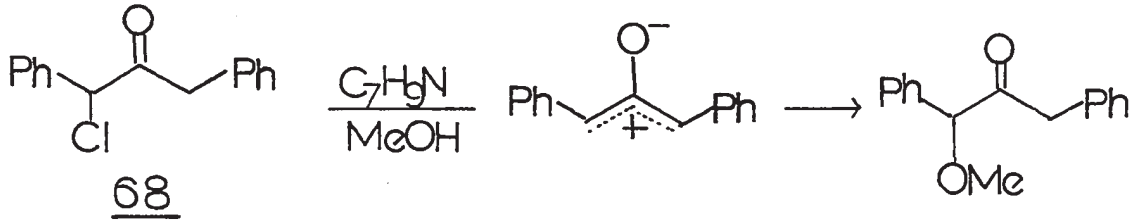


58C

in comparison to the carbanion 58C if formed to give rearrangement product. The steric effect may not be important, for 58(6) did rearrange by the semibenzilic mechanism. These findings clearly demonstrate that the mechanism of the rearrangement of the bicyclic bromoketones is dependent on the acidity of the α'-hydrogen and the basicity of the base. The details of the mechanism will be discussed later.

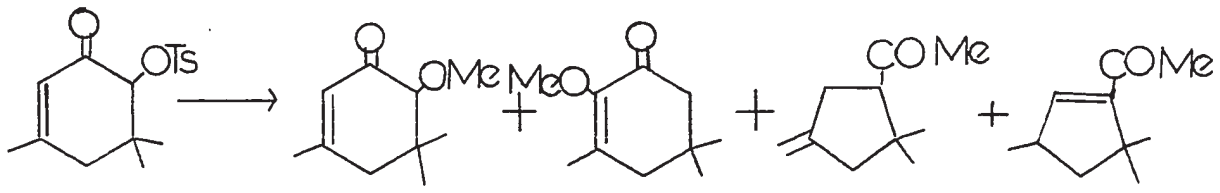
The oxyallyl mechanism was first proposed to explain the rearrangement of isomeric haloketones to give the same product. The experimental findings for the cyclopropanone mechanism are also consistent with the oxyallyl mechanism and therefore the findings of Loftfield, Smith and Warnhoff can also be explained in terms of the oxyallyl mechanism. The feasibility of the direct formation of a cyclopropanone in α-chlorocyclohexanone was questioned on steric grounds, and the formation of oxyallyl from an enolate ion was calculated to increase the conjugation energy by 14 kcal (49). The collapse of the zwitterion to cyclopropanone was estimated to be an exothermic process. On the other hand, extended Huckel calculations also showed that the oxyallyl was more stable than cyclopropanone by

23 kcal/mole. There is no easy way that the oxyallyl ion can rearrange directly to the rearranged Favorskii acid. It has to go through the cyclopropanone and then to final product. For this reason, it is very difficult to differentiate between the oxyallyl and cyclopropanone mechanism. The isolation of the cyclopropanone 63 does not necessarily mean that the rearrangement does not involve oxyallyl; the oxyallyl could be the precursor of the cyclopropanone. Therefore, any experimental evidence for cyclopropanone might well fit the oxyallyl mechanism. Before the cyclopropanone was isolated and well characterized, there were several pieces of evidence that supported the oxyallyl mechanism. The reaction of α-chlorodibenzyl ketone 68 with methanolic 2,6-lutidine gave α-methoxydibenzyl ketone (50). The reaction was first order in both 2,6-lutidine and chloroketone. Later the oxyallyl mechanism was disproved by Bordwell. The α-methoxydibenzyl ketone was shown to come from an enol allylic chloride rather than from an oxyallyl (36).



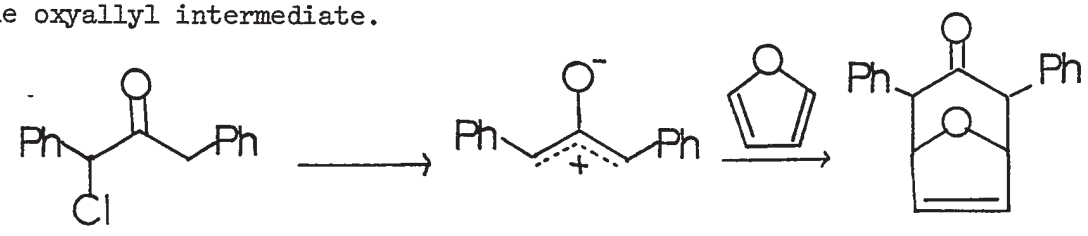
68

The reaction of 6-tosyloxyisophorone 27 with sodium methoxide to afford the substitution and Favorskii products is consistent with the intervention of the oxyallyl intermediate (17). Other evidence for oxyallyl

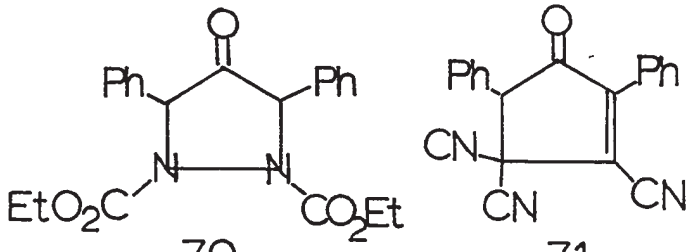


27

intermediate was the isolation of an adduct 69 from the reaction of α-chlorodibenzyl ketone in furan (51). Similar adducts 70 and 71 were isolated by Cookson (52) from the reaction of di-(α-bromobenzyl) ketone with sodium iodide in acetone containing azodicarboxylate or tetracyanoethylene. The above adduct evidence was consistent with the oxyallyl intermediate.



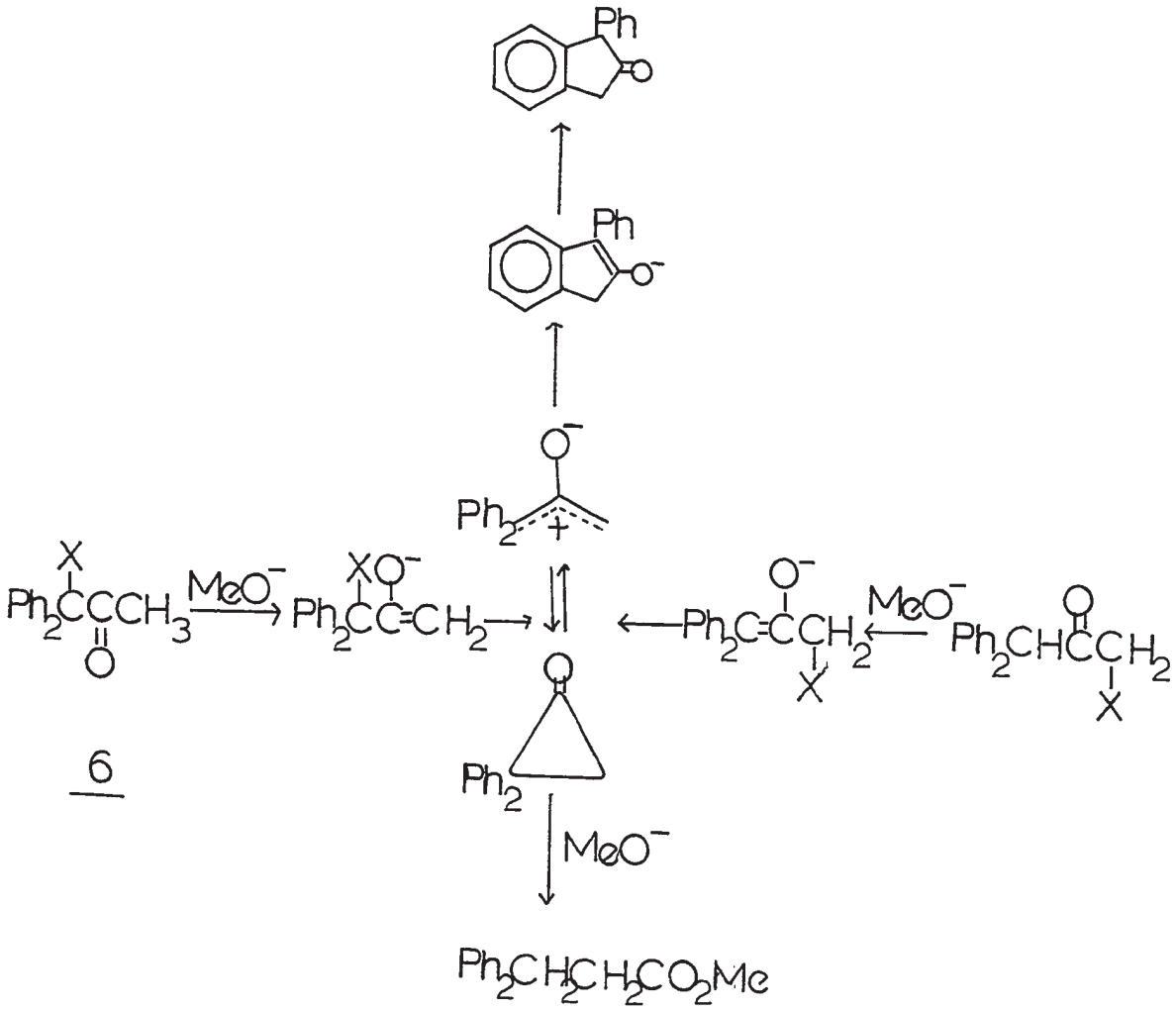
68 69

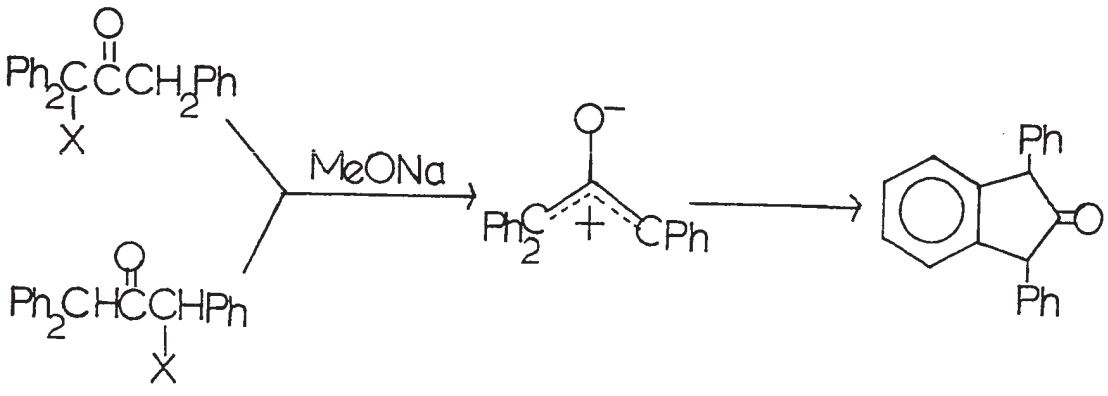


70 71

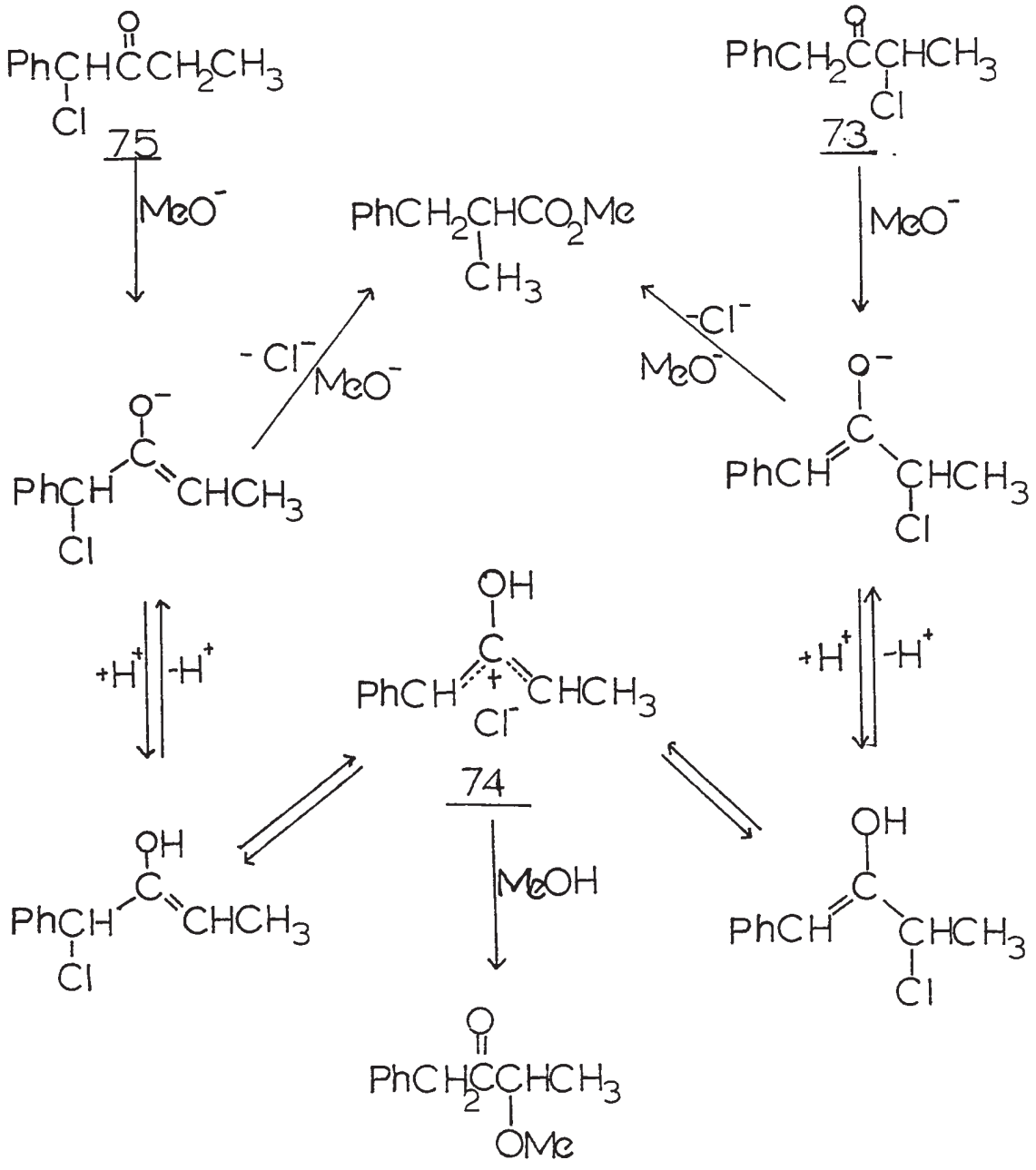
The latest strong evidence for an oxyallyl intermediate came from the isolation of 1-phenyl- and 1,3-diphenyl-2-indanone from the rearrangement of diphenyl-α-halopropanones and triphenyl-α-halopropanones. The 2-indanone was formed by the internal trapping of the oxyallyl by electrophilic attack on one of the benzene rings. The exclusive formation of the 1,3-diphenyl-2-indanone from triphenyl-α-halopropanones might indicate that the equilibrium between the oxyallyl and cyclopropanone strongly favoured the oxyallyl intermediate (53).

The isolation of an adduct from Favorskii rearrangement conditions is consistent with the oxyallyl mechanism as well as the cyclopropanone mechanism because cyclopropanones have been shown to


Ph
Ph
O⁻
Ph2
X
Ph2CCCH3
O
MeO⁻
XO⁻
Ph2CC=CH2
Ph2C=CCH2
X
MeO⁻
Ph2CHCCH2
X
6
Ph2
MeO⁻
Ph2CH2CH2CO2Me

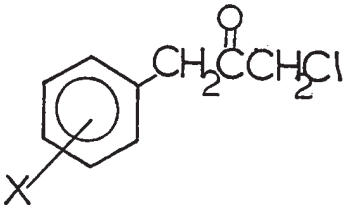

Ph2CCCH2Ph
X
Ph2CHCCHPh
X
MeONa
O⁻
Ph2
CPh
Ph
Ph

undergo cycloaddition with furan. The distinction between the oxyallyl and cyclopropanone cannot be made from kinetic studies (54). On the basis of the weak C_2-C_3 bond in cyclopropanone and by analogy to the opening of the cyclopropyl cation, the cyclopropanone has probably assumed a large degree of oxyallyl character in the transition state for cycloaddition (54). This point awaits further experimentation. The oxyallyl is 23 kcal/mole more stable than the cyclopropanone by extended Huckel calculation and there is no activation energy for the conversion of cyclopropanone to oxyallyl (55). In view of the fact that cyclopropanones do exist, the approximation in the calculation might not be correct. Furthermore, the evidence for the oxyallyl mechanism from the isolation of methoxyketone was refuted by the recent work of Bordwell (36) on 3-chloro-1-phenylbutan-2-one 73 and α-chloro-dibenzyl ketone 68. Both ketones 73 and 68 underwent acid and base catalyzed solvolysis to give methoxy ketones. The methoxy ketones were shown to come from an enol allylic chloride 74 instead of from an oxyallyl. The conclusion was drawn from the close similarity of the product distribution in the basic media from 73 or 68 with that observed for solvolysis in acidic media. Since the solvolyses in acidic media no doubt proceed by an enol mechanism, this mechanism is apparently operative in basic media also. With a low concentration of methoxide ion the enol allylic chloride was in higher concentration than the enolate. Further work on 1-chloro-1-phenylbutan-3-one 75 showed that it gave the same product ratio as its isomer 73. This may show that the chloroketone 73 and 75 both went through a common intermediate 74, an enol carbonium ion pair to give the methoxy ketone. Hence, in any event, the formation of the α-methoxyketone can no longer be construed

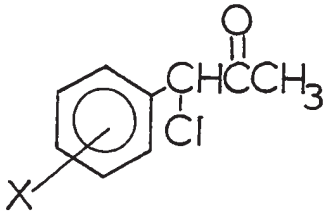

PhCHClCCH2CH3
O
75
MeO-
PhCH2CHCO2Me
CH3
PhCH2CCHCH3
O
Cl
73
MeO-
-Cl-
MeO-
-Cl-
MeO-
PhCH
C
CHCH3
O-
Cl
+H+
-H+
OH
PhCH
C
CHCH3
Cl-
74
MeOH
PhCH2CCHCH3
O
OMe

as strong evidence for an oxyallyl intermediate. The product forming steps are the loss of halide ion from the enolate ion via a dipolar-ion-like transition state to form probably a cyclopropanone which gives the rearranged product.

The nature of halide release in α-chlorobenzylmethyl ketone 34 and 3-chloro-1-phenyl acetone 50A was well studied (25). It was found that both chloroketones involved reversible carbanion formation and showed positive salt effects. The Hammett ρ for the rearrangement of 4-substituted aryl analogs was found to be -2.37 and -4.47 respectively. The higher negative value ρ for 50A showed that the chloride ion loss

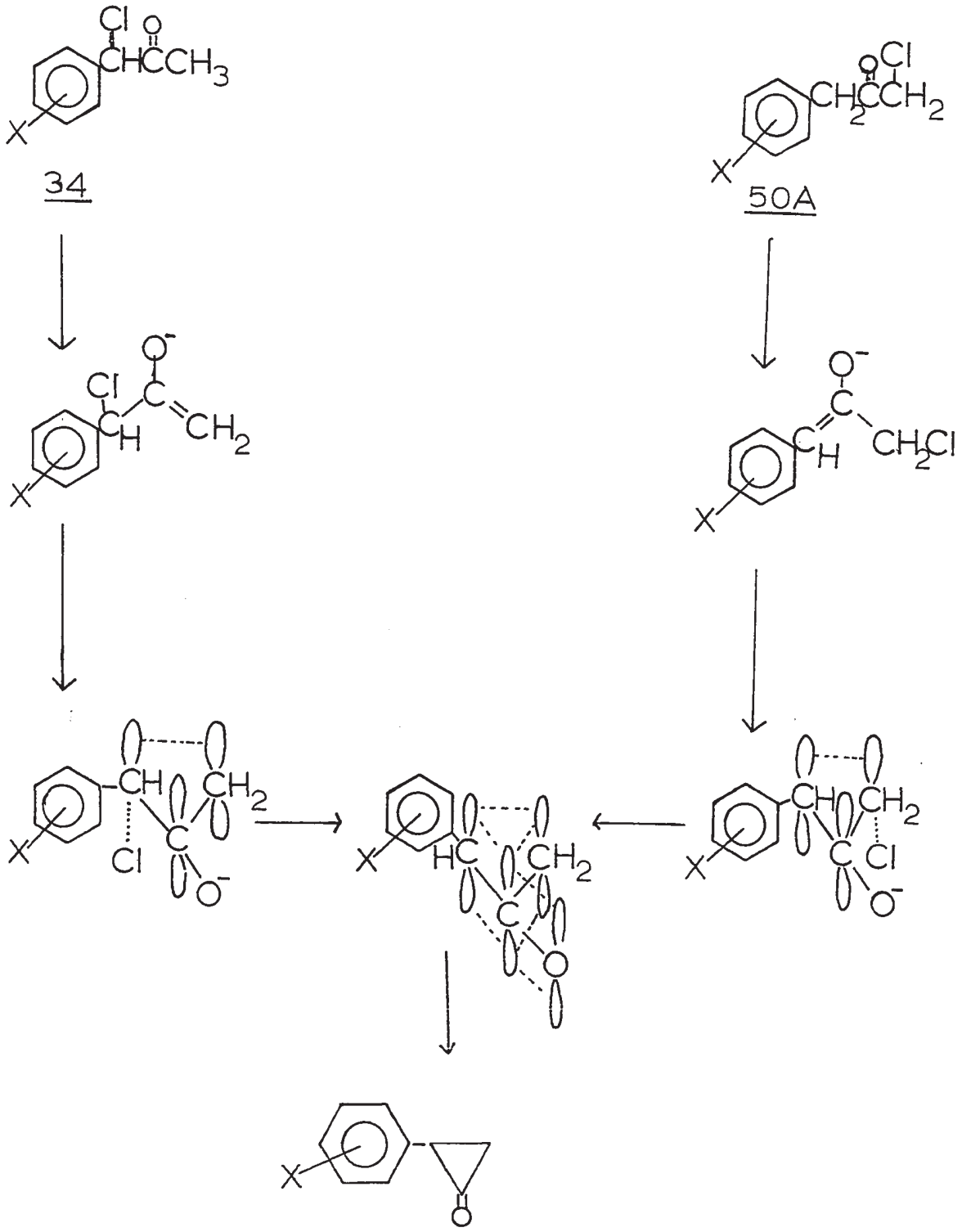


50A



34

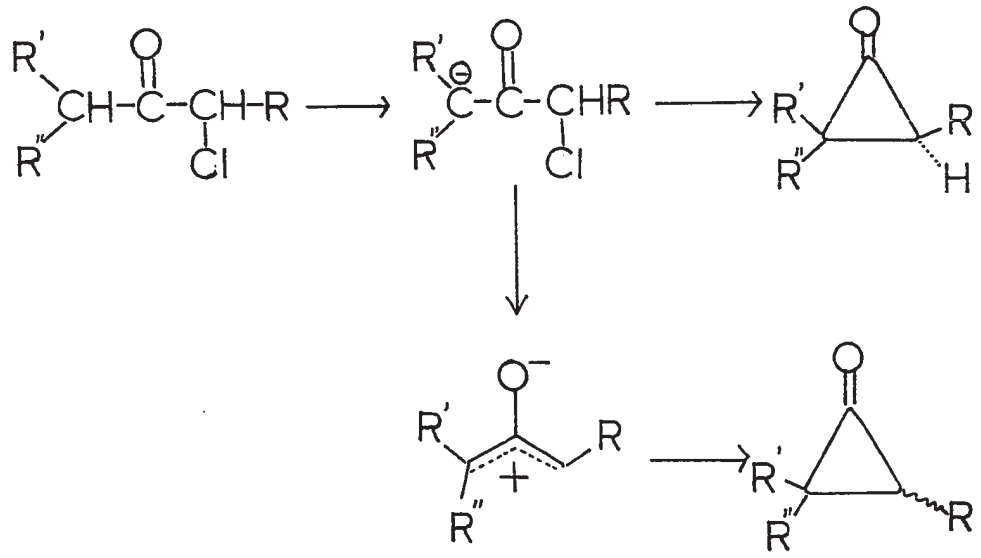
from the anion 50A is even more favored by the presence of electron-donating substituents than is true for anion 34. An appreciable positive charge was being developed on the carbon holding the chloride in anion 50A as ionization occurred, and that this positive charge was being effectively delocalized by electron releasing substituents. There was a large Br/Cl rate ratio for both the haloketones 50A and 34 indicating that the C-X bond was extensively broken in the transition state. The results imply that a high degree of ionic character in the C-Cl bond at the transition state. The ionization of the halogen in the rate determining step, is aided by participation from the parallel p orbitals of the enolate ion. The


34
50A

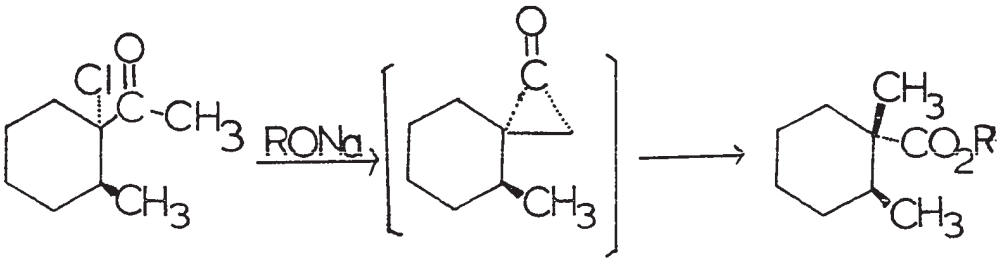
formation of the C-C bond is not complete at the transition state.

From the above result whether the dipolar-ion-like transition state goes to oxyallyl with complete loss of halide or whether it cyclizes to cyclopropanone is still an unanswered question. The large negative ρ value provides strong evidence against an internal S_N2 type displacement of halide ion in the rearrangement. It is worthy pointing out that there is a change in mechanistic pathway between haloketone 50 and its methyl substituted analog 73. There is an increase of 220-fold in the rate for 73. The deuterium exchange prior to rearrangement and the Br/Cl leaving group effect are absent in 73. There is a change in ρ value from -5.0 in 50 to +1.4 in 73. The products from 73 are base concentration dependent and appreciable amounts of α-methoxy ketone by-product are formed. The results showed a change in mechanism in the two chloroketones, the halide release is the rate determining step in 50 and α'-proton abstraction is the rate determining step in 73.

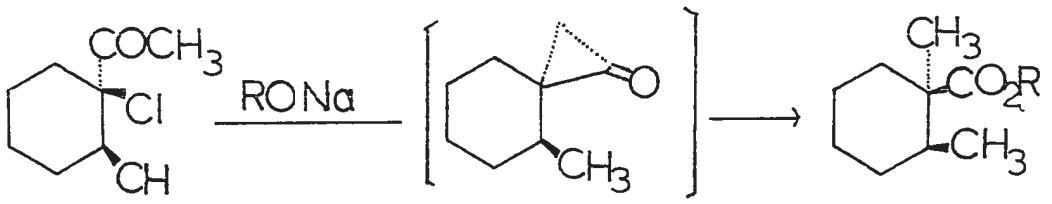
Even though both the cyclopropanone and the oxyallyl mechanisms explain most of the rearrangements well, they differ in stereochemical implications in the rearranged product of acyclic haloketone. The synchronous cyclopropanone formation from the α'-enolate entails steric inversion at the halogen-bearing carbon. However, the formation of a cyclopropanone through a discrete oxyallyl of high resonance energy would predict racemization of the α-carbon atom. Since the oxyallyl is planer, the stereochemistry at the α-carbon will be lost.



A clear cut synchronous stereospecific rearrangement of acyclic haloketones 19 and 76 with sodium benzyloxide in benzyl ether to give 20 and 21 respectively was observed by Stork and Borowitz (56). These results are consistent with cyclopropanone mechanism and suggest



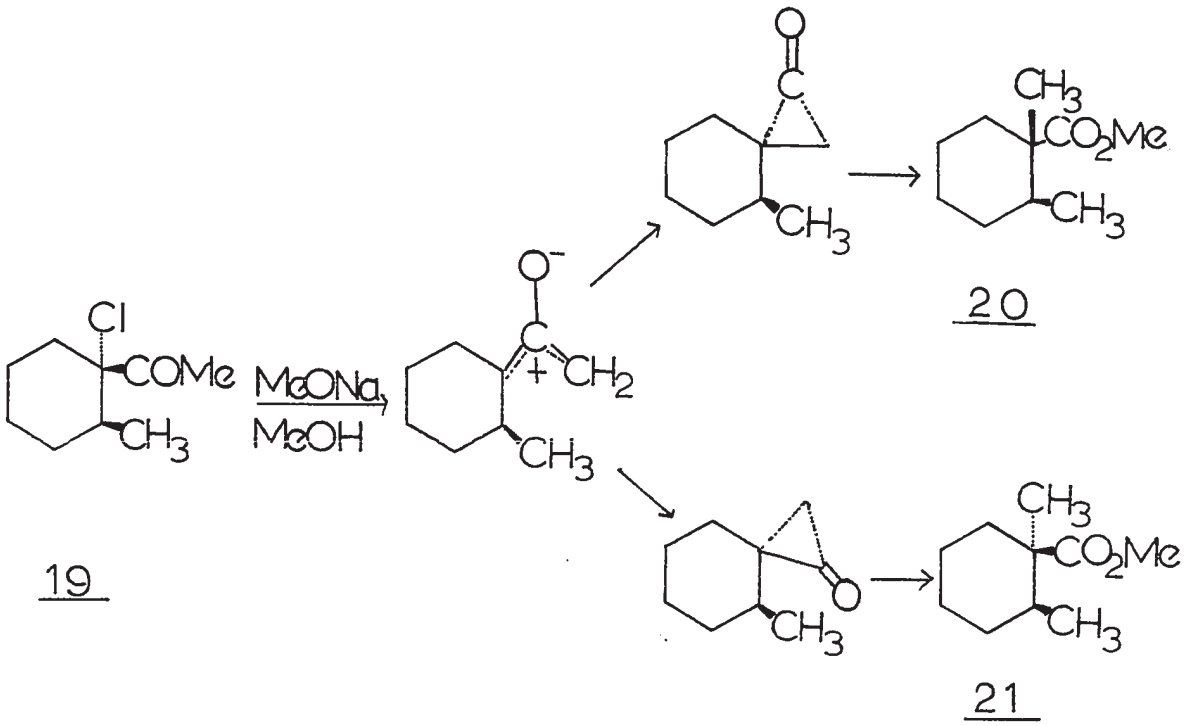
19 R = $PhCH_2$ 20



76 R = $PhCH_2$ 21

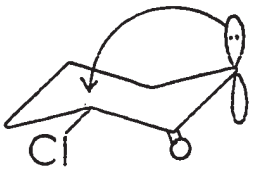
that the cyclopropanone formation and halide release are synchronous or very nearly so. The rearrangement of 19 becomes non-stereospecific in methanol; this might imply an oxyallyl mechanism is followed in the more polar solvents.

There has been some speculation about stereoelectronic effects

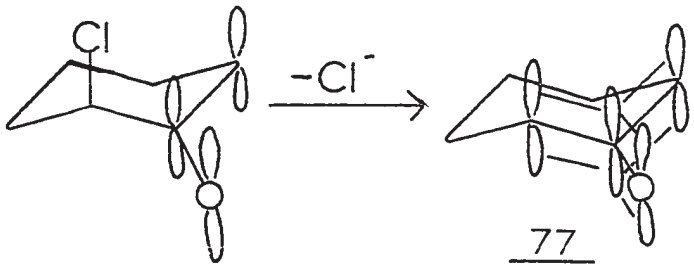


19

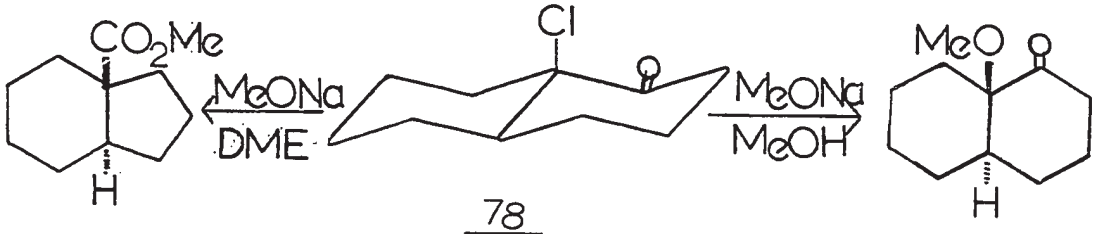
and solvent effects on the formation of synchronous cyclopropanone or oxyallyl. House (57) postulated that in the α-halocyclohexanone system an intramolecular S_N2 displacement to form a cyclopropanone with inversion of configuration at α-carbon atom will be favoured by an equatorial halogen atom 82, whereas in formation of oxyallyl the axial atom will be favoured in order to maintain continuous π orbital overlap during ionization as in 77. The ionization process should be enhanced not only by an increase in solvent polarity but also by the presence of an axial halogen. The postulate does not agree with the rearrangement of 9-chloro-trans-1-decalone 78 and 9-chloro-cis-1-decalone 79 in non-polar and polar solvents. In polar solvent the haloketones give only substitution products but in non-polar solvent stereospecific rearrangement products are obtained (58). The chlorine in 78 is axial whereas in 79 it is axial and equatorial in equilibrium. The equatorial conformation of 79 would be more favourable for the internal displacement over 78 for Favorskii rearrangement. But 88% of the yield from trans-chloroketone 78 was the rearranged ester and only 32% of the yield from cis-chloroketone 79 in non-polar solvent. Moreover, the trans-chloroketone 78 gave trans-methoxyketone and cis-chloroketone 79 gave cis-methoxyketone which was also not compatible with the planar oxyallyl intermediate supposed to be favoured in polar solvents and should give a mixture of products. The 3e-bromo-trans-2-decalone 80 undergoes rearrangement in both polar and non-polar solvents to the same extent and the 3a-bromo-trans-2-decalone 81 does not give rearranged product in non-polar and polar solvents. These results are compatible with the cyclopropanone intermediate which would predict no rearrangement from the axial isomer on the geometrical grounds



82

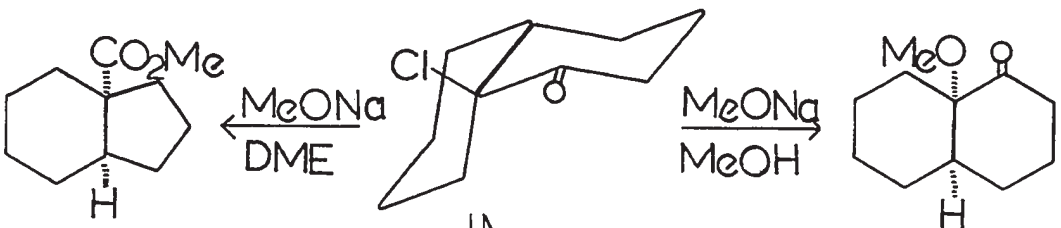


77

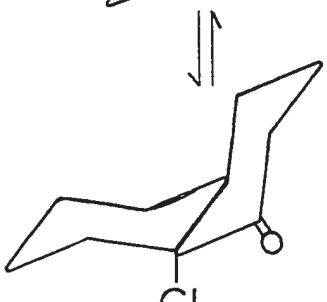


78

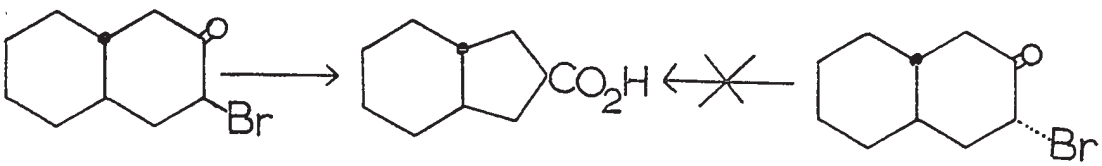
88 %



32 %



79



80

81

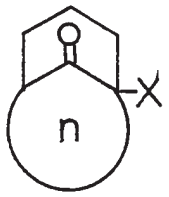
proposed by House. Since the rearrangement of 80 was successful in polar and nonpolar solvent to an equal extent, it appeared that the rearrangement was not solvent dependent. From this study, Smissman and his co-workers (59) suggested that without more extensive studies, an oxyallyl cannot be proposed as a general intermediate in the Favorskii rearrangement in polar solvent. However, these experiments may be irrelevant in that the failure to obtain a Favorskii rearrangement may merely be a reflection of increased rate of other reactions in the axial haloketone 81 (25). From the above considerations the evidence supporting the oxyallyl mechanism becomes weaker as more becomes known about cyclopropanones. Since there is no direct way that the oxyallyl can give the Favorskii product without bond formation between the α- and α'-carbon atoms, it may be more correct to say that the oxyallyl may be a direct precursor of cyclopropanone which gives the Favorskii rearrangement.

As of now, it is well known that the Favorskii rearrangement can occur via a semibenzilic mechanism or cyclopropanone mechanism. It was shown before with the bicyclic bridgehead bromoketones, that the change of ring size effects a change in mechanism. The change in mechanism was attributed mainly to the increase in acidity of the α'-hydrogen. Besides the acidity of the α'-hydrogen, do other factors such as solvent effects, basicity and nucleophilicity of the reagent have any effect on the rearrangement? If cyclopropanone were formed as an intermediate, could it be isolated? Is the formation of cyclopropanone concerted or stepwise? What is the rate determining step? The purpose of the present investigation was therefore an attempt to answer the above questions.

CHAPTER II

Rearrangement of Optically Active 1-Halobicyclo[4.3.1]decan-10-one 6(7)

An α-haloketone can react with a base in several ways. In order to study the mechanism of the rearrangement of an α-haloketone, the reaction should give a high yield of rearranged acid and the side reactions should be minimized. The bicyclic haloketones 6(n)* studied before have a favourable structure that prohibits the side reactions.



6(n)

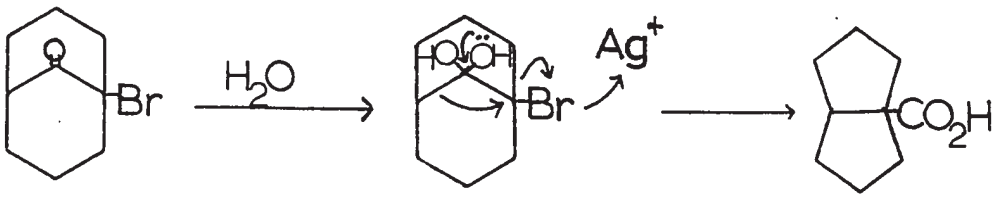
The yield of the rearrangement product is usually high. The rearrangement of 1-bromobicyclo[3.3.1]nonan-9-one 6(6)B was first studied by Cope and co-workers (60). The rearrangement was affected by silver nitrate, potassium hydroxide and sodamide in liquid ammonia. A priori, cyclopropanone** and semibenzilic mechanisms are possible for the

---

* The bicyclic haloketones and products will be numbered according to the size of the rings, such as 1-bromobicyclo[4.3.0]decan-10-one 6(7)B and the letter is used to distinguish different compounds with the same ring size.

** The term "cyclopropanone mechanism" is used here loosely to imply any mechanism involving a symmetrical intermediate.

rearrangement, but the semibenzilic mechanism was favoured in view of the non-acidic α'-hydrogen of the bicyclic ketone. The reduced acidity of the α'-hydrogen is the result of the ring size of the ketone which will not enolize without violating Bredt's rule (61a)*. The reaction of silver nitrate with the bromoketone 6(6)B was thought to proceed by a "push-pull" mechanism which is equivalent to the semibenzilic mechanism. The mechanism of the rearrangement of 6(6)B and its higher homologs 6(7)B and 6(8)B was further studied by Warnhoff



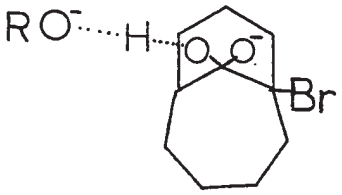
6(6)B 5(5)C

and co-workers (38). With the next higher homolog, 1-bromobicyclo-[4.3.1]decan-10-one 6(7)B, the acidity of the α'-hydrogen increases as the ring size increases. The ring size of 6(7)B is large enough to tolerate violation of Bredt's rule and it might well rearrange by a different mechanism under comparable conditions. It was in fact found that the bromoketone 6(7)B was rearranged by the semibenzilic mechanism with sodium hydroxide and sodium methoxide but by a cyclopropanone mechanism with t-butoxide. The change in mechanism could be attributed

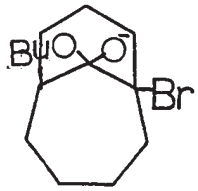
---

* Bredt's rule as stated by Fawcett is that the minimum geometrical requirement to accommodate a double bond without strain at a bridgehead position is S=9, where S refers to the total number of atoms between the two bridgehead atoms. The rule also applies to the formation of carbanion or partial double bond at the bridgehead but with smaller S. Recent preparation of $\Delta^{1,2}$-bicyclo[3.3.1]nonene has set the practical limit of S to 7 (61b) in a strained system.

to one or more of the possible causes: (a) difference in base strength between sodium hydroxide and potassium t-butoxide, (b) inability to form dianion 90, conceivably a required intermediate for semibenzilic rearrangement, (c) insufficient concentration of 58A for rearrangement by 58A to compete with cyclopropanone formation, and (d) change in solvent polarity. The fact that bromoketone 6(7)B will rearrange with methoxide ion by a semibenzilic path excludes 90 as a generally required

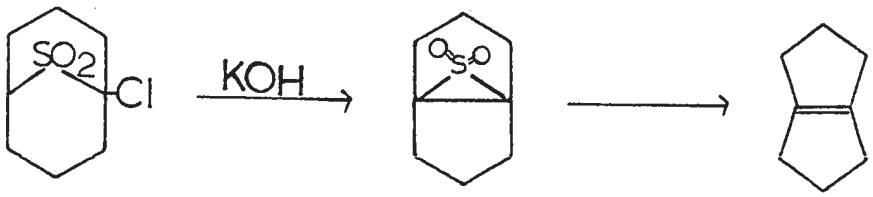


90



58A

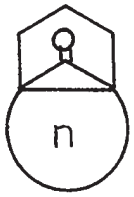
intermediate. The addition of t-butoxide to a carbonyl group and the abstraction of an α'-hydrogen are competitive. The steric effect is not the main reason for the change in mechanism from semibenzilic for bromoketone 6(6)B to cyclopropanone for 6(7)B . The most likely cause is the increase in acidity of the α'-hydrogen of 6(7)B. The rearrangement of halosulfone 91 gave $\Delta^{1,5}$-bicyclo[3.3.0]octene 93 (62). In view



91 92 93

of the isolation of $\Delta^{1,5}$-bicyclo[3.3.0]octene 93 which indicates the formation of epi-sulfone 92, the bromoketone 6(6)B might well rearrange by the cyclopropanone mechanism, if a suitable base were used.

The present work studies the effect of the base strength and solvent polarity on the rearrangement of haloketones 6(7) and 6(8) in order to get deeper understanding of the mechanism. The study involved deuterium incorporation in the product and an optical activity test for symmetrization during rearrangement. The two tests clearly differentiate the two mechanisms. For the semibenzilic mechanism, there will be no deuterium incorporation onto carbon in the product provided that there is no exchange by enolization before rearrangement, and if the starting bromoketone is optically active, the product will retain the optical activity. On the other hand, with the cyclopropanone mechanism one deuterium will be incorporated onto carbon in the product and the product will be racemic after going through a symmetrical intermediate 94 which has a plane of symmetry.



94

(A) 1-Bromobicyclo[4.3.1]decan-10-one 6(7)B

The products of the rearrangement were checked by TLC, purified by column chromatography and identified by PMR, IR spectra, GLPC retention time and melting point.* The absorption at 2-3 ppm in

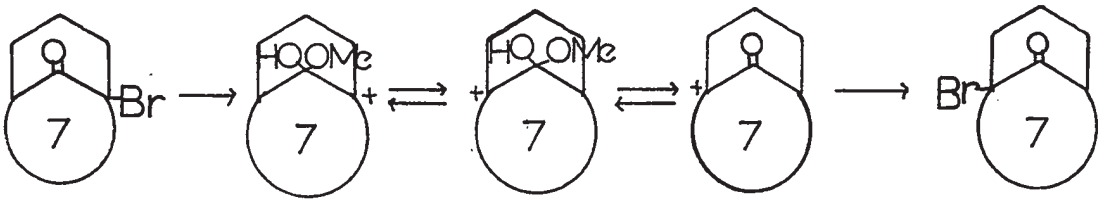
* Abbreviations used in this thesis: TLC (Thin Layer Chromatography), PMR (Proton Magnetic Resonance), IR (Infrared), ORD (Optical Rotatory Dispersion), CD (Circular Dichroism) and GLPC (Gas Liquid Partition Chromatography).

the PMR spectrum of the product was especially useful for the deuterium incorporation study. It is assigned to the absorption of the tertiary hydrogen at the ring junction. The deuterium incorporation was quantitatively determined by mass spectrometry. The GLPC technique was used to check the product purity and to identify the epimeric products by retention time. Rotations were taken by measuring the ORD curve of the purified product taking advantage of greater rotations at shorter wavelengths. Since the optical purity of the bromoketone is not known and the bromoketone has a small rotation at the sodium D-line (589 nm.), a considerable amount of product was needed to measure the rotation accurately at sodium D-line. The study was made easier by measuring the ORD curve with as little as 5-10 mg. of purified product.

In order to study quantitatively the mechanistic change in the rearrangement of an optically active bromoketone, a reaction which will give 100% retention of optical purity was needed. As was seen before, the reaction of silver nitrate with bromoketones 6(6)B, 6(7)B and 6(8)B caused rearrangement by the semibenzilic mechanism with inversion of configuration at the halogen bearing carbon, and this reaction serves as a control reaction. The rotation of product from this reaction is taken as a standard for 100% semibenzilic mechanism. A sample of bromoketone 6(7)B, $[\alpha]_D$+ 12.7°, reacted with silver nitrate to give the cis-bicyclo[4.3.0]nonane-1-carboxylic acid 5(6)C with rotation $[\alpha]_D$-10.7°. The result shows that an optically active bromoketone reacts with silver nitrate to give an optically active acid, but we have to be sure that there is no loss of optical activity during the reaction.

A priori, there are several ways that the optical activity

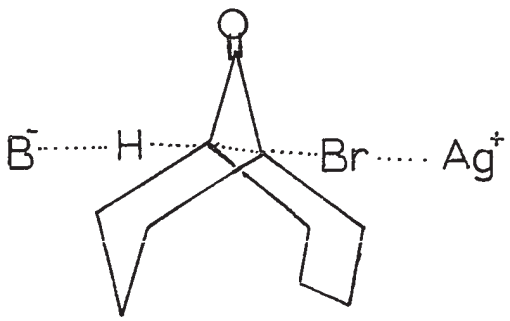
could be lost during the reaction. Firstly, the optical purity of the bromoketone might be lost by hydride transfer. The bromide ion is pulled off by the silver ion and then 1,3-hydride shift across the carbonyl group to give the mirror image of the initially formed keto carbonium ion or hemiketal ion. 1,3-Hydride shift between C-2 and C-6 of bicyclo[2.2.1]heptane system is well established (63). The endo-endo 1,3-hydride shift is a fast process in that system in which an edge protonated cyclopropane intermediate is formed (63). In the present case the 1,3-hydride shift is geometrically unfavoured. Furthermore, the α-ketocarbonium ion or the hemiketal ion is a high



6(7)B 6(7)B

energy species. Thus, there is no conceivable driving force for the 1,3-hydride shift to occur.

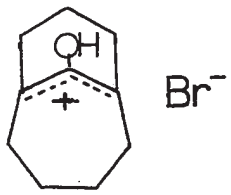
Secondly, the optical purity of the acid might be lost by a concerted mechanism to form a cyclopropanone intermediate by losing the α'-hydrogen and removal of bromide ion without intervention of an enol or enolate as shown in 95. The loss of bromide ion with the aid



95

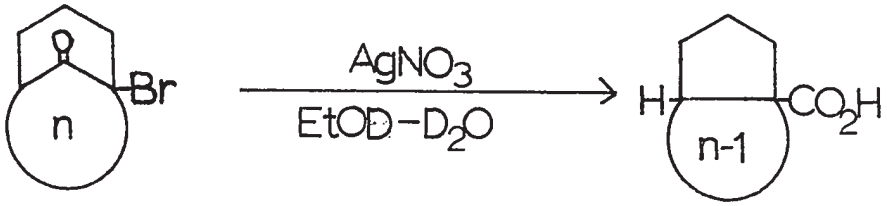
of silver ion is reasonable but the loss of hydrogen in the neutral or acidic condition is not likely. The nitrate ion is too weak a base to pull off the hydrogen.

Thirdly, the optical purity might be lost by an enol allyl bromide ion-pair 96. The formation of such an ion-pair would require



96

the prior enolization of the bridgehead hydrogen. The structure of the bromoketone 6(7)B is such that the formation of a double bond at the bridgehead will be highly strained, so that formation of the ion-pair would be highly unlikely in the present case. The above considerations would exclude these possibilities of losing the optical purity of the acid. The reaction of bromoketones 6(6)B, 6(7)B and 6(8)B with silver nitrate in ethanol-d and deuterium oxide showed little or no deuterium incorporation in the acid. This result is the strongest and most



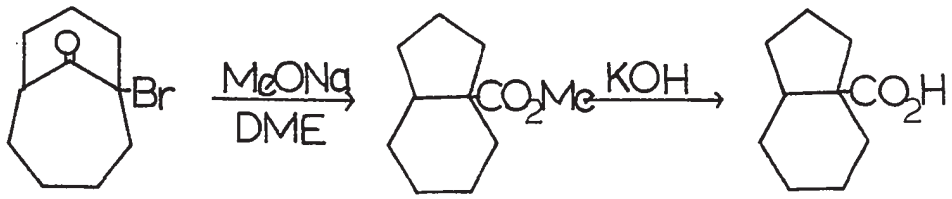
6(n) 5(n-1)C

conclusive evidence against the involvement of any symmetrical intermediate. Furthermore, the rearrangement of bromoketone specimens with $[\alpha]_{325}$+761° and $[\alpha]_{325}$-896° to give acid with rotations $[\alpha]_{300}$-31.4° and $[\alpha]_{300}$+35.5°, respectively, under the same conditions indicates the two rearrangements proceed with exactly the same degree of retention of

optical purity. Judging from the deuterium incorporation result mentioned above, the degree of retention of optical purity is nearly 100%. The optical activity and deuterium incorporation results are entirely consistent with the unsymmetrical mechanism, i.e. the semibenzilic mechanism.

With the control experiment well established, the studies of the base strength and solvent effect on the mechanistic change of the bromoketone 6(7)B were begun. The results of the reaction of bromoketone 6(7)B with various bases and solvents are listed in Table II.

The rearrangement of bromoketone 6(7)B $[\alpha]_{325}$-896° with sodium methoxide in dimethoxyethane gave 62% of liquid methyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)E, $[\alpha]_{300}$-32.3°, which was hydrolyzed to the corresponding cis-bicyclo[4.3.0]nonane-1-carboxylic acid 5(6)C, $[\alpha]_{300}$-31.4° (run 7). The rotations of the acid at various



6(7)B 5(6)E 5(6)C

wavelengths are nearly equal to those for the silver nitrate reaction, i.e. the rearrangement of bromoketone 6(7)B with sodium methoxide in dimethoxyethane does not lose any of the optical activity. The result is consistent with the semibenzilic mechanism. It was previously shown that rearrangement of 6(7)B with sodium methoxide in methanol followed the semibenzilic pathway. The pK_a of methanol is 16 and a ketone is in the order of 19-20 (64). Since the α'-hydrogen is at the

TABLE II

Rearrangement of 1-Bromobicyclo[4.3.1]decan-10-one 6(7)B

Run	Condition	 COOH %	 COOR %	Rotation at 300 nm. (CH_3OH)	Deuterium	Racemization[g]
1[a]	$AgNO_3$-EtOH-H_2O	61	R=$(CH_3)_2CH$[h]	-31.4±0.6 (acid) $[\alpha]_{350}$ -12±1	-	0
2	$AgNO_3$-EtOH-H_2O	71		+35.5±1°	-	0
3[a]	$AgNO_3$-EtOD-D_2O	85		-	0.00	0
4[b]	NaOD-EtOD-D_2O	80		-	0.01D	0
5[b]	NaOMe-MeOD		R=Me 96	-	0.00	0
6[b]	KOBu^t-Bu^{t}OD		R=Bu^t 67	-	0.83D	100
7	MeONa-DME	82[c]	R=Me 62	-32.3°±0.8° -31.4°±0.6°[c]	-	0

TABLE II (contd.)

Run	Condition	COOH %	COOR %	Rotation at 300 nm (CH_3OH)	Deuterium	Racemization[g]
8	Bu^tOK-DME		R=Bu^t 70	0	-	100
9	$(CH_3)_2CHONa$-$(CH_3)_2CHOD$		R=$(CH_3)_2CH$ 26(67)[d]	$[\alpha]_{350}$ -9.9°±.4°	92.1% d_o, 7.9% d_1	17
		74(67)[d]		-32.3°±0.8	0.0	0
10	Bu^tOK-Bu^tOD-D_2O	74	Traces	-32.2°±0.6°	95.5% d_o, 4.5% d_1	0
11	Bu^tOK-Bu^tOD-D_2O	37	NIL	+35.5°±1°	99.5% d_o, 0.5% d_1	0
12	NaOH-xylene	77		-38.4°±.7		0
13	KOAc-HOAc			$[\alpha]_{325}$ +796°±1°		0
14[f]	NaOD-EtOD-D_2O	75		+12.9°±.9°	99.1% d_o 0.9% d_1	0

TABLE II (contd.)

a. Runs 1, 7, 8, 9, 10, 12, 13 were done with bromoketone 6(7)B, $[\alpha]_{325}$+ 762°; runs 2, 11 with bromoketone 6(7)B $[\alpha]_{325}$- 896°

b. From previous work (38).

c. Obtained from hydrolysis of the methyl ester.

d. Total yield of product.

e. Recovered bromoketone

f. Chloroketone 6(7)C $[\alpha]_{320}$- 262°

g. The percentage of racemization was estimated by $\frac{[\alpha]^{AgNO_3} - [\alpha]^{Reaction}}{[\alpha]^{AgNO_3}} \times 100\%$

h. Obtained from esterification of the acid.

bridgehead it is less acidic than that of an ordinary ketone. Because the basicity of methoxide increases in an aprotic solvent such as dimethoxyethane, the increase in base strength may cause a change in mechanism. The result indicates the solvent has no effect on the mechanism for methoxide, perhaps the increase in base strength is not big enough to force a change. There are two competing reactions: the abstraction of the α'-hydrogen and the attack of methoxide at the carbonyl group. The change in solvent affects both the basicity* and nucleophilicity* of the methoxide, but still the attack of methoxide on the carbonyl group is faster to give a semibenzilic mechanism.

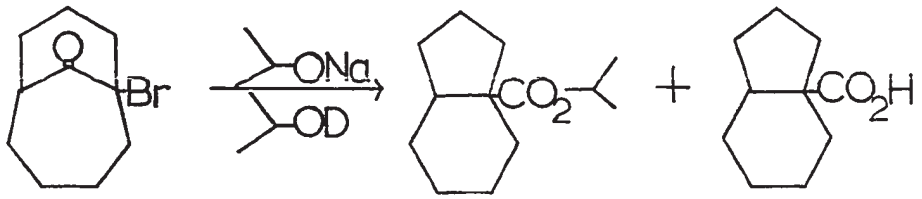
The second stronger base used was sodium isopropoxide in isopropyl alcohol-d. Isopropyl alcohol is two pK_a units less acidic than methanol. When the bromoketone 6(7)B was rearranged with sodium isopropoxide in isopropyl alcohol-d, a total yield of 67% of product was obtained, 26% isopropyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)I and 74% of the acid 5(6)C. The acid was invariably the major product in several attempts. Great pains were taken to make sure the apparatus was dry, and still the acid was predominant. Since the reaction was carried out on a small scale, traces of water in the alcohol may result in the formation of the acid.** The isopropyl ester 5(6)I resisted hydrolysis when it was subjected to the

---

* The term basicity is used for equilibrium and is measured by pK_a scale (116); the term nucleophilicity is used here in connection with the rate of polar reaction such as the nucleophilic reaction of cyanide with p-nitrophenyl acetate (69).

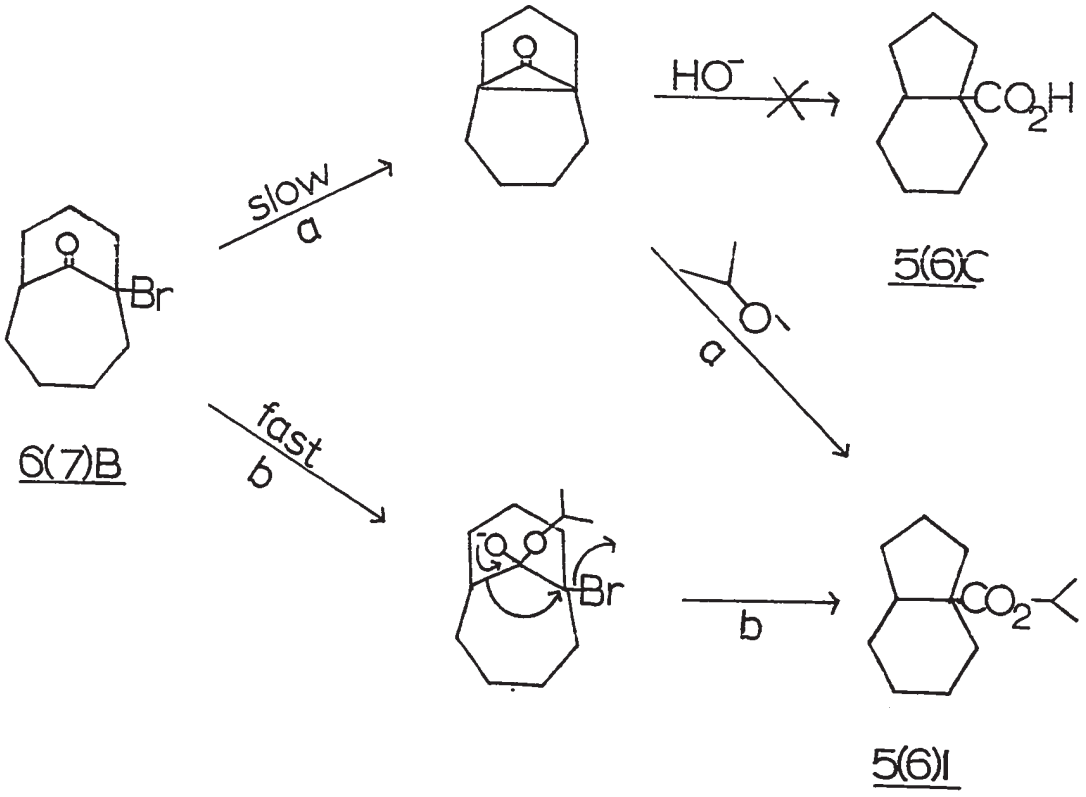
** Recently it was found that the deuterated isopropyl alcohol contained about 6 mg. of water per gm. of alcohol. Even with this amount of water present the concentration of sodium isopropoxide is 4 times over the sodium hydroxide [See Experimental].

rearrangement condition at 110° for 4 hours. This showed that the acid does not come from the hydrolysis of the isopropyl ester but comes directly from the reaction of hydroxide, which was present in

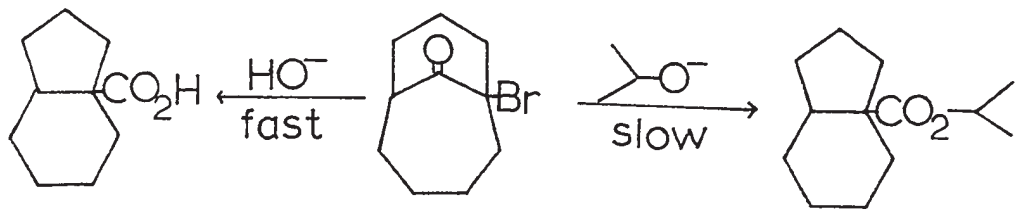


6(7)B 5(6)I 5(6)C

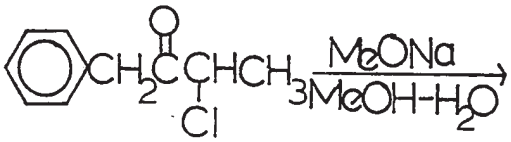
small amount with the bromoketone. The rotations of the ester and acid are listed in Table II (run 9). The acid has rotation exactly equal to that of the product from the silver nitrate reaction. The result shows that a semibenzilic mechanism is followed. Further evidence comes from the IR and PMR spectra of the acid. IR showed no C-D absorption and PMR showed absorption at 2.10-2.70 ppm which was the position for tertiary hydrogen at the ring junction. The isopropyl ester 5(6)I had rotation $[\alpha]_{350}$-9.9° and mass spectroscopic analysis showed 92.1% d_0, 7.9% d_1. The acid 5(6)C from silver nitrate reaction was converted into the isopropyl ester $[\alpha]_{350}$-12° for comparison. There was 17% racemization. There are two possible routes for the formation of isopropyl ester. Firstly, the α'-hydrogen can be abstracted, followed by the formation of a cyclopropanone which is attacked by isopropoxide or hydroxide. Since the acid with full retention of optical activity came entirely from the semibenzilic mechanism the attack on the cyclopropanone could only have been by isopropoxide (path a). Secondly, the isopropoxide attacked the

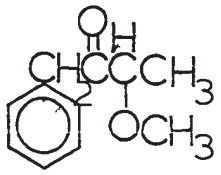


carbonyl group and followed the semibenzilic mechanism (path b). The isopropyl ester 5(6)I came partly from cyclopropanone (17%) and partly from the semibenzilic mechanism. The present result showed that the semibenzilic process is faster than cyclopropanone formation judging from the percentage of semibenzilic mechanism. The amount of acid to ester is in the ratio of 2:1, which implies that in the case of competition of isopropoxide and hydroxide, hydroxide reacts faster.

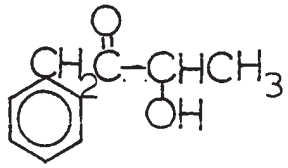


It was found by Bordwell that the rearrangement of 3-chloro-1-phenylbutan-2-one 74 in 75% (v/v) H_2O-MeOH gave invariably higher yields of methoxy product than hydroxy product (a preference of 30 to 1)(36).

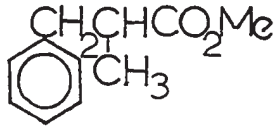




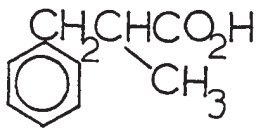
49%



7%

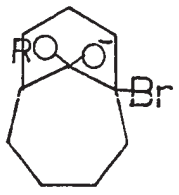


36%



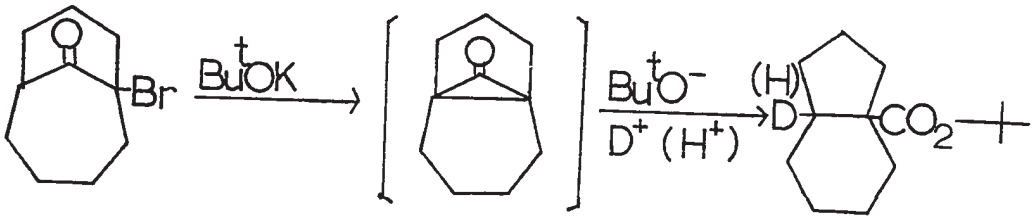
8%

This result is different from what we observed. The difference in reactivity between methoxide and hydroxide toward carbonyl groups is very common (65). The greater reactivity of methoxide over hydroxide could be attributed to the more electron releasing character of the methyl group than the hydrogen. But the reverse in reactivity between isopropoxide and hydroxide requires another explanation of which the steric effect is the most obvious one at hand. The difference in rate could be due to the difference in rate of rearrangement of 58A where R is hydrogen or isopropyl group. The observation of only 17% of racemization showed that the attack at the carbonyl group is faster than abstraction of the α'-hydrogen.



58A

If a base has a higher pK_a than isopropyl alcohol, a cyclopropanone mechanism could occur. This was found to be the case with potassium t-butoxide. The previous result of potassium t-butoxide in t-butyl alcohol-d gave t-butyl ester containing 0.83 deuterium atom per molecule which was the expected value of deuterium incorporation by cyclopropanone mechanism (38). The value 0.83 allows for competition between the t-butyl alcohol-d and the t-butyl alcohol formed on hydrogen abstraction by t-butoxide. When the reaction of bromoketone 6(7)B with potassium t-butoxide was carried out in dimethoxyethane, 70% of t-butyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)B was obtained. The ORD of the purified ester showed no rotation at all from 600-300 nm. The result is consistent with the cyclopropanone mechanism and at the same time supports the deuterium incorporation observation. The change of solvent from polar to non-polar has not increased the carbonyl



6(7)B

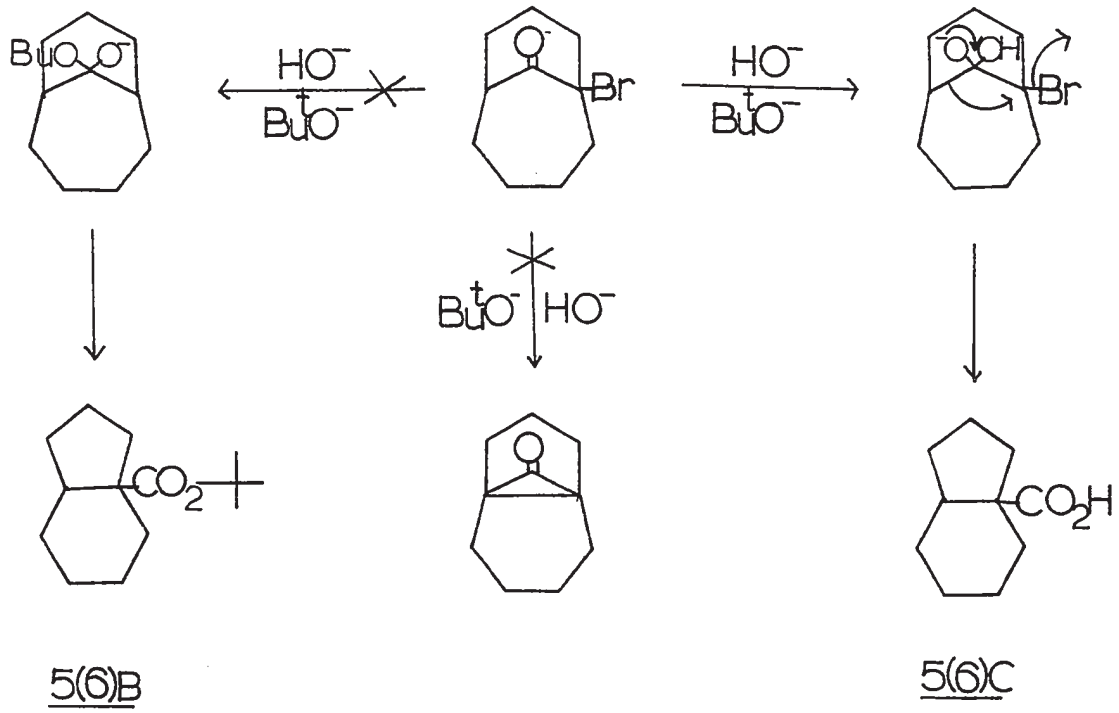
5(6)B

reactivity (semibenzilic rearrangement) to a greater extent than α'-hydrogen removal as seen from methoxide in methanol to dimethoxyethane and t-butoxide in t-butyl alcohol to dimethoxyethane. From the above results there is a gradual change in mechanism of rearrangement of bromoketone 6(7)B from semibenzilic to cyclopropanone with sodium methoxide, sodium isopropoxide and potassium t-butoxide. The change follows the change of pK_a of the alcohols: $pK_a^{MeOH} = 16$, $pK_a^{PrOH} = 18$,

pK_a t-BuOH = 19. It is noteworthy that the alkoxide also increases in size from methoxide to t-butoxide and one might argue that the direct attack of the alkoxide to the carbonyl group might be increasingly difficult from methoxide to t-butoxide so that the t-butoxide would rather abstract the α'-hydrogen. We have no evidence to show that the steric effect of t-butoxide is so large that the attack at the carbonyl group is entirely excluded. As a matter of fact the increase in pK_a also increases the nucleophilicity of the base, the attack at the carbonyl will also be favoured by this factor. But the results are just the reverse. Because the bromoketone 6(6)B is rearranged by the semibenzilic mechanism with t-butoxide, we may argue that if a steric effect is in operation at all it should occur in both bromoketones 6(6)B and 6(7)B. Therefore, the steric effect is not the main reason for the change of mechanism in bromoketone 6(7)B.

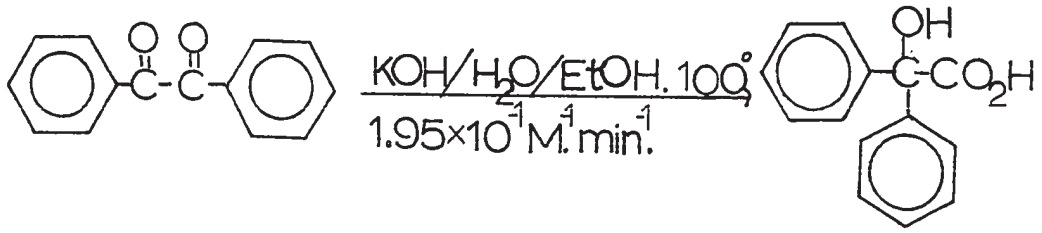
It was observed above that the rearrangement of bromoketone 6(7)B with sodium isopropoxide gave considerable amount of acid when about equivalent amount of water was present. Since t-butoxide reacts with bromoketone 6(7)B entirely by a cyclopropanone mechanism, it is interesting to see which process will be faster if t-butoxide and hydroxide are present in the same amount. When the reaction was carried out with equal amount of t-butoxide and deuteroxide, 74% of acid 5(6)C was obtained with traces of t-butyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)B. The acid has a rotation which is equal to that of the silver nitrate reaction as shown in Table II (run 10). Mass spectroscopic analysis of the acid showed that it contained 95% d_o and no more than 5% d_1. In another run 37% of acid was obtained and the acid had a rotation equal to that of the silver nitrate reaction.

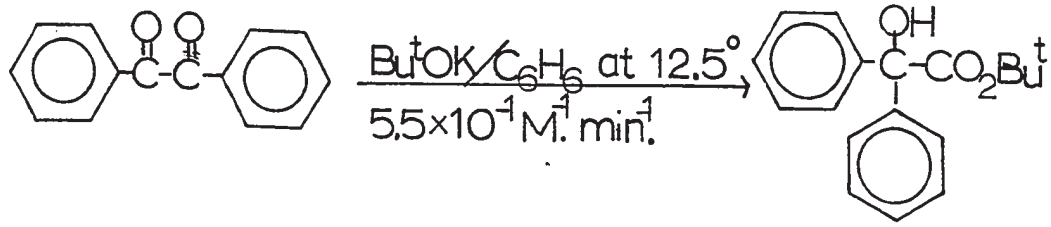
Mass spectrum showed 99.5% d_o and 0.5% d_1. Since little or no t-butyl ester is formed, this indicates that the hydroxide attacks the carbonyl faster than the t-butoxide or hydroxide abstracts the α'-hydrogen. Since the acid is 100% pure in optical activity, cyclopropanone is not involved in the rearrangement. The acid is formed entirely from



5(6)B 5(6)C

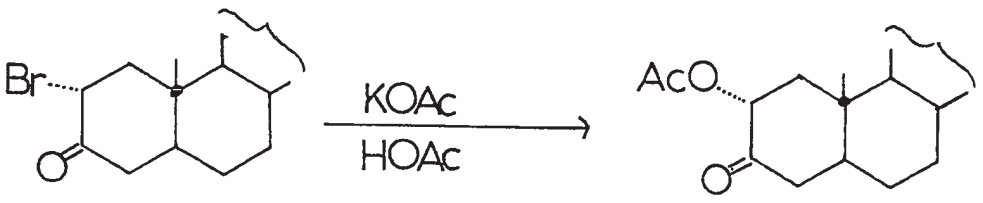
the hydroxide reaction with the bromoketone since the t-butyl ester is not hydrolyzed under the reaction conditions. The result once again shows that there is a great preference in reactivity of hydroxide over t-butoxide in rearrangement of bromoketone 6(7)B. It is contrasted with the benzilic acid rearrangement where t-butoxide is much faster than hydroxide in attacking the carbonyl (66). The difference in behavior of t-butoxide and hydroxide towards benzil and bromoketone 6(7)B is probably due to a steric effect.





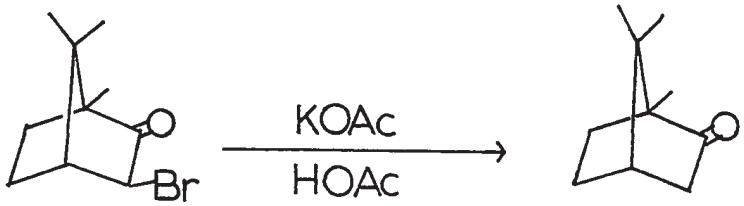
Generalizing the above observations, during the Favorskii rearrangement of bicyclic haloketone 6(7)B a strong base will promote the rearrangement by a cyclopropanone mechanism and a strong nucleophile but weaker base will lead to semibenzilic mechanism. In case of a weak base and poor nucleophile, there will be no rearrangement unless something such as silver ion is pulling on the halide.

In fact, this was found to be the case for potassium acetate in acetic acid. The bromoketone 6(7)B was recovered without racemization when heated at 140° with potassium acetate in acetic acid for 46 hours. This reaction of bromoketones has been well studied in monocyclic and steroid cases (67).



10

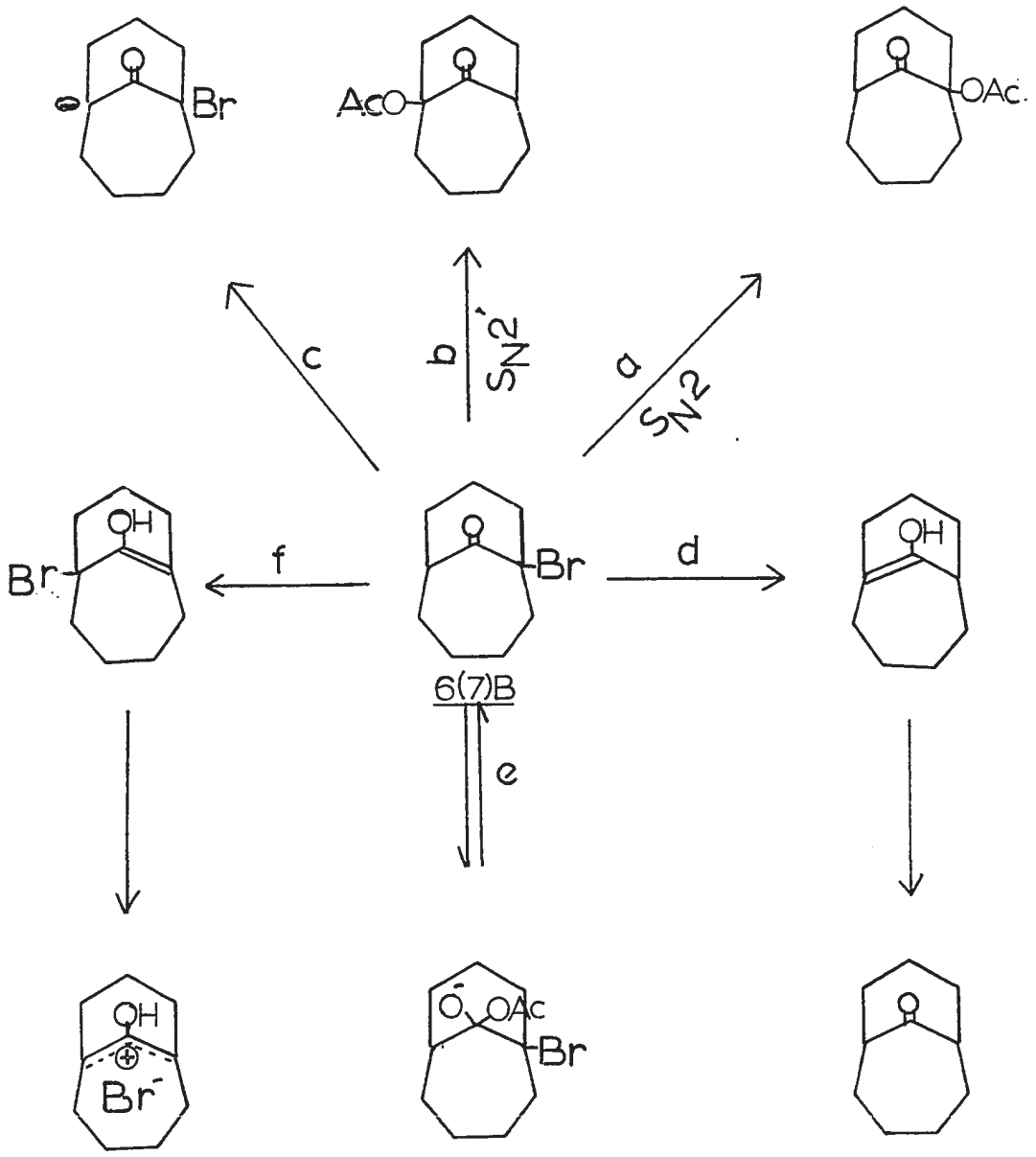
The inertness of the bromoketone 6(7)B in refluxing potassium acetate-acetic acid mixture excludes the following reactions: (a) A direct S_N2 reaction. The structure of the bromoketone is well set up to prevent attack at the back side of the carbon; (b) An S_N2' reaction. The bromoketone would first be enolized by acid catalysis and then attacked by acetate ion or bromide ion at the α'-carbon. The bridgehead α'-hydrogen was restricted in enolization by the ring size of the molecule; (c) Formation of a carbanion. The acetate is not strong enough to abstract the α'-hydrogen, even much stronger bases like hydroxide do not do that; (d) Reductive debromination. It was observed that when α-bromacamphor was treated with potassium acetate-acetic acid mixture in a sealed tube that camphor was the major product (68). Since the formation of a double bond at the C_1-C_{10} position is highly strained in 6(7)B, the enol is difficult to form by reductive debromination; (e) Reversible addition of acetate to carbonyl. This



possibility is difficult to exclude. Since the acetate ion is a weak nucleophile, the rate of attack on the carbonyl of an ester is very slow and reversible ($k=5.1\times10^{-4}M^{-1}min.^{-1}$) comparing to hydroxide ($570M^{-1}min.^{-1}$) and methoxide ($2.9\times10^{4}M^{-1}min.^{-1}$)*; (e) Enol allylic bromide ionization. The enol allylic halide is an important intermediate

---

* These are the rates of reaction of p-nitrophenyl acetate with nucleophiles in water (69).


Br
AcO
OAc
c
b
SN2
a
SN2
OH
Br
f
Br
d
OH
6(7)B
e
OH
Br⁻
O⁻
OAc
Br

in acid or base catalyzed formation of alkoxyketones from bromoketones (36). The enol allylic halide proceeds further to an ion-pair which gives the alkoxyketone. The fact that the recovered bromoketone retains its optical activity argues strongly against the formation of the ion-pair.

The rearrangement of bromoketone 6(7)B with sodium deuteroxide in deuterated alcohol was shown to go by the semibenzilic mechanism, but the quasi-Favorskii reaction of the optically active 44 with powdered sodium hydroxide in xylene gave racemic products which was contradictory to the semibenzilic pathway. The reaction medium in this case was a heterogeneous phase which might have some effect on the reaction mechanism and the stereochemical result. Therefore a reaction under the same conditions was tried with the bromoketone 6(7)B. The acid from the rearrangement of bromoketone 6(7)B in powdered sodium hydroxide in xylene was optically active with rotation slightly greater than those from the silver nitrate reaction as seen in Table II (run 12)*. The result is consistent with the semibenzilic mechanism and supports the deuterium incorporation result. It is seen that there is no change in mechanism in xylene.

(B) Rearrangement of Optically Active 1-Chlorobycyclo[4.3.1]-decane-10-one 6(7)C

The mechanism of the rearrangement of the bicyclic bromoketone 6(6)B, 6(7)B and 6(8)B was shown to depend on the acidity of the α'-hydrogen which is controlled by the ring size of the molecule.

---

* The discrepancy of the result may be caused by the old lamp of the machine.

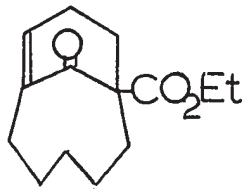
The mechanism was changed gradually by increasing the ring size with methylene groups. It may be that changing the substrate to the chloroketone may change the mechanism in 6(7)C to cyclopropanone because the chlorine has a stronger inductive effect than the bromine. The α'-hydrogen might then be acidic enough to effect the change. In order to test this idea, the chloroketone 6(7)C was synthesized. The Hunsdiecker method did not work very well with chlorine and the yield was low. A sample of chloroketone 6(7)C, $[\alpha]_{325}$ -262°, was rearranged with sodium deuteroxide in deuterium oxide to give cis-bicyclo[4.3.0]-nonane-1-carboxylic acid 5(6)C in 75% yield. The acid was identified by mixed mp and comparison of GLPC retention time with authentic methyl ester. The mass spectrum of the acid showed no deuterium incorporation (<1% d_1) and the ORD of the pure acid had a positive plain curve, $[\alpha]_{300}$ +13.0°. Since no control experiment was done on the chloroketone with silver nitrate, the rotations of the acid from the control experiment were unknown. Judging from the deuterium incorporation content however, the result was consistent with the semibenzilic mechanism. Hence by changing bromine to chlorine does not effect a change in mechanism of the bicyclic haloketone 6(7)B and 6(7)C with sodium hydroxide.

CHAPTER III

Rearrangement of 1-Halobicyclo[5.3.1]undecan-11-one 6(8)

(A) 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

The bromoketone 6(8)B was found to rearrange by the cyclopropanone mechanism or its equivalent with sodium hydroxide in aqueous ethanol as shown by deuterium incorporation and optical activity studies (38). The bromoketone 6(8)B with the strain number S=9 by Bredt's rule, which would tolerate a double bond at bridgehead without strain, as is proven by the isolation of the α,β-enone 6(8)D during the synthesis. The acidity of the α'-hydrogen would be expected to be close to that of ordinary ketones: pK_a= 19-20. Therefore the cyclopropanone mechanism or its equivalent would be favoured for the rearrangement of



6(8)D

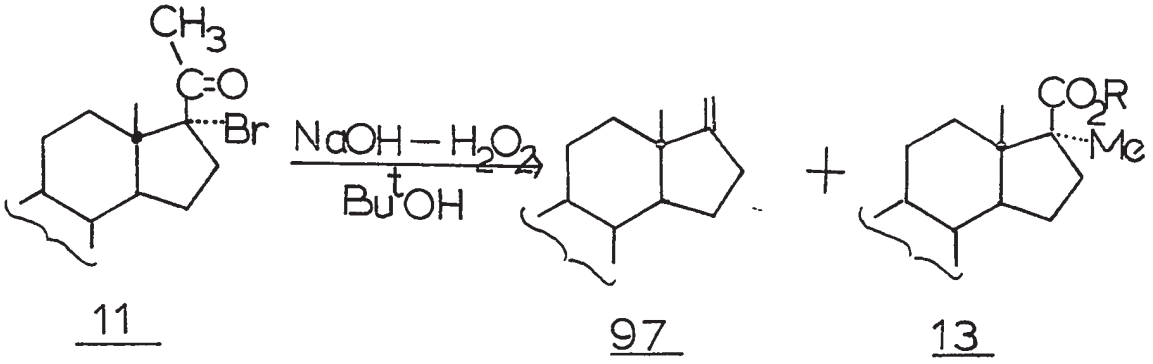
bromoketone 6(8)B. The study of mechanistic variation of the haloketones 6(6)B, 6(7)B and 6(8)B seems to be complete at the present stage, since the results obtained are all consistent with expectations, i.e. the bromoketone 6(6)B will rearrange mainly by semibenzilic mechanism, 6(8)B by mainly cyclopropanone and 6(7)B will by both semibenzilic or

cyclopropanone depending on the base strength. So far we have not been able to persuade the bromoketone 6(6)B to rearrange by a cyclopropanone mechanism with the bases used, but is it possible to induce 6(8)B to rearrange by the semibenzilic mechanism? From the observation of the result of competition of equal amounts of t-butoxide and hydroxide toward 6(7)B, hydroxide reacts faster in a semibenzilic rearrangement than t-butoxide reacts by hydrogen abstraction. This result implies that if a highly reactive nucleophile but weaker base is used the bromoketone 6(8)B might rearrange by the semibenzilic mechanism. If the bromoketone 6(8)B rearranges by a cyclopropanone intermediate, can it be isolated or trapped? During the course of our study of the rearrangement,two stable cyclopropanones were isolated at room temperature, and one of them thermally decomposed only at 150° (70). This prompted us to attempt to isolate the cyclopropanone.

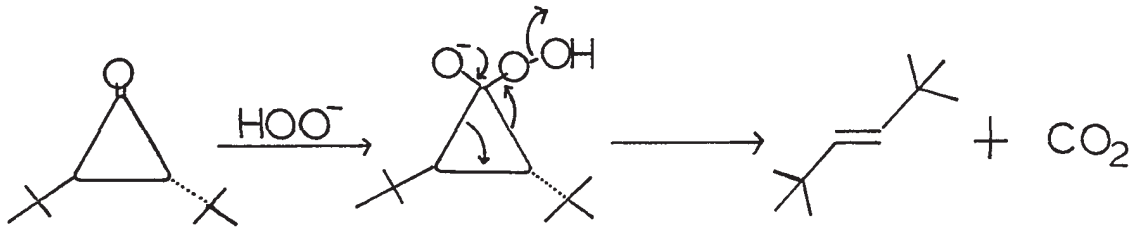
As in the case of bromoketone 6(7)B the reaction of bromoketone 6(8)B with silver nitrate proceeded with no loss of optical activity during reaction as seen from the deuterium incorporation study in Table III (reaction 1). The proof against the loss of optical activity during the semibenzilic mechanism still holds for bromoketone 6(8)B. It is to be noted that the reaction of bromoketone 6(8)B with silver nitrate in aqueous methanol is much slower than for bromoketone 6(7)B, judging from the rate of formation of the silver bromide. In fact it needed refluxing for 2 to 3 days to complete the reaction and the methyl cis-bicyclo[5.3.0]decane-1-carboxylate was sometimes the main product. Part of the ester may be formed from acid catalyzed esterification of the first formed cis-bicyclo[5.3.0]-decane-1-carboxylic acid. Little or no ethyl ester was obtained in

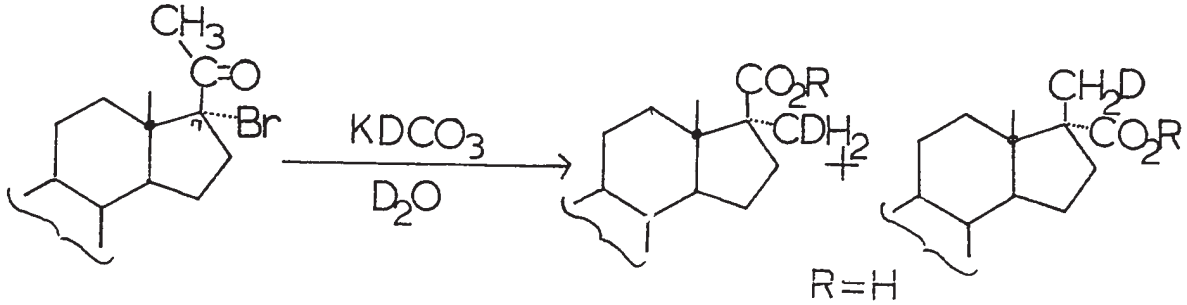
aqueous ethanol. The slow rate may be due to the 1,5-transannular interaction in eight member ring which blocks the incoming nucleophile (71).

In the course of our study, the following reaction was noted. When a 17α-bromo-20-ketosteroid was treated with a mixture of t-butyl alcohol, hydrogen peroxide and sodium hydroxide, a mixture of 97 and 13 was obtained (72). The formation of the olefin 97 can be



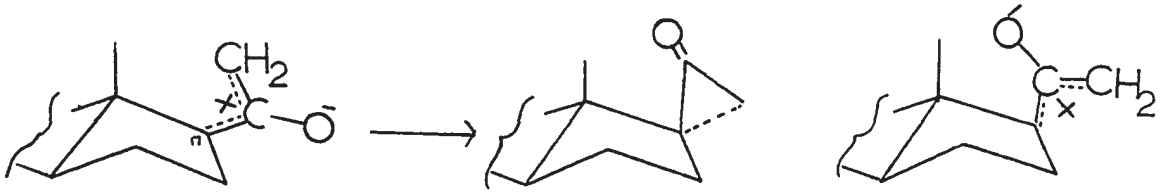
11 97 13





11 13 14

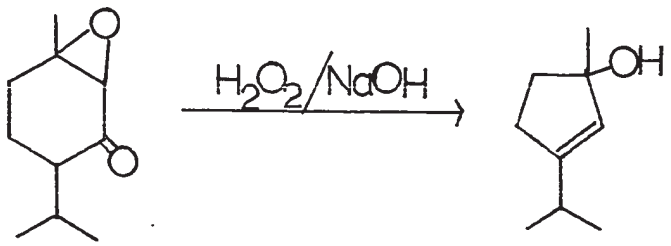
explained by decarbonylation of the cyclopropanone intermediate. Some cyclopropanones do in fact decarbonylate when treated under these conditions (72). By elegant deuterium incorporation studies the bromoketone 11 was shown to rearrange by cyclopropanone mechanism (73). The product contained one and only one deuterium per molecule as shown by mass spectrometry, non-deuterated or polydeuterated products being absent. There is no deuterium-hydrogen exchange before rearrangement and the abstraction of α'-hydrogen is the slow step. One might argue that the olefin 97 came via cyclopropanone mechanism whereas the acid 13 came via the semibenzilic mechanism. The stereochemistry at C_{17} of the product 13 was the same as the starting bromoketone. If a semibenzilic mechanism is followed the configuration at C_{17} must be inverted. Therefore the semibenzilic mechanism is excluded. The stereochemistry of C_{17} is best explained by oxyallyl mechanism. The oxyallyl was first formed; there would be two conformations of the



98 100 99

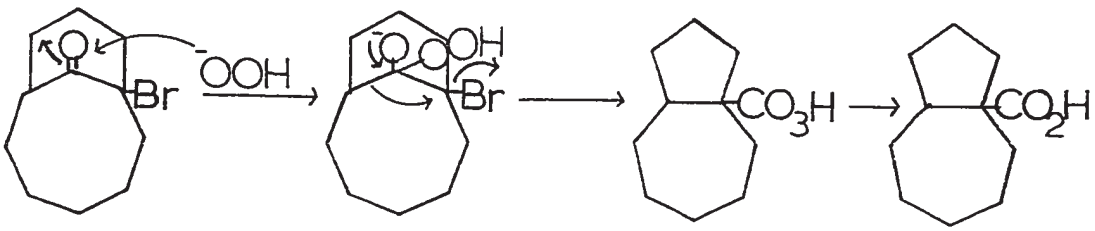
oxyallyl, and due to the C_{18} methyl group, the conformer 98 should predominate. The oxyallyl 98 cyclized to the cyclopropanone 100 which then reacted with hydroxide or peroxide to give the observed product. Furthermore,the epoxyketone 28 also gave olefin with alkaline hydrogen peroxide (74). It looks like the alkaline peroxide is a

potential reagent for trapping the cyclopropanone. However, when the



28

optically active bromoketone 6(8)B was rearranged in the alkaline peroxide medium 80% of acid 5(7)C and 3% of neutral material were obtained. The neutral material contained at least six compounds as revealed by TLC analysis. Our result on the rearrangement of bromoketone 6(8)B was contrary to that observed by Baldwin and Greene. There was no indication of the expected $\Delta^{1,7}$-bicyclo[5.3.0]decene from TLC analysis. The acid was purified by column chromatography and identified by comparing the IR, PMR spectra and GLPC retention time of its methyl ester with those of authentic cis-bicyclo[5.3.0]decane-1-carboxylic acid. To our great astonishment the reaction product retained at least 96% of its optical activity, as seen in Table III (reactions 4 and 12). The rearrangement of bromoketone 6(8)B with alkaline peroxide had occurred via the semibenzilic mechanism! In this rearrangement the attacking group is the hydroperoxide ion. Presumably the peracid 5(7)B was first formed and then decomposed to



6(8)B 5(7)B 5(7)C

TABLE III

Rearrangement of 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

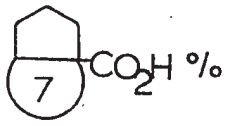
Run	Condition	 %	 %	Rotation at 300 nm. of product ($CHCl_3$)	Deuterium Content	% Racemization
1[a]	$AgNO_3$-EtOD-D_2O	25		$[\alpha]_D$ + 31.3°	0.005 D	0
2[a]	NaOD-EtOD-D_2O	88		$[\alpha]_D$ 1.1°	0.90 D	96
3	$AgNO_3$-MeOH-H_2O		R=Me 14	150 ± 1°		0
4[b]	$AgNO_3$-EtOH-H_2O	70		178° ± 2° 177 (CH_3OH)		0
5	$KHCO_3$-MeOH-H_2O	43	R=Me 39	14 ± 0.6° (ester) 27.2° (ester from acid)		91 82
6	NaCN-MeOH		R=Me 71	65.2° ± 0.7°		57
7	NaOD-EtOD-D_2O	34	0	14.7 ± 0.5° 11.7°(ester)[d]	19.5% d_1, 80.5% d_0	92

TABLE III (contd.)

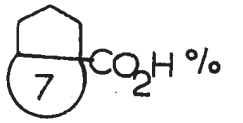
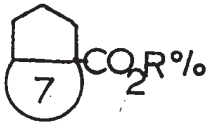
Run	Condition	 %	 %	Rotation at 300 nm. of product ($CHCl_3$)	Deuterium Content	% Racemization
				$[\alpha]_{320}$ - 594.7°	99.2% d_o 0.8% d_1	0[e]
8	NaSH-EtOH-H_2O	27	0	51.1° ± 0.5 (ester from acid) 64.1 (Acid)		66
9[b]	NaSH-EtOH-H_2O	59	0	75 ± 1° (MeOH)		57
10	PhONa-dioxane		R=Ph 87	0		100
11	NaOH-H_2O_2-Bu^tOH	80		150 ± 2° 120° d		32
12[b]	NaOH-H_2O_2-Bu^tOH	80		171.2 ± 2° (MeOH)		<4
13[c]	NaOH-H_2O_2-Bu^tOH	57			37.3% d_o 62.7% d_1	26

TABLE III (contd.)

a. From previous work (38).

b. Runs 4, 9, 12 with bromoketone $[\alpha]_D$- 17.6°

Runs 3, 5, 6, 7, 8, 10, and 11 with bromoketone $[\alpha]_{321}$- 564.7°.

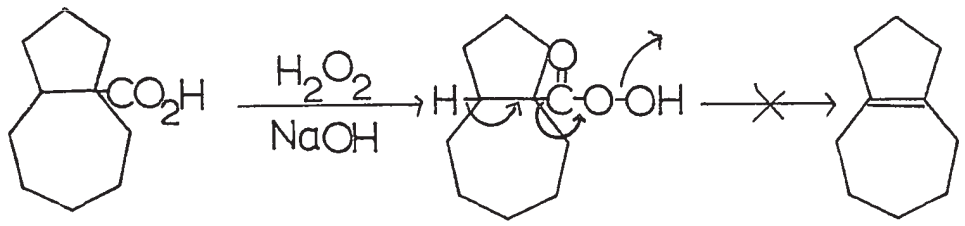
c. With deuterated bromoketone 12% d_o, 85.3% d_1, 1.9% d_2.

d. This value was caluclated from the correcting factor from Run 8.

e. Recovered bromoketone 6(8)B

cis-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C.

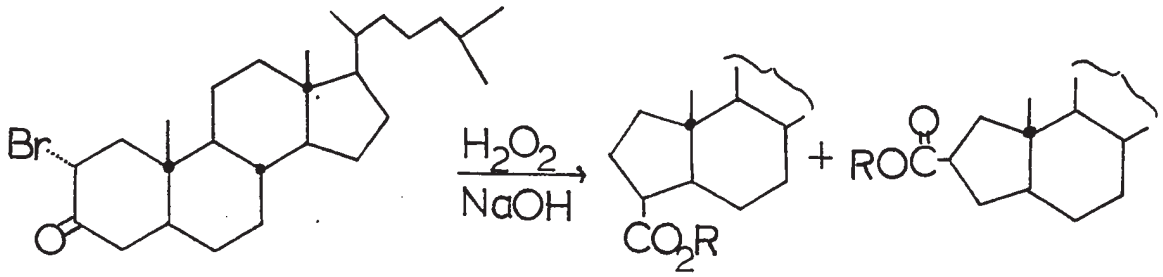
A control experiment showed that p-chloroperbenzoic acid decomposed completely on refluxing in alkaline solution for 20 minutes, as determined by sodium thiosulfate back titration of the iodine liberated from potassium iodide by the peracid. Why then does the bromoketone 6(8)B rearrange with alkaline peroxide entirely via the semibenzilic mechanism? The acidity of the α'-hydrogen comes into play again. The acidity of the bridgehead α'-hydrogen of bromoketone 6(8)B is less than that of the acetyl group in a steroid even with strain number equal to nine as seen from the rate of base catalyzed enolization of acetone at 1.1° in water ($1.48 M^{-1} min^{-1}$)(75, 91) to that of the rate of rearrangement of bromoketone 6(8)B ($2.32 \times 10^{-1} M^{-1} min^{-1}$) at 75° where the rate determining step is abstraction of the α'-hydrogen so the cyclopropanone mechanism is faster than the semibenzilic mechanism in the steroid case even with the highly reactive nucleophile, peroxide ion. It could be the hydroxide that abstracts the α'-hydrogen in the steroid case. A control experiment on the acid 5(7)C with alkaline peroxide showed no $\Delta^{1,7}$-bicyclo[5.3.0]decene. This substantiated that the olefin 97 is not formed from the rearranged acid but from the cyclopropanone intermediate. The high nucleophilicity



5(7)C 5(7)B

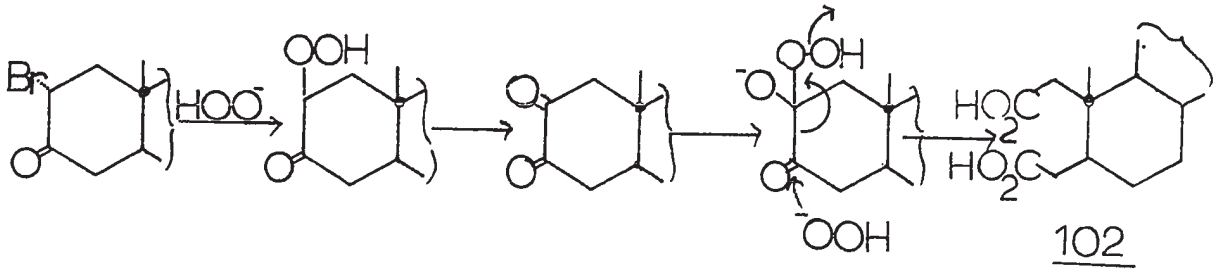
of peroxide is well known. The rate of reaction of peroxide with the carbonyl group of p-nitrophenyl acetate is $2.75 \times 10^{5} M^{-1} min^{-1}$ compared to $570 M^{-1} min^{-1}$ for hydroxide with the same substrate. Therefore the semibenzilic mechanism observed is understandable. If the reaction is general to all haloketones, the reaction might be of synthetic value. In the case of isomeric haloketones the desired product could be obtained at will by using the appropriate reagent.

The reaction was tested with the 2α-bromo-cholestan-3-one which had been shown to rearrange with sodium ethoxide to give 8 and 9. It was hoped to obtain only 8 when 2α-bromo-cholestan-3-one was rearranged with the alkaline peroxide. But the reaction products



10 9 8

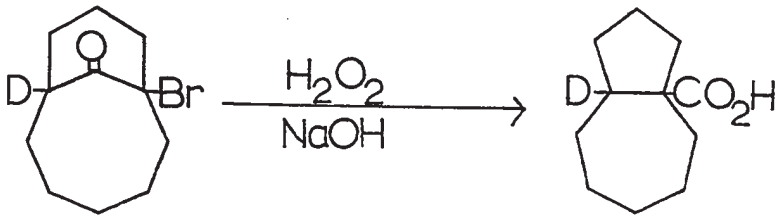
contained at least six compounds shown by TLC analysis. The major product (23%) isolated was the diacid 102, mp 186-189°, which was identified by comparing mixed mp and TLC behaviour with an authentic sample. Due to the complexity of the reaction, it was not investigated



102

further.

But the mechanism of the reaction of the bromoketone 6(8)B with alkaline hydrogen peroxide was further tested with the deuterated bromoketone 6(8)H. The deuterium content of the bromoketone should be retained with the semibenzilic mechanism if there is no prior exchange by the bromoketone. However, the product obtained retained only 74%



6(8)H 5(7)C

of the original deuterium content. The loss of deuterium content in the product might be due to prior exchange before rearrangement or some of the rearrangement occurred by cyclopropanone mechanism. But it was shown that there was no prior exchange before rearrangement in sodium deuteroxide (Table III, reaction 7) by deuterium analysis of the recovered bromoketone 6(8)B. Therefore the loss of deuterium content in the product was due to the rearrangement partly going by cyclopropanone mechanism. It should be pointed out that the reaction medium was two phases and the stirring of the mixture might be important because the amount of semibenzilic mechanism varies in different runs.

The result of the alkaline peroxide rearrangement implies that other strong nucleophiles but weak base would react with the bromoketone 6(8)B by the semibenzilic mechanism. It is worthwhile

looking at other nucleophiles to test this hypothesis.

The next nucleophile tried was cyanide ion. The pK_a of hydrogen cyanide is 10.4, but the rate of nucleophilic displacement ($10.8 M^{-1} min^{-1}$) with p-nitrophenyl acetate is much slower than peroxide and hydroxide. Since the pK_a of hydrogen cyanide is smaller than that of water (15.7) the cyanide ion might promote rearrangement of the bromoketone 6(8)B by the semibenzilic mechanism.

When the bromoketone was treated with sodium cyanide in methanol, a neutral compound, presumably 103, showing IR absorption at 3100-3600 $cm.^{-1}$ and 2240 $cm.^{-1}$ for hydroxyl and cyanide respectively was obtained. There was only 4% of an acidic fraction of complex TLC behaviour. The neutral product was subjected to further reflux in methanol for two days. A yield of 71% of methyl cis-bicyclo[5.3.0]-decane-1-carboxylate and 4% of acidic fraction was obtained. The methyl ester 5(7)E had rotation $[\alpha]_{300}+65.2^{\circ}$ as shown in Table III (reaction 6). It was 57% racemized. The result clearly demonstrated that the rearrangement of bromoketone 6(8)B with sodium cyanide occurred by 57% of cyclopropanone and 43% semibenzilic mechanism.

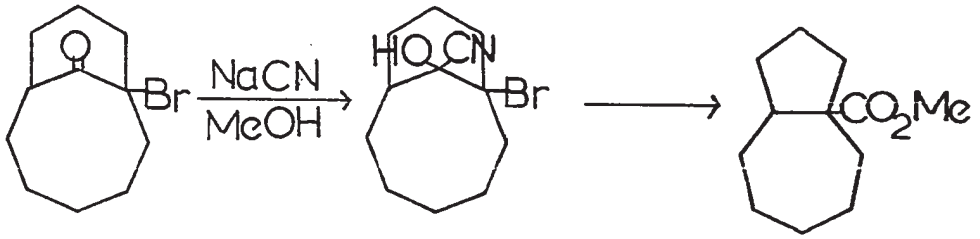
In the system sodium cyanide-methanol there is an equilibrium:

$$NaCN + MeOH \underset{}{\overset{K}{\rightleftharpoons}} NaOMe + HCN \qquad K = \frac{k_1}{k_2}$$

$$MeOH \xrightarrow{K_1} H^+ + MeO^-$$

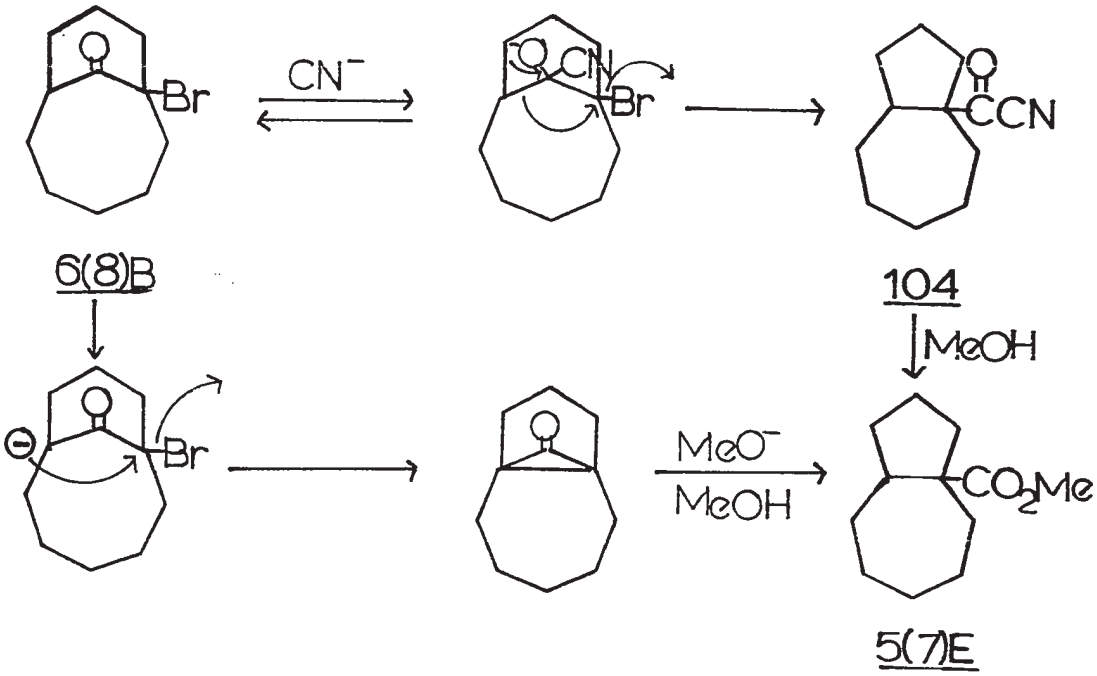
$$HCN \xrightarrow{K_2} H^+ + CN^-$$

The equilibrium constant, K, is calculated to be $10^{-5.6}$, generating a low concentration of methoxide compared to cyanide. The cyanide ion and methoxide ion are in competition for the bromoketone 6(8)B. The



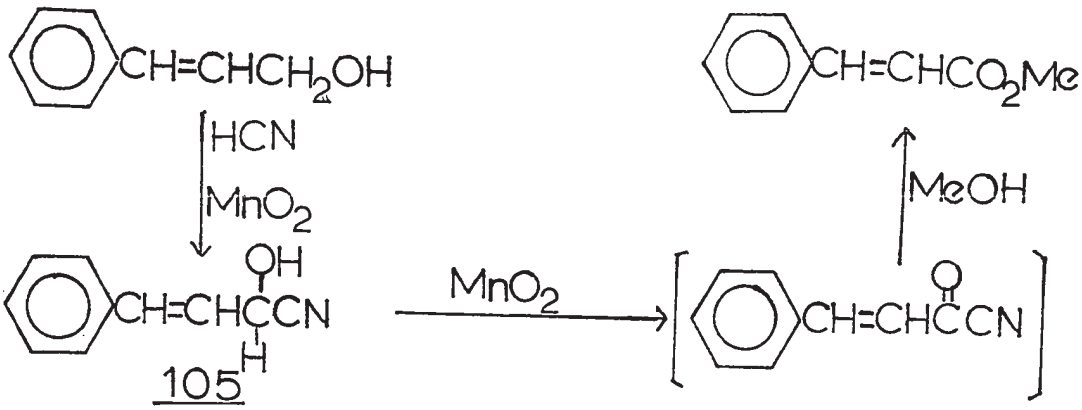
6(8)B 103 5(7)E

cyanide ion is solely responsible for the semibenzilic rearrangement.



The observation of the cyanohydrin 103 and further rearrangement of 103 to product with partial retention of optical purity is strong evidence for semibenzilic mechanism. It is the first time that a semibenzilic mechanism intermediate has been isolated in the Favorskii rearrangement. The acyl cyanide 104 could not be isolated for it was too reactive. Its transient existence was supported by the oxidation of cyanohydrin 105 which gave the methyl ester shown (76). There is

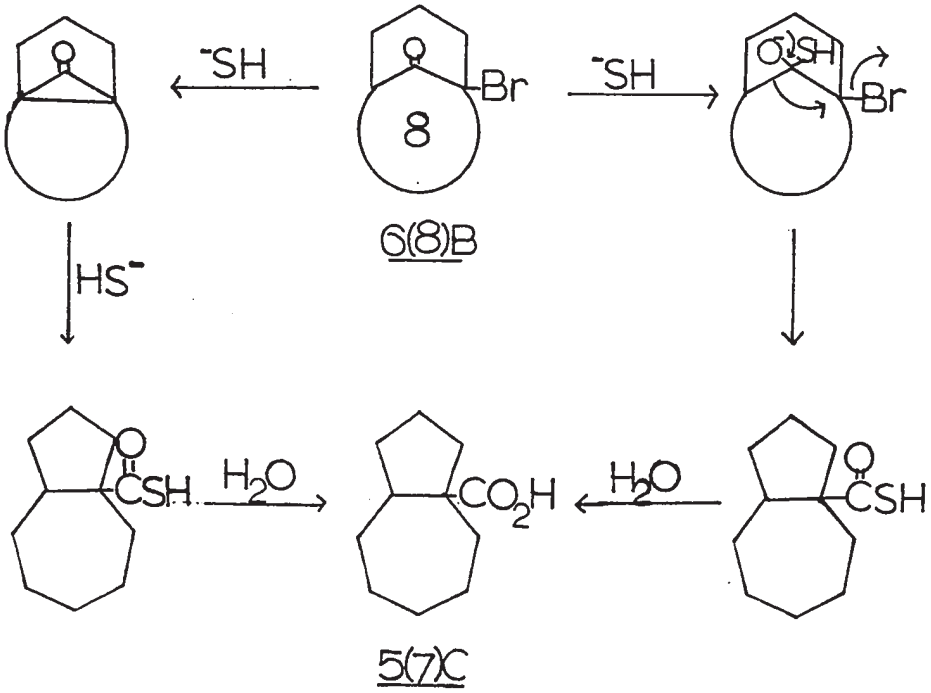
only about 43% of the rearrangement by semibenzilic mechanism and still



57% of cyclopropanone mechanism even at such a low concentration of methoxide. It is quite certain the cyanide ion and not the methanol attacks the carbonyl group to initiate the semibenzilic mechanism because a methanol solution of 6(8)B under reflux for one week showed no methyl ester formation by GLPC analysis.

In continuation of the study of nucleophilicity on the mechanism of rearrangement of bromoketone 6(8)B, the next nucleophile used was hydrosulfide. Hydrogen sulfide has two pK_as, 7.4 and 11.9 and its nucleophilicity towards the carbonyl group is not known. But its nucleophilicity towards saturated carbon is quite high n = 5.1. We may have some rough idea of its nucleophilicity by estimating the nucleophicity from thioethanol, its reaction rate with p-nitrophenyl acetate is 660 $M^{-1}min$ which is comparable to the hydroxide, 570 $M^{-1}min^{-1}$. Therefore, we would expect the hydrosulfide ion to react like cyanide ion. Reaction of bromoketone 6(8)B with sodium hydrosulfide at 90° gave a 27% yield of acid 5(7)C. The acid has rotation $[\alpha]_{300}$+64.1° which corresponds to 66% of racemization (reaction 8) after conversion into ester $[\alpha]_{300}$+51.2°. Another run was performed with a different batch

of bromoketone $[\alpha]_D$-17.6°. A yield of 57% of acid was obtained. The acid was 57% racemized (reaction 9). The results demonstrate that about half of the rearrangement proceeds by the semibenzilic mechanism. No thioacid was detected. This does not mean that the hydrosulfide ion is not the attacking group. Thioacids are known to hydrolyze with water



readily, e.g. the thioacetic acid which hydrolyzes with water to give acetic acid and hydrogen sulfide under heating (77).

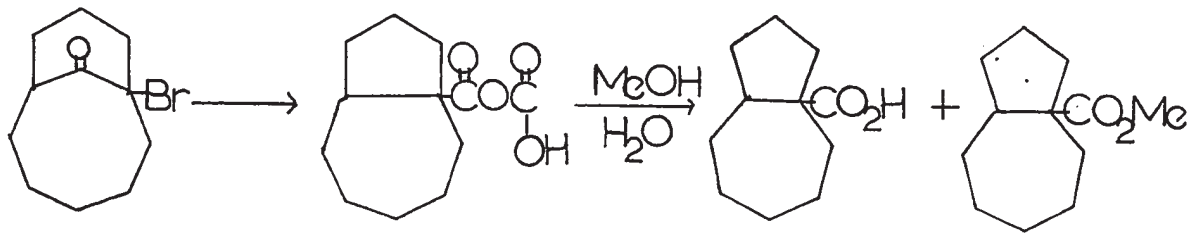
The next nucleophile was bicarbonate ion which is relatively poor in nucleophilicity but which is an even weaker base with pK_a 6.4 and 10.4. The bicarbonate ion is readily hydrolyzed in water to give carbonate which is more basic than bicarbonate. If the carbonic acid decomposes into water and carbon dioxide which is driven off, the

$$2HCO_3^- \rightleftharpoons CO_3^= + H_2CO_3 \qquad HCO_3^- + H_2O \rightleftharpoons H_3O^+ + CO_3^=$$

$$\Downarrow\Uparrow$$

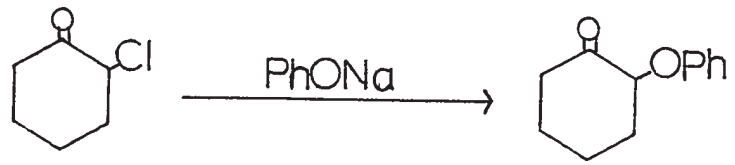
$$CO_2 + H_2O$$

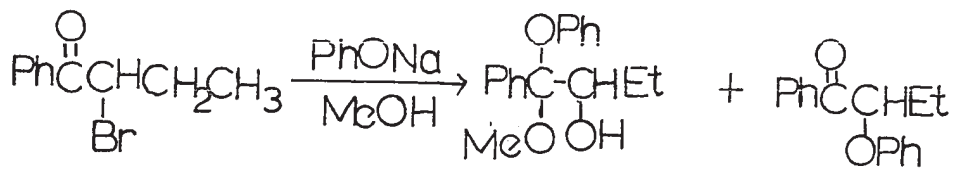
resulting solution would be strongly alkaline which means there will be more racemization. Reaction of bromoketone 6(8)B with a methanolic solution of potassium bicarbonate gave 39% of methyl ester 5(7)E and 43% of acid 5(7)C. The acid was converted into ester 5(7)E and the esters had rotations $[\alpha]_{300}$+27.2° (from acid) and $[\alpha]_{300}$+14.0° (from reaction) which corresponded to 82% and 91% racemization respectively (reaction 5). The rearrangement was mainly by cyclopropanone mechanism. The 10% to 18% of semibenzilic mechanism may come from the attack by one of the three bases, bicarbonate ion, methoxide and hydroxide, on the carbonyl group. If the bicarbonate ion were the attacking group, the acyl carbonate would be first formed and was hydrolyzed or methanolyzed to acid or ester.



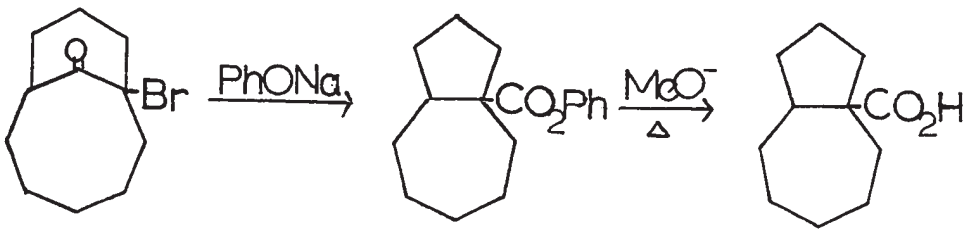
6(8)B 5(7)C 5(7)E

The last nucleophile to be studied was the phenolate ion. This ion had been reported in several instances to give no Favorskii product but only substitution product (39, 79). It was of interest to see whether our bicyclic system, which excludes substitution reactions,





would give Favorskii rearrangement, and at the same time what effect the phenolate would have on the mechanism of the rearrangement. The rate of nucleophilic attack at the carbonyl group of p-nitrophenyl acetate is relatively slow ($58 M^{-1} min^{-1}$) as compared to unhindered alkoxides such as methoxide ($2.9 \times 10^{4} M^{-1}$). Since it is a poor nucleophile it may give more cyclopropanone than semibenzilic mechanism even with a low pK_a, 10.0. The reaction of bromoketone 6(8)B with sodium phenolate in dioxane gave a 54% of phenyl cis-bicyclo[5.3.0]-decan-1-carboxylate 5(7)P. The IR spectrum of the ester showed 1740 cm^{-1} for the ester carbonyl and the PMR spectrum showed absorptions at 2.5-2.9 ppm for the tertiary hydrogen at the ring junction and 6.8-7.3 ppm for the five protons of the phenyl group. No precipitate was obtained when the neutral product was treated with 2,4-dinitro-phenylhydrazine reagent. The ORD curve of the purified product showed no rotation from 700-300 nm. The phenyl ester was hydrolyzed into acid 5(7)C whose ORD curve also showed no rotation from 700-300 nm. The

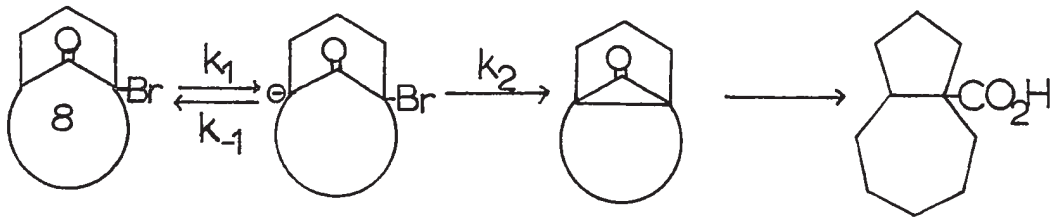


6(8)B 5(7)P 5(7)C

racemic product indicates that the rearrangement occurred by a symmetrical mechanism. The phenol has a low pK_a (10.0) compared to other bases, but 100% of cyclopropanone mechanism was observed. The base strength of

sodium phenolate will be considerably larger in dioxane than in water.

It was shown before that the rearrangement of bromoketone 6(8)B with sodium hydroxide in aqueous ethanol was by cyclopropanone mechanism. The first step for the cyclopropanone formation is the abstraction of the α'-hydrogen to form a carbanion. This step is reversible for an ordinary ketone under base catalyzed exchange. But in the case of a haloketone this may not be so, the consequent step of cyclopropanone formation may be faster than the reversal (73). The relative rates for hydrogen abstraction and cyclopropanone formation were measured. When an excess of bromoketone 6(8)B, $[\alpha]_{321}$ -564° was allowed to react with a limited amount of sodium deuteroxide in ethanol-d, the acid was 91% racemized and contained 19.5% d_o and 80% d_1. The recovered bromoketone $[\alpha]_{320}$ -594° contained 99.2% d_o and 0.8% d_1, i.e. the bromoketone retained its full optical activity and there was no exchange before rearrangement. The relative rates are $k_2 \geq k_{-1} \gg k_1$. The complete retention of optical activity in the recovered bromoketone

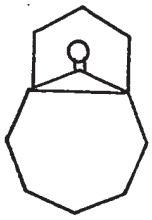


6(8)B 5(7)C

means that the carbanion goes to a symmetrical intermediate, oxyallyl or cyclopropanone, irreversibly.

(B) Attempts to Detect the Cyclopropanone 94

During our course of investigation of the mechanism of rearrangement of bicyclic haloketones, it was reported that two stable cyclopropanones had been isolated and characterized (47). The exceptional stability of cyclopropanones prompted us to attempt to isolate the elusive cyclopropanone 94. Since our work is mainly on the study of the



94

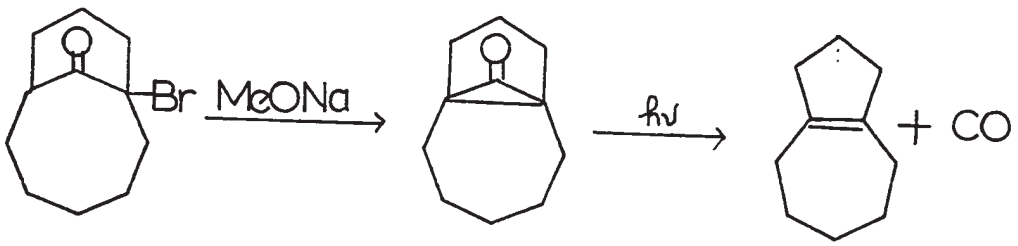
mechanistic variations of the rearrangement of haloketones 6(6), 6(7) and 6(8), only relatively little effort was devoted to attempt to isolate the cyclopropanone.

From the fact that the two stable cyclopropanones contain two bulky t-butyl groups which presumably protect the carbonyl group from nucleophilic attack, therefore the addition of a bulky nucleophile to the carbonyl group will be slower so that if a cyclopropanone were formed under the reaction conditions it might survive. A solution of the sodium alkoxide of 3-ethyl pentan-3-01 and the bromoketone 6(8)B was stirred at room temperature for 24 hours, TLC of the solution showed no reaction. The reaction was too slow at room temperature. The alkoxide might be too bulky to abstract the α'-hydrogen.

In the hope of seeing the cyclopropanone directly in the IR spectrum, the bromoketone 6(8)B was pressed into a potassium bromide disk with sodium hydroxide and the disk was directly attached to the

IR spectrometer. The absorption at 1810 $cm.^{-1}$ of cyclopropanone did not show up even after several hours. The reaction may have been over for the heat developed in pressing of the disk may already have caused reaction in the press.

Attempts were also made to isolate the $\Delta^{1,7}$-bicyclo[5.3.0]-decene by irradiation of a Pyrex tube containing bromoketone 6(8)B and sodium methoxide. The reaction gave a complex mixture of products and GLPC analysis of the product did show some material possibly



6(8)B 94

corresponding to the retention time of $\Delta^{1,7}$-bicyclo[5.3.0]decene assuming the retention time close to $\Delta^{9,10}$-octalin. Due to the complexity of the products, it was not investigated further.

The geometry of the dibromoketone 6(8)F is favourably set up for formation of cyclopropanone if a 1,3-diradical is generated. A solution of dibromoketone in tetrahydrofuran was stirred with magnesium turnings for several hours, TLC analysis of the reaction mixture showed no reaction. A few pieces of lithium foil were added with further stirring for a few hours but still TLC showed no reaction. The starting

dibromoketone 6(8)F was recovered.

From the above observations the cyclopropanone 94 is not as easily formed as we first thought. Since our major work is not on the study of cyclopropanones in general, no further investigation was done.

(C) 1-Chlorobicyclo[5.3.1]undecan-11-one 6(8)C

In the study of the halogen effect on the rearrangement mechanism of the haloketone 6(7) it was found that the halogen had no effect on the mechanism. One of the possible reasons is the α'-hydrogen in the haloketone 6(7) is so non-acidic that the chlorine atom was not able to increase its acidity enough to effect a change in the mechanism. The rearrangement of 1-chlorobicyclo[5.3.1]undecan-11-one 6(8)C was studied. The yield of product, rotations, deuterium contents and percentage of racemization are tabulated in Table IV. The yields of the product from the chloroketone, as with the bromoketone 6(8)B, are good. Only the cis-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C was identified; the neutral fractions (10%-20%) were not investigated. The acid was characterized by comparing its PMR, IR spectra, mp and retention time of its methyl ester with those of the authentic sample.

At the beginning of the study, the silver nitrate aqueous methanol reaction was done with the chloroketone 6(8)C. The reaction, as with that of bromoketone 6(8)B, was slower than the bromoketones 6(6)B and 6(7)B, but gave a yield of 69% of cis-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C, $[\alpha]_{300}$ -92° (reaction 1). The chlorine atom being more electronegative than the bromine would acidify the α'-hydrogen more so that the chloroketone 6(8)C might rearrange by the cyclopropanone

TABLE IV

Rearrangement of 1-Chlorobicyclo[5.3.1]undecan-11-one 6(8)C

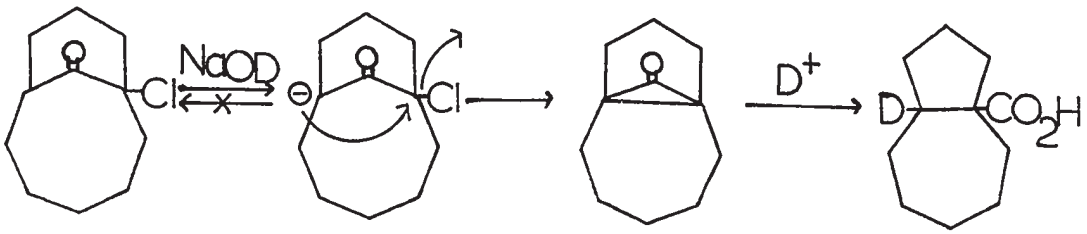
Run	Conditions	 COOH %	Rotations at 300 nm.	Deuterium Content	% Racemization
1	$AgNO_3$-MeOH-H_2O	69	-92 ± 2		0
2	NaOH-H_2O_2-Bu^tOH	80	-19 ± 1^o		79
3	NaOH-H_2O_2-Bu^tOH	86	-18 ± 1^o		80
4	NaOH-EtOH-H_2O	73	0		100
5	$KHCO_3$-MeOH	37	0		100
6[a]	NaOD-EtOD-D_2O	21	$+8 \pm 2^o$	11.3% d_o 88.7% d_1	94
			$[\alpha]_{318}$ -607.9[c]	98.7% d_o 1.3% d_1	9.8
7[b]	MeONa-MeOH	 COOMe	0		100

a. With chloroketone $[\alpha]_{322}$ - 674°; the other with $[\alpha]_{320}$ + 479.4°

b. Preliminary kinetic run on ORD cell, product was not isolated but identified by TLC.

c. Recovered chloroketone 6(8)C, Vpc of the sample showed about 1% of other material.

mechanism to a greater extent with ordinary basic conditions. But at the same time the chlorine atom increases the electrophilicity of the carbonyl carbon and the attack on the carbonyl group will also increase. Reaction of the chloroketone 6(8)C with sodium hydroxide gave a 73% yield of acid 5(7)C which was entirely racemic (reaction 4). Another run with excess chloroketone in deuterated solvent, the acid contained 11.3% d_o, 88.7% d_1 and had rotation $[\alpha]_{300}+8.0^{\circ}$. The recovered chloroketone contained 98.7% d_o, 1.3% d_1 and retained at least 90.2% of its optical activity.* The results showed that the rearrangement was essentially 100% by the cyclopropanone mechanism and that there was no exchange before rearrangement. Even with the weaker base potassium bicarbonate in methanol, the acid obtained was 100% racemic (reaction 5).

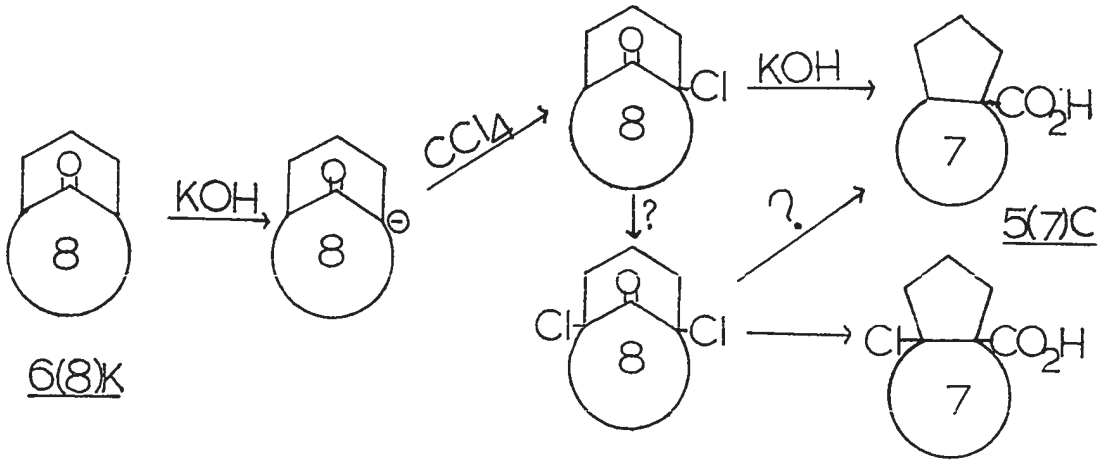


6(8)C 5(7)C

* The deuterium analysis data 1.3% d_1 is not compatible with the optical rotation result with 9.8% of racemization. GLPC analysis revealed that recovered chloroketone contained about 1% of an impurity. If this impurity were optically active and with opposite sign of rotation, it might account for the discrepancy. Therefore, greater reliance is placed on the deuterium analysis to indicate that essentially no racemization occurred.

With sodium methoxide in methanol also 100% of cyclopropanone mechanism was observed. The bicarbonate result clearly showed that the chlorine atom has considerable effect on the mechanism of rearrangement which is dependent on the acidity of the α'-hydrogen. Finally the alkaline hydrogen peroxide reagent was used for the rearrangement. It was found that the acid 5(7)C obtained was 80% racemized (reaction 3). There was almost a complete change of mechanism from bromoketone 6(8)B to chloroketone 6(8)C with the same reagent. It can be seen that the α'-hydrogen of chloroketone 6(8)C is comparable in acidity to those of ordinary α-haloketones which rearrange by a cyclopropanone. It is noteworthy that only 5% of neutral product was produced, and there was no evidence of the formation of $\Delta^{1,7}$-bicyclo[5.3.0]decene.

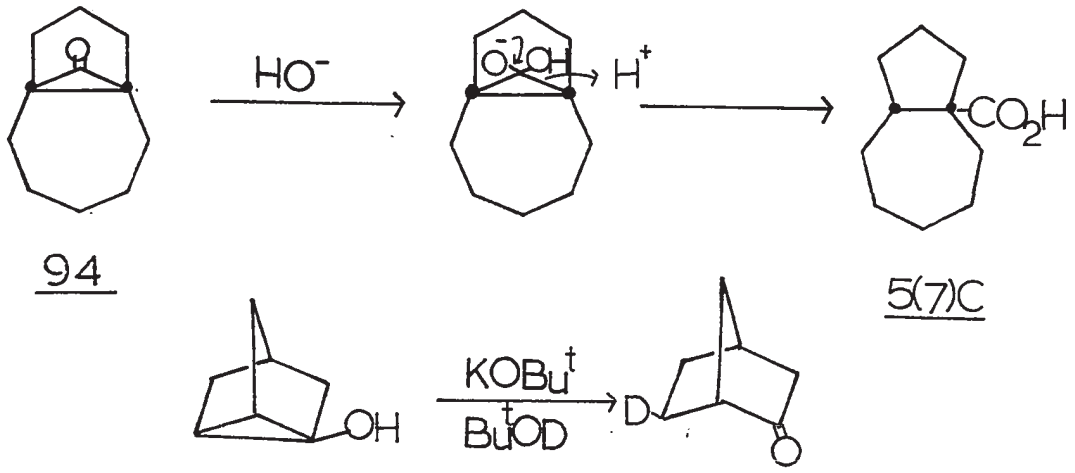
It was reported that a Favorskii acid was isolated when a mixture of base, carbon tetrachloride and a ketone were heated, and the reaction was rationalized as generation of the haloketone in situ and further reaction with base to give acid (78). A yield of 78% of acid 5(7)C was obtained in the reaction of alkaline carbon tetrachloride with ketone 6(8)K. There was no 7-chloro-cis-bicyclo[5.3.0]decane-1-carboxylic acid detected. This indicates that the intramolecular cyclopropanone formation was faster than the second chlorination step. In fact this reaction also gives an indication of the existence of carbanion at the bridgehead for chlorination.



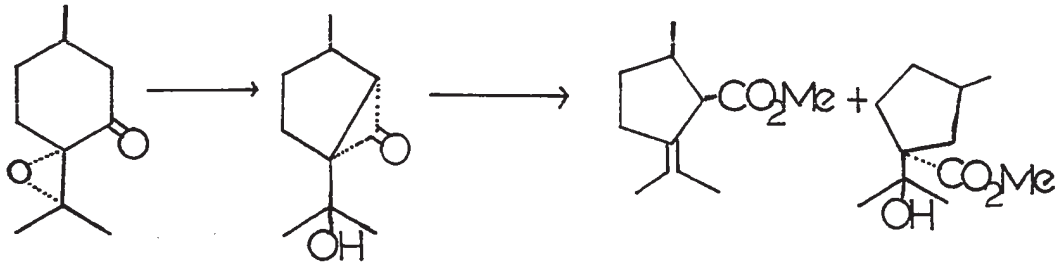
(D) Stereochemistry of the Product

The product obtained from the rearrangement of the haloketones 6(8)B and 6(8)C was cis-bicyclo[5.3.0]decane-1-carboxylic acid. There was no trace of trans-acid 5(7)T within the sensitivity of the GLPC technique (<0.1%). The stereochemistry of the product was determined by comparing the mp, IR spectra and GLPC behaviour of the methyl ester of the product with authentic cis and trans-acids, 5(7)C and 5(7)T. The preparation of the authentic cis- and trans-acids, 5(7)C and 5(7)T is discussed in Chapter V.

In contrast to the cyclopropanol opening (80), the exclusive formation of the cis-acid 5(7)C from the cyclopropanone mechanism means that the opening of the cyclopropanone ring occurs with retention. Reusch and Gassman have also observed the opening of cyclopropanone and



cyclopentanone rings with retention of configuration (81, 82). For the case of the semibenzilic mechanism the acid 5(7)C was also cis. Furthermore, the rearrangement of haloketones 6(6)B, 6(7)B and 6(7)C also gave cis product, as was proved by Dr. W.T. Tai. In short all



the three homologous haloketones all give cis product exclusively. The cis product was the consequence of the stereochemistry of the starting bromoketones. For the bromoketones 6(6)B and 6(7)B the bromine atom and the α'-hydrogen have to be cis and diequatorial, for trans or diaxial configurations are too strained as seen from Dreiding models. The bromoketone 6(8)B ring is large enough to have cis-diaxial and trans configurations. But in the preparation of bromoketone 6(8)B there were many opportunities for a less stable trans ring fusion to epimerize to cis by enolization. Spectroscopic evidence showed that the configuration of the halogens in haloketones 6(7)B, 6(7)C, 6(8)B and 6(8)C were all nearly equatorial with respect to the cyclohexane ring, (Chapter V). If the hydrogen and halogen are in the cis-diaxial and trans configurations, the rings will be highly strained. Therefore, the haloketones 6(6)B, 6(7)B, 6(7)C, 6(8)B and 6(8)C all have cis-diequatorial configurations. The cis-diequatorial configuration is well set up for semibenzilic mechanism to give cis-product. In order to form a cyclopropanone a double inversion at the α and α'-carbons is required. The

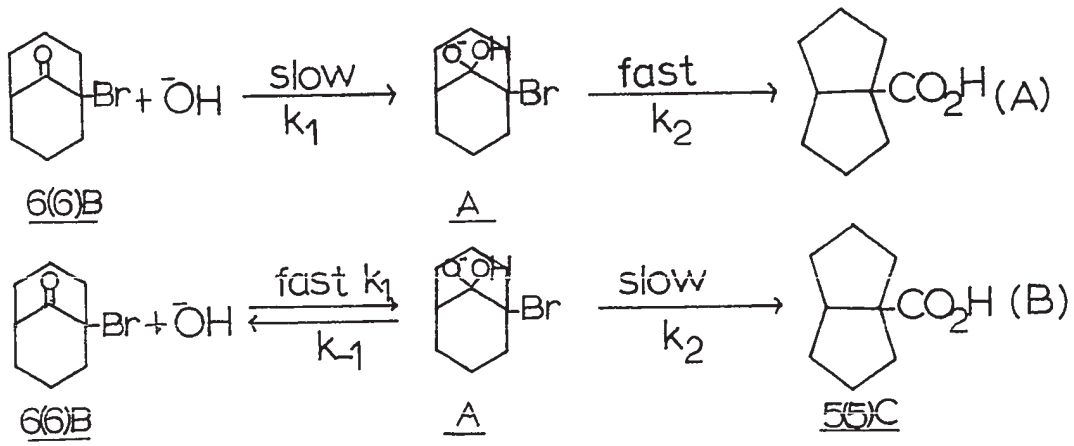
cis diequatorial configuration of hydrogen and bromine will give the *cis* cyclopropanone whereas the *trans* configuration will give *trans* cyclopropanone which is not possible in our system. Therefore, the *cis* cyclopropanone gives *cis* product which proves that the ring opening of the cyclopropanone occurs with retention of configuration.

CHAPTER IV

Kinetic Study of the Favorskii Rearrangement of 1-Halobicycloalkanones

Discussions in the previous sections were mainly concerned with the studies in determining the overall mechanisms of the rearrangement of the haloketones 6(6), 6(7) and 6(8). The relative rates of the rearrangements, the detailed steps of the rearrangement, such as the rate determining step and the rate of halide release, have not been considered. In the case of the cyclopropanone mechanism, it is not clear that whether the mode of forming the cyclopropanone intermediate is concerted or stepwise. The above information can be obtained from deuterium exchange study, kinetic isotope effect and leaving group effects. Therefore a kinetic study on the bicyclic haloketones was carried out.

For the bromoketones 6(6)B and 6(7)B, it was shown that both bromoketones rearranged by the semibenzilic mechanism. There are variations for the semibenzilic mechanism as shown below. In path (A) the addition of hydroxide is a slow step followed by the fast



ejection of bromide. Path (B) involves a fast reversible addition of hydroxide on the carbonyl group and then the bromide is released in a slow step. If the rate of the reaction is followed by the rate of halide release, the observed rate for path (A) is simply

$$\text{Rate} = k_1 \text{ (bromoketone)(base)}$$

The reaction is second order being first order each in bromoketone and base. The observed rate constant will be k_1 and the second fast step (k_2) is not included in the observed rate. For path (B), the rate of halide release is

$$\text{Rate} = k_2 (\underline{A}) \tag{1}$$

from the steady-state approximation, the small concentration of the intermediate $\underline{A}$ may be considered essentially constant. Therefore, the following relation holds

$$k_1\text{(bromoketone)(base)} = (k_{-1} + k_2)(\underline{A}) \tag{2}$$

Substitution of ($\underline{A}$) from equation (2) into equation (1),the observed rate of the halide release in terms of k_1, k_{-1} and k_2 is obtained as (3).

$$\text{Rate} = \frac{k_1 k_2}{(k_{-1} + k_2)}\text{(bromoketone)(base)} \tag{3}$$

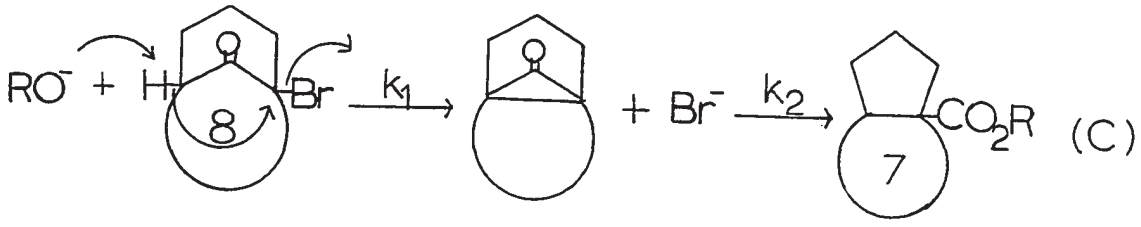
If $k_2 > k_{-1}$, the rate of halide release is equal to k_1 which is the same as in the path (A). We may say path (A) is a special case of path (B). If $k_{-1} > k_2$, the observed rate will be

$$\text{Rate} = Kk_2 \text{ (bromoketone)(base)} \tag{4}$$

where K is the equilibrium constant for the formation of $\underline{A}$. The halide

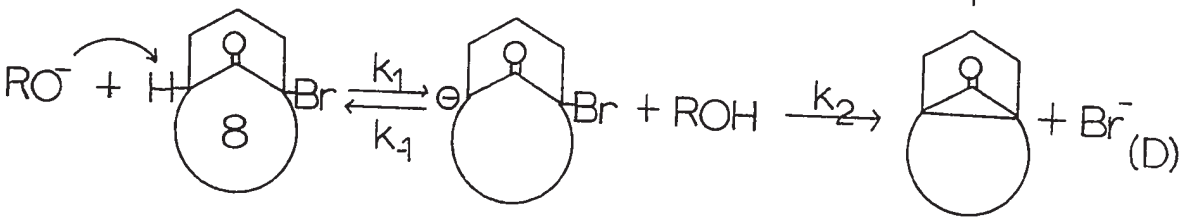
release will be the rate determining step. It is to be noted that in path (A), k_1 is the rate determining constant whereas in path (B), k_2 is rate determining if $k_{-1} > k_2$. Both being second order, they are kinetically indistinguishable. For the path (A) mechanism since the C-X bond is not broken at the rate determining step the nature of the halogen affects the rate primarily by the inductive effect of the halogen on the reactivity of the carbonyl group. For path (B) the rate of halide release is dependent on the nature of the halide if $k_{-1} > k_2$. The change of halide should show a greater change on the rate of reaction since the C-X bond is broken in the rate determining step.

For haloketone 6(8) which most likely rearranges by a cyclopropanone intermediate, there are two paths for the formation of the cyclopropanone, (C) and (D). Path (C) is a concerted mechanism, the



6(8)B

5(7)C



6(8)B

hydrogen abstraction and halide release occur simultaneously to give the cyclopropanone. The product formation step, k_2, does not affect the rate of halide release. The observed rate would be

$$\text{Rate} = k_1 \text{ (bromoketone)(base)} \qquad (5)$$

The rate of halide release is also the rate of formation of the cyclopropanone. The rate of halide release is determined mainly by the breaking of the C-X bond. The change of halogen should have a profound influence on the rate of halide release. Since the C-H bond is broken at the rate determing step, an appreciable deuterium kinetic isotope effect should result. Path (D) is a stepwise mechanism which involves the abstraction of hydrogen to form a carbanion first and then halide release follows. Whether the cyclopropanone is formed directly from the carbanion or by way of oxyallyl is not known. The two possibilities are kinetically indistinguishable. The abstraction of hydrogen could be reversible depending on the relative rates of k_{-1} and k_2. For $k_2 > k_{-1}$, the first step is irreversible. The rate of halide release is

$$\text{Rate} = k_2 \text{ (carbanion)}$$

Applying the steady-state approximation as before, the rate can be derived in terms of k_1, k_2 and k_{-1}

$$\text{Rate} = \frac{k_1 k_2}{k_{-1}[\text{Base-H}] + k_2} \text{ (bromoketone)(base)} \qquad (6)$$

If $k_2 > k_{-1}$ the observed rate is reduced to

$$\text{Rate} = k_1 \text{ (bromoketone)(base)}$$

The rate of hydrogen abstraction is the rate determining step. The nature of the halogen has little effect on the rate of the reaction except for the inductive effect on the α'-hydrogen. At the same time the reaction will show an appreciable deuterium kinetic isotope effect. Furthermore the recovered haloketone will not have incorporated deuterium when the rearrangement is done in deuterated solvent. If k_{-1}[Base-H] > k_2, the first step is reversible. The observed rate reduces to

$$\text{Rate} = Kk_2 \text{ (bromoketone)} \frac{\text{(base)}}{\text{(base-H)}} \qquad (7)$$

where $K = k_1/k_{-1}$. Here the observed rate involves the rate of halide release. For this case, the nature of the halogen will have a profound effect on the observed rate and the rate of halide release is the rate determining step. Due to the preequilibrium, there will be extensive α'-H exchange before halide release and a small or unity deuterium isotope effect will be observed for the rearrangement. There is no distinct difference between the semibenzilic and cyclopropanone mechanism kinetically in the overall reaction order but for the cyclopropanone mechanism, the rate is dependent on the concentration ratio of the base and its conjugate acid if k_{-1}[Base-H] > k_2 provided that the solvent used is not Base-H.* The rate of formation of product is the same as the observed rate of halide release in the semibenzilic mechanism, but the rate of product formation might not be the same as

---

* If a neutral base is used and tight ion pair is formed, the rate of reversal of the first step is independent on [Base-H]. Therefore the rate will not be dependent on the concentration ratio of the base and base-H. This possibility does not apply to our case for sodium methoxide is used as base.

the observed rate of halide release in the cyclopropanone mechanism which involves a further step in collapse of cyclopropanone to product. We do not know the relative rates for the cyclopropanone formation and decomposition with base.

The kinetic study was carried out by determining the amount of halide released in the rearrangement solution by potentiometric titration or by the Volhard method (see experimental). Both methods gave satisfactory results. Potentiometric titration was better in the case of reactive bromoketone which might react with the silver nitrate. The low concentration of halide ion and relatively high solubility of silver chloride sometimes caused difficulty in detecting the end-point in the Volhard method for the present studies. The relative rates of the rearrangement of the haloketones 6(6), 6(7) and 6(8) had been noted already, bromoketone 6(6)B being the fastest and 6(8)B being the slowest in the series. The preparative experiments of all three haloketones gave excellent yields of rearranged product. The yields of the products were not determined in the kinetic runs, but the reaction solution was checked by GLPC or TLC analysis which showed the starting haloketones and the Favorskii products, and sometimes only the products. Therefore it is safe to say that the rearrangement of haloketones under the kinetic condition also gave quantitative yields of Favorskii products only and no other products.

The bromoketone 6(6)B was most reactive and its rearrangement was conveniently studied at 0°. It was observed that this bromoketone even reacted with methanol solvent slowly at room temperature. The stock solution of bromoketone 6(6)B did not give reproducible results after a week, so a fresh solution of bromoketone 6(6)B was used for

every run. On the other hand, bromoketone 6(7)B and 6(8)B are stable in methanol at room temperature for weeks. A control experiment had shown that the bromoketone 6(8)B was stable in refluxing methanol for a week. The order of the reaction was determined by changing of the substrate to base ratio in the kinetic run. The kinetics gave good straight lines for second order plots. Some of the second order plot of haloketones 6(6), 6(7) and 6(8) are shown in Figures 1-7. The kinetic data were analyzed using a computer program, written by Dr. S.C. Liao*, from which the slope of the best straight lines ($Y = mx + b$) was obtained by the least squares method. The rate constants were determined from the slope of the line.

The rate constants and activation parameters for haloketones 6(6), 6(7) and 6(8) are listed in Table V. The bromoketone 6(6)B is about 300 times** faster than bromoketone 6(7)B in semibenzilic rearrangement at 0°. The greater rate of bromoketone 6(6)B might be attributed to higher strain in the carbonyl group of the bromoketone 6(6)B compared to bromoketone 6(7)B (vide infra). It is interesting to compare the rate of bromoketone 6(7)B and of bromoketone 6(8)B although the mechanisms are different, the former is about 2-3 times faster than the latter. In the bromoketone 6(7)B, the cyclopropanone mechanism is excluded by the ring size and only the semibenzilic mechanism is in operation with sodium methoxide, whereas in bromoketone 6(8)B both semibenzilic and cyclopropanone mechanisms could operate.

---

* We thank Dr. S.C. Liao for lending us the program.

** It was estimated from the activation energy of the bromoketone 6(7)B (113).

TABLE V

Kinetic Data for the Rearrangement of 1-Halobicycloalkanones

Substrate	Temperature	Base/Solvent	k x 10 ($M^{-1}min^{-1}$)	K_{Br}/K_{Cl}	E_a	$\Delta S^{\neq}$	K_H/K_D
Bromoketone 6(6)B	0°	MeO^-/MeOH	0.927[a]				
			0.934[a]				
	0°	NaOH/  /H_2O	141[b] 169				
	0°	NaOH/  /H_2O	140[b]				
Bromoketone 6(7)B	75°	MeO^-/MeOH	6.16		21±0.6[d]	-9.7[c,d]	
	83	MeO^-/MeOH	11.7				
Bromoketone 6(8)B	75°	MeO^-/MeOH	2.23	2.1	21±0.9	-9.8	
	84°	MeO^-/MeOH	5.42	2.1			
	95°	MeO^-/MeOH	12.2	1.9			
Bromoketone 6(8)H	84°	MeO^-/MeOH	.908	1.1			6.0
Chloroketone 6(8)C	75°	MeO^-/MeOH	1.09		22±0.6	-9.5	
	84°	MeO^-/MeOH	2.59				3.1
	95°	MeO^-/MeOH	6.25				
Chloroketone 6(8)J	84°	MeO^-/MeOH	.842				

TABLE V (contd.)

a. The ratio of concentration of haloketone to base was 1:4 and 1:8

b. The concentration ratio of haloketone to base was 1:4 and 1:2

c. Calculated from $k = e(\frac{kT}{h})e^{\Delta S^{\neq}/R} e^{-Ea/RT}$ (113)

d. E_a(kcal/mole), $\Delta S^{\neq}$ (eu)

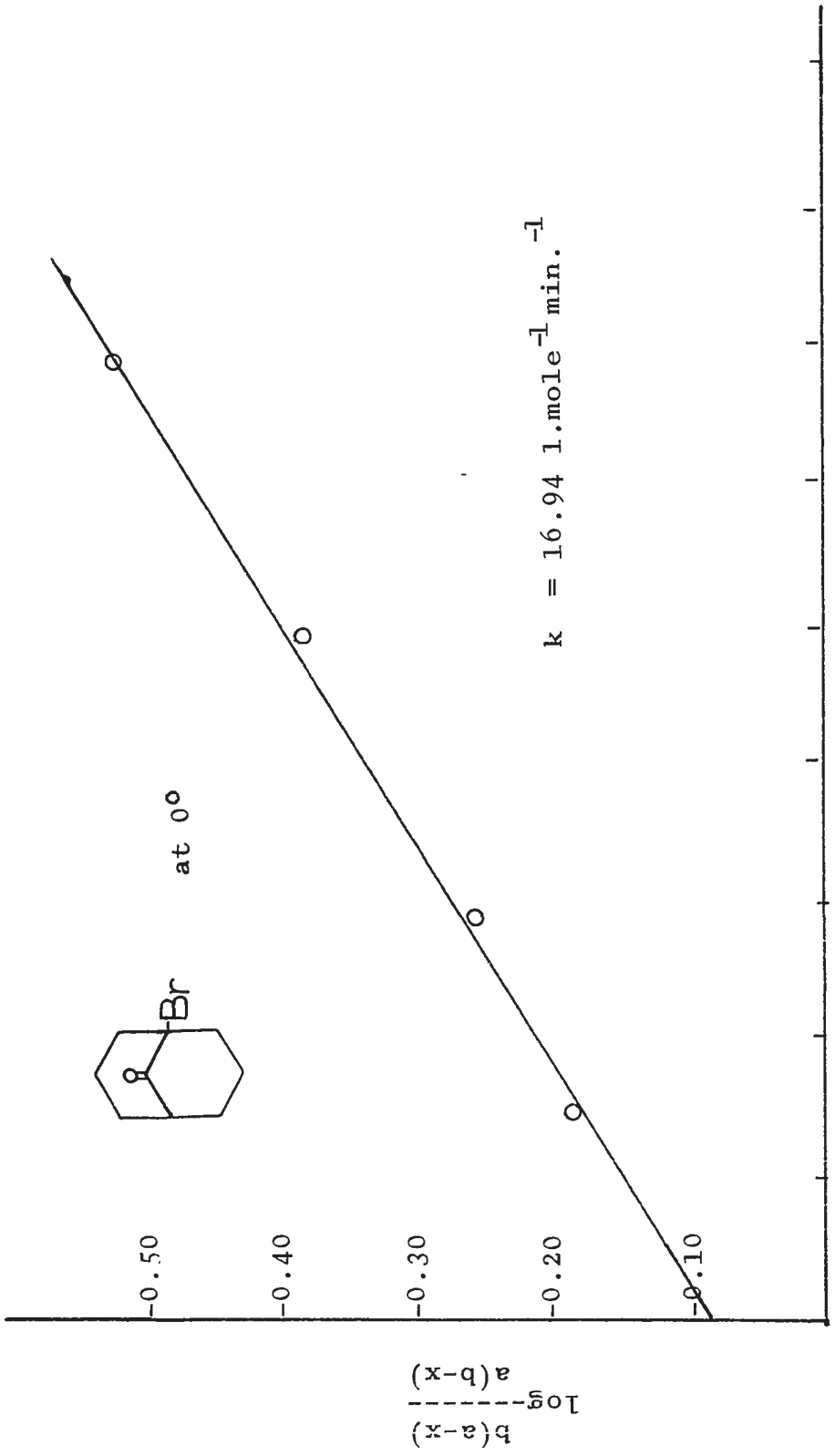


Fig.1. Reaction of Bromoketone 6(6)B with sodium hydroxide in aqueous dioxane.

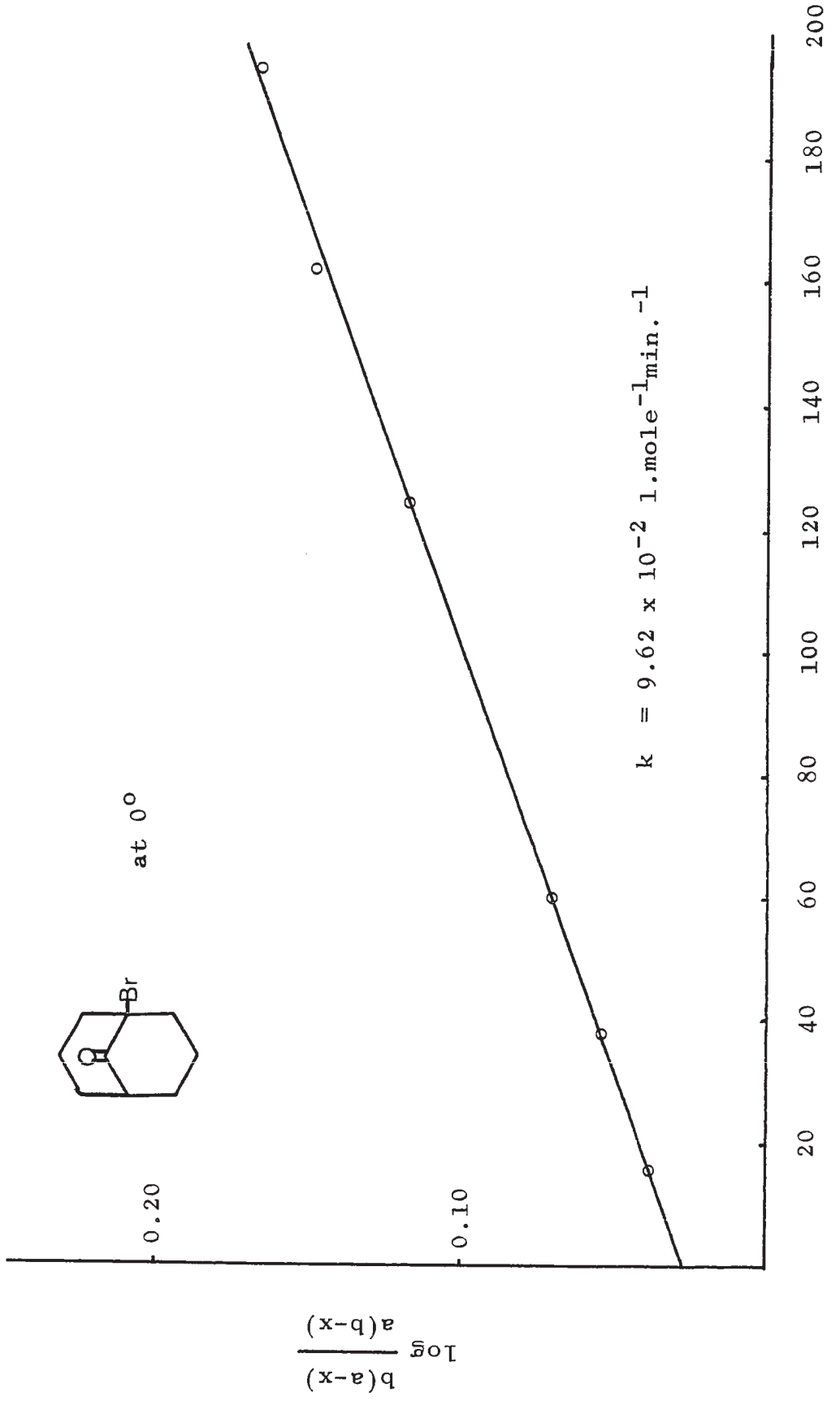


Fig. 2. Reaction of Bromoketone 6(6)B with sodium methoxide in methanol.

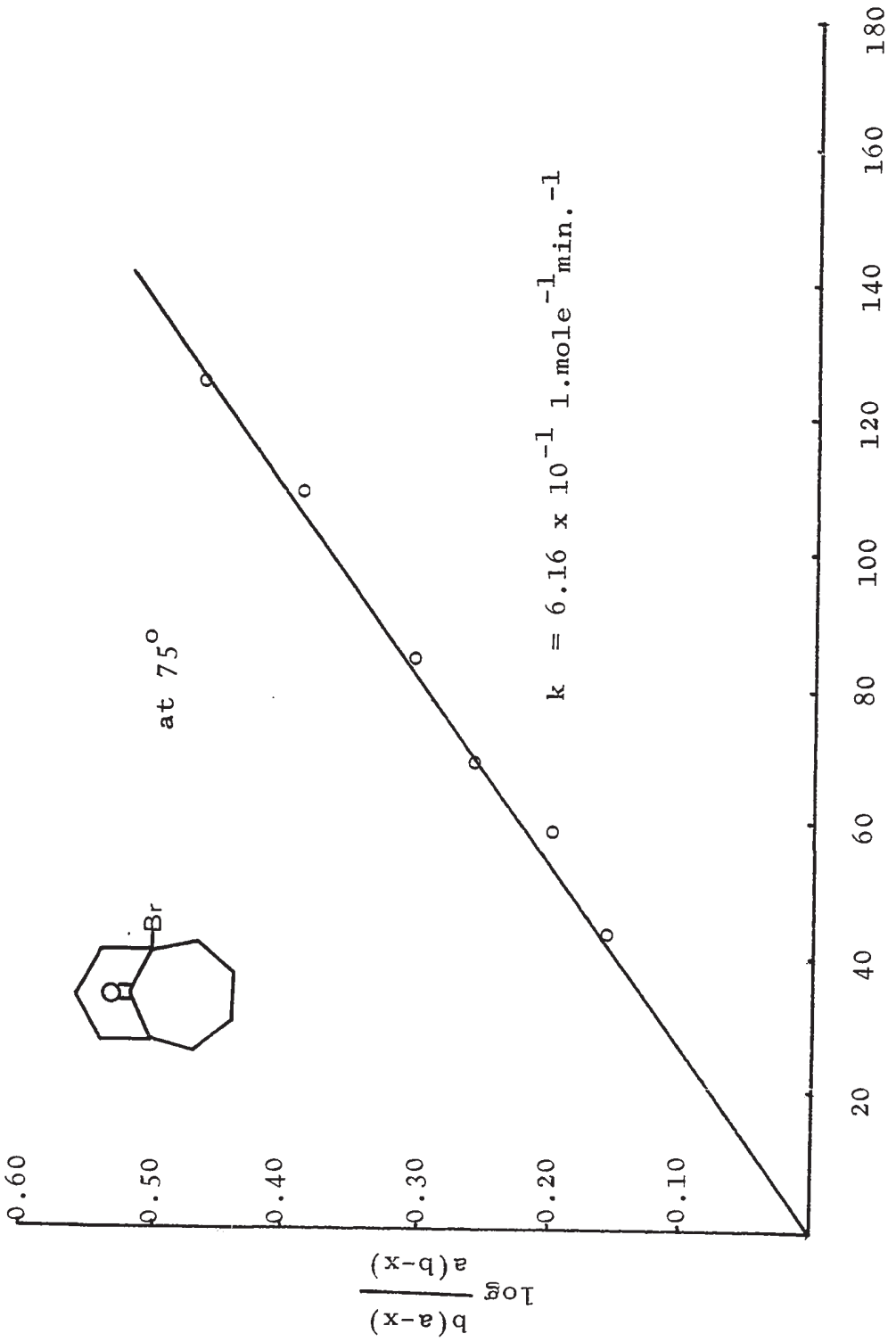


Fig. 3. Reaction of Bromoketone 6(7)B with sodium methoxide in methanol.

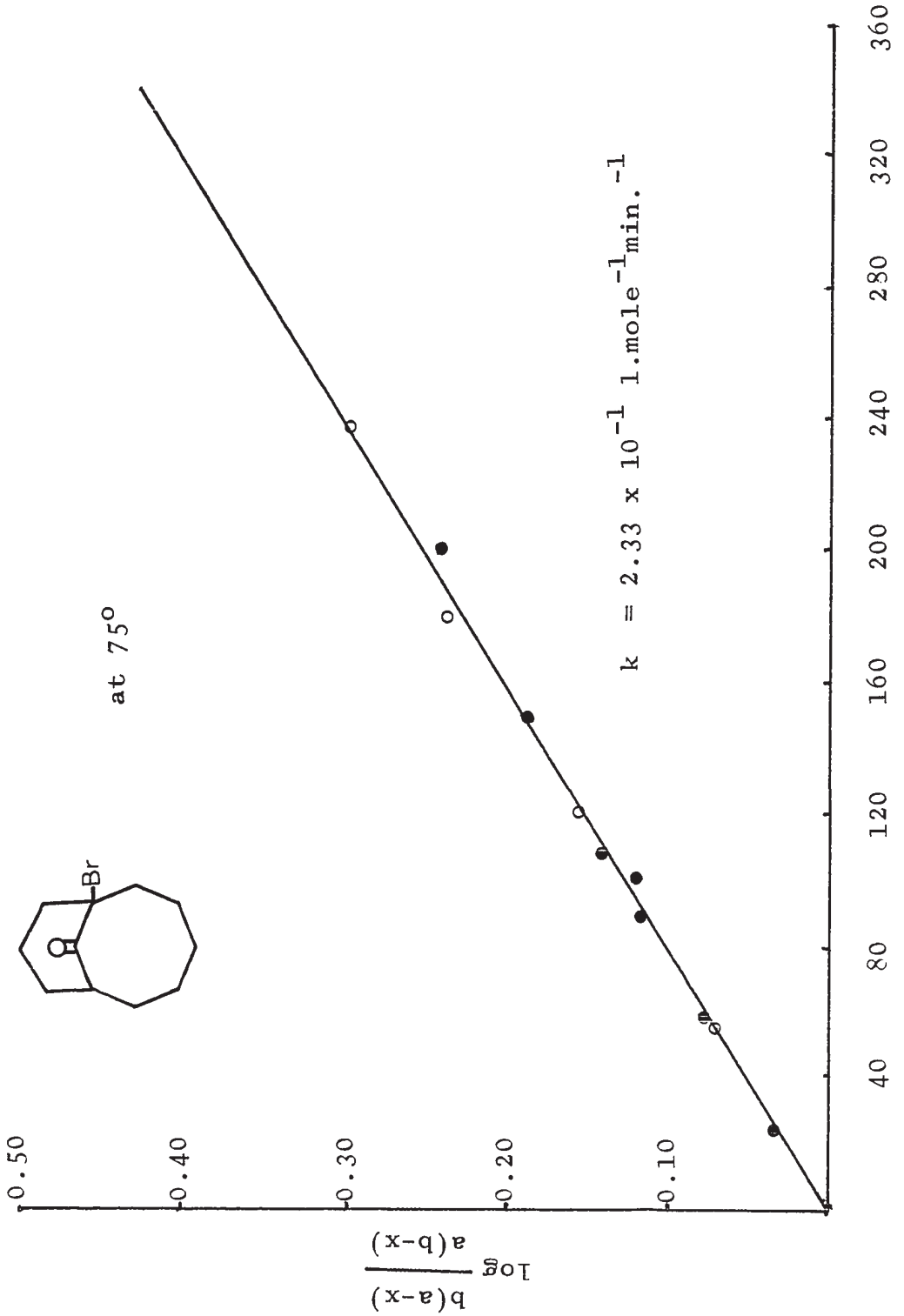


Fig. 4. Reaction of Bromoketone 6(8)B with sodium methoxide in methanol.

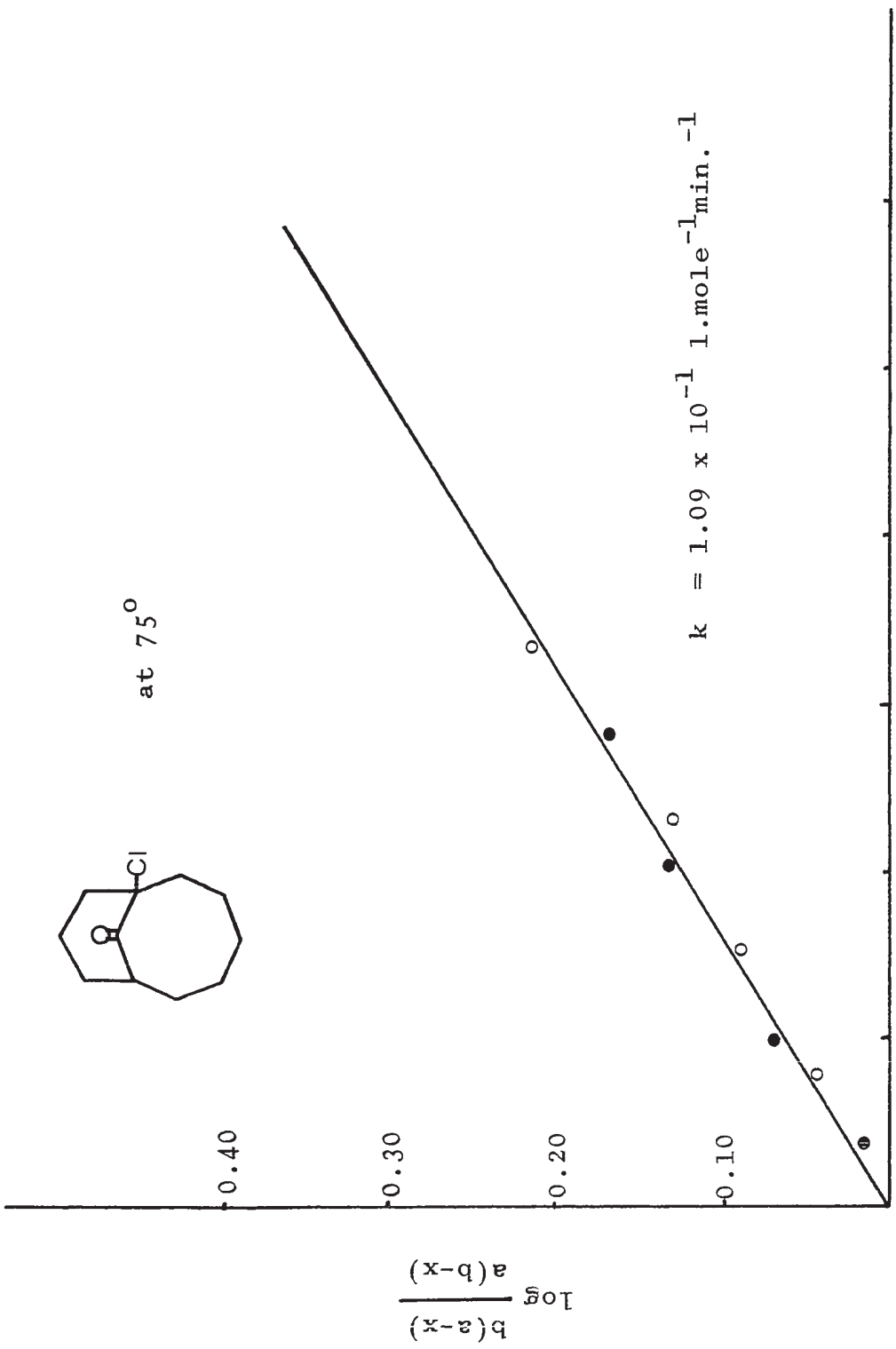


Fig. 5. Reaction of Chloroketone 6(8)C with sodium methoxide in methanol.

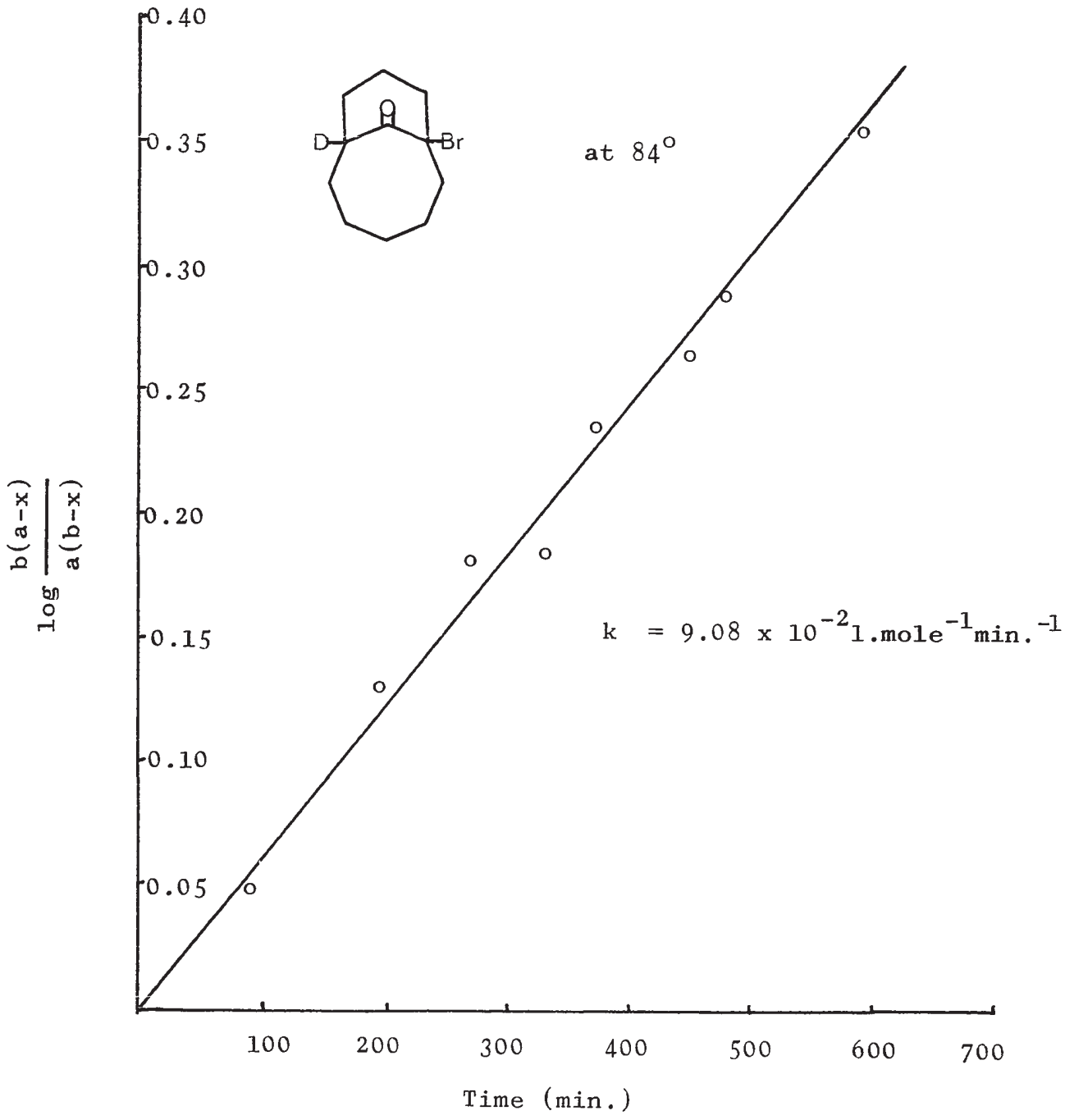


Fig. 6. Reaction of deuterated Bromoketone 6(8)H with sodium methoxide in methanol.

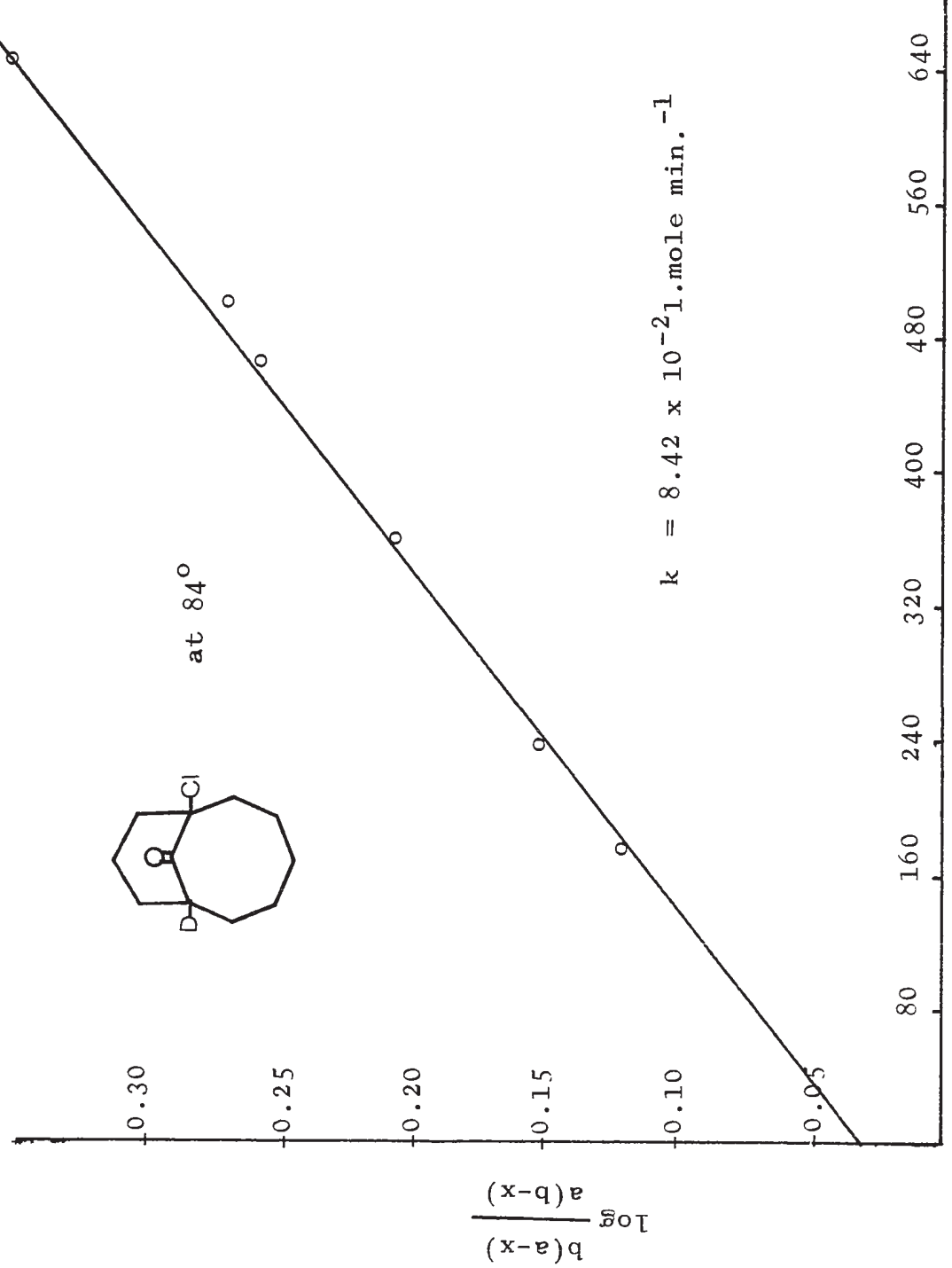


Fig.7. Reaction of Deuterated Chloroketone 6(8)D with sodium methoxide in methanol.

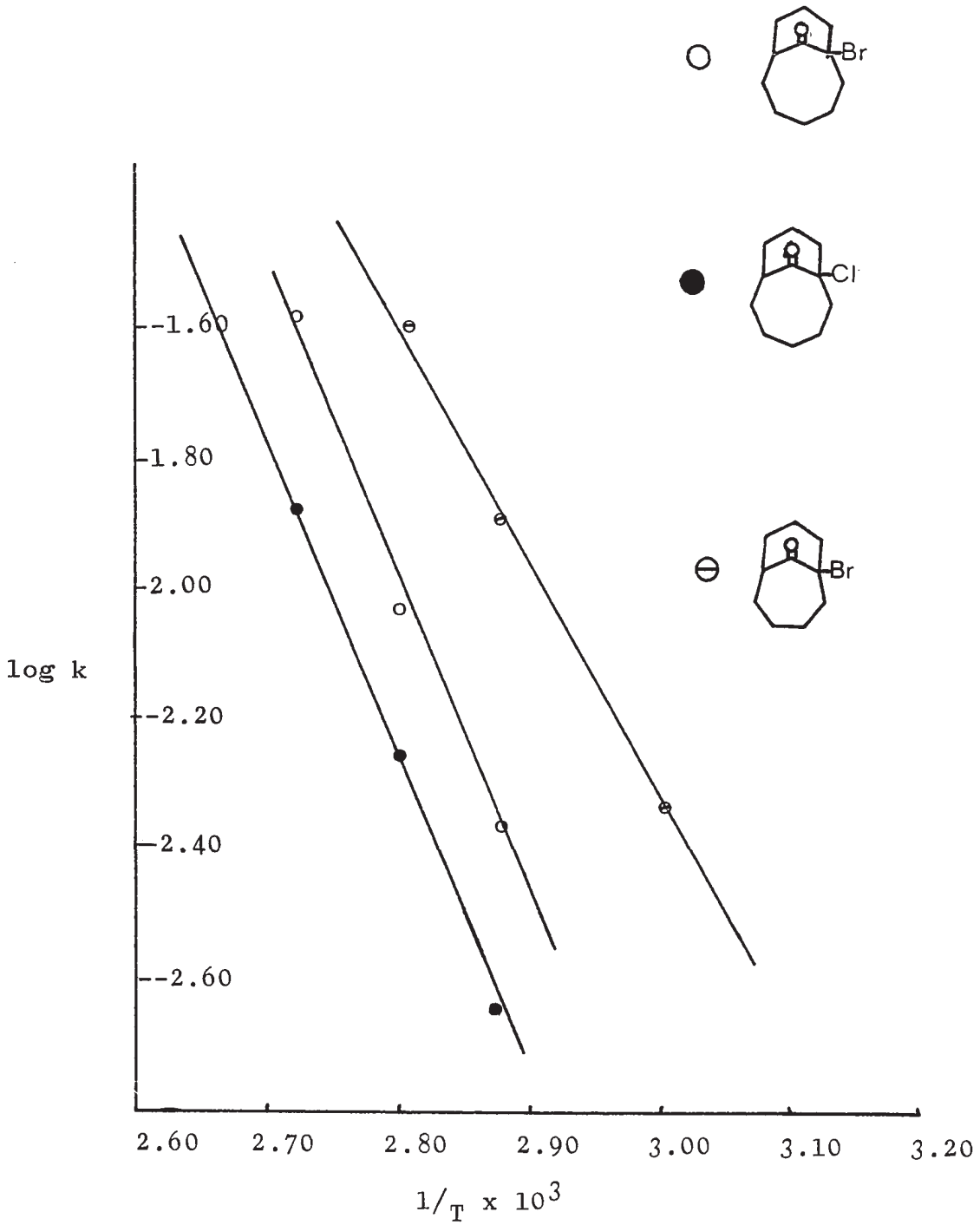


Fig.8. Arrhenius Plot of Reaction of 1-Halo-bicyclo-[n.3.1]alkanones with sodium methoxide in methanol.

The cyclopropanone mechanism is faster than the semibenzilic mechanism in bromoketone 6(8)B, therefore the semibenzilic mechanism in bromoketone 6(7)B is faster than the semibenzilic mechanism would be in bromoketone 6(8)B. It is clear that the rate of the semibenzilic mechanism gradually decreases from bromoketone 6(6)B to bromoketone 6(8)B and the reverse is true for the cyclopropanone mechanism. There is a correlation of the decrease in rate of the bromoketones with the infrared carbonyl absorption of the bicyclic ketones. The bromoketone 6(6)B (ν = 1745 cm^{-1}) is relatively more strained than the bromoketones 6(7)B (ν = 1730 cm^{-1}) and 6(8)B (ν = 1710 cm^{-1}). That is to say the relative reactivity of the carbonyl groups is in the order 6(6) > 6(7) > 6(8). The relative reactivity of carbonyl groups in monocyclic ketones can be seen from the rate of reduction of cyclanones with sodium boronhydride in 2-propanol which established an order of dependence on ring size of 6 > 7 > 8 as shown in Table VI.

The decrease in reactivity of the carbonyl groups of the haloketones 6(6)B, 6(7)B and 6(8)B can also be explained in terms of steric effects in the bicyclic system. It has been shown by conformational analysis, X-ray and infrared data on bicyclo[3.3.1]nonane system that there is considerable C_3-C_7 non-bonded interaction. In order to relieve the interaction the bicyclo[3.3.1]nonane adopted a distorted chair-chair conformation (85, 86). The steric hindrance to the bicyclic ketone carbonyl which is common to both rings of the bicyclic system increases from haloketone 6(6) to haloketone 6(8). Therefore, the reactivity of the carbonyl groups of the bicyclic system decreases from 6(6) to 6(8).

The relative reactivity of the carbonyl groups, whatever the

TABLE VI

Carbonyl Absorptions of Ketones[a] and Rate of Reduction of Ketones with Sodium Boronhydride[b]

Ketones	(cm^{-1}) in CCl_4	$k \times 10^4$ at 0° (M^{-1} sec^{-1})
Cyclohexanone	1714	61.7
Cycloheptanone	1705	1.02
Cyclooctanone	1702	0.078

a. Reference 83.

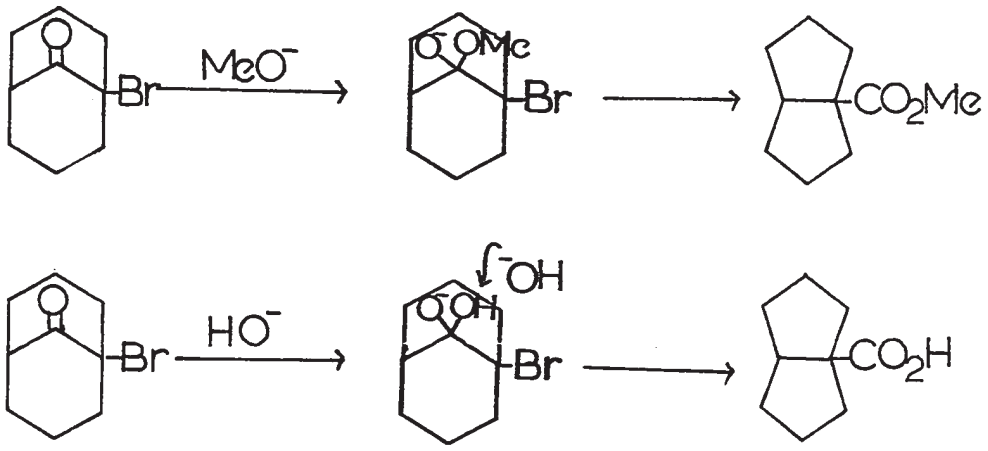
b. Reference 84.

factors, may be part of the reason for the change in mechanism in bromoketone 6(7)B and 6(8)B. Looking back into the literature there was only one proved case of the semibenzilic mechanism for a bromoketone with an α'-hydrogen, α-bromocyclobutanone (87). The mechanism can be rationalized in terms of a very reactive carbonyl group even though the α'-hydrogen is relatively acidic in α-bromocyclobutanone. In this particular bromoketone the cyclopropanone if formed will be very strained, therefore, the semibenzilic mechanism is favoured.

There are several cases in which haloketones without an α'-hydrogen do not rearrange; this may be due to the low reactivity of the carbonyl group (3, 4, 110). The gradual change in mechanism and rate are consistent with the increasing acidity of the α'-hydrogen of the haloketones 6(6), 6(7) and 6(8). The relative acidity of the α'-hydrogen of the bromoketones 6(7)B and 6(8)B can be deduced from the deuterium exchange study on 10-oxo-bicyclo[4.3.1]decane-1-carboxylic acid 6(7)A. There was no observable exchange in the PMR spectrum after refluxing the acid with sodium ethoxide in ethanol-d for 24 hours (88). On the other hand, the 11-oxobicyclo[5.3.1]undecane-1-carboxylic acid was partially decarboxylated under basic conditions to form the bicyclo[5.3.1]undecan-11-one which readily exchanged under acidic or basic condition. 9-oxo-bicyclo[3.3.1]nonane-1-carboxylic acid also showed no decarboxylation when heated with quinoline and copper (89).

It is noteworthy that the bromoketone 6(6)B rearranges 170 times faster in dioxane-water with sodium hydroxide than in methanol with sodium methoxide. The difference in rate might be due to change of solvation or change of basicity. It should be pointed out that there could be a slight difference in mechanism with the two bases.

It is known that alkaline hydrolysis of amide such as urea and anilides contain both first order and second order terms in hydroxide (69). It might be true also in our case for the hydroxide promoted rearrangement of bromoketone 6(6)B since an increase of rate was observed with the hydroxide. A second hydroxide is needed to catalyze



6(6)B 5(5)C

the reaction. The kinetics fit the second order plot. Reproducible second order rate constants were obtained by varying the base concentrations. The third order plot did not give reproducible rate constant by varying the base concentrations. Therefore, a third order reaction was ruled out.

Going back to path (A) and path (B) for the semibenzilic mechanism, we do not have enough data to determine the relative rates k_1, k_{-1} and k_2. Furthermore, path (A) and path (B) are kinetically indistinguishable. But by analogy with the benzilic acid rearrangement and alkaline hydrolysis of amides, we can say that the tetrahedral intermediate A may have considerable life time. And there is rapid exchange of H_2O^{18} in the benzilic rearrangement and alkaline hydrolysis of amides (90). In view of the isolation of the cyanohydrin and the

optical activity result for the bromoketone 6(8)R the tetrahedral intermediate A is no doubt on the reaction path. If we assume that the fast preequilibrium is set up in the semibenzilic mechanism, then k_2 will be the rate determining step for $k_{-1} > k_2$, i.e. the collapse of the tetrahedral intermediate A or halide release. A distinction between path (A) and path (B) could be made from the k_{Br}/k_{Cl} ratio, for path (B) should show a larger ratio.

For the haloketones 6(8)B, all the kinetic runs were carried out in sodium methoxide in methanol at temperatures of 75° to 95°, for comparison with the data in the literature. The reaction was too slow at 0°. The kinetic studies were performed by mixing a solution of haloketone and base in a tube which was then sealed and heated at the appropriate temperature. The kinetics gave good straight lines for second order plots as shown on Figures 4-7. The second order rate constants, activation parameters, halogen effect and kinetic isotope effect are listed in Table V. In Table VII are listed the rate constants, halogen effect and kinetic isotope effects from related work in the literature (25, 12). They presumably will all go through a cyclopropanone mechanism. It can be seen that all the chloroketones are considerably slower than the corresponding bromoketone except for 3-chloro-1-phenylbutan-2-one.

In the cyclic haloketones the Br/Cl rate ratio ranges from 36 to 116 at 0° but in our bicyclic haloketone the Br/Cl rate ratio is only 2 at 75°, 84° and 95° and does not change with temperature, although the Br/Cl rate ratio of the rearrangement of benzyl-α-halobenzyl sulfone was temperature dependent (94). The ratio decreases with increasing temperature, it was 620, 280 and 143 at 0°, 25° and

TABLE VII

Rates of Halide Release for 2-Halocyclohexanones and α-Haloalkanones with Sodium Methoxide in Alcohol at 0° *

Substrate	$k, M^{-1} min.^{-1}$	k_{Br}/K_{Cl}	K_H/K_D
4,4-diphenyl-2-bromocyclohexanone	4.26×10^{-1}		4.1
		116	
4,4-diphenyl-2-chlorocyclohexanone	3.66×10^{-3}		1.05
4-phenyl-4-methyl-2-chlorocyclohexanone	1.26×10^{-2}		
		52	
4-phenyl-4-methyl-2-bromocyclohexanone	6.6×10^{-1}		
2-chlorocyclohexanone	2.40×10^{-1}		
2α-bromocholestan-3-one	5.76×10^{-1}		4.2
		36	
2α-chlorocholestan-3-one	1.62×10^{-2}		4.0
1-chloro-3-phenylacetone**	15.7×10^{-1}	6.3	
3-chloro-1-phenylbutan-2-one	401.4	0.9	
1-bromo-3-phenylacetone	100.2		
3-bromo-1-phenylbutan-2-one	384		

* From references 25, 12

** $\Delta S^{\ddagger}$ for the reaction is +16 eu (25)

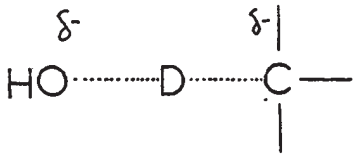
50° respectively. The difference in activation energy in the halosulfones was 4 kcal/mole at 25° but in our case it was only 0.7 kcal/mole at 75° which explains the small rate ratio. In comparing the rates of bromoketones, the monocyclic haloketones are about 10,000 times* faster than bromoketone 6(8)B, but for chloroketones the rates difference ranges from 150 to 12,000*. The faster rate of the monocyclic haloketones might well be attributed to the easier abstraction of the α'-hydrogen in the monocyclic cases in comparison with the bicyclic haloketones 6(8). The difference can be seen in Table VIII. The chloroketones are more extensively exchanged than the bromoketones. It is clear that the acidity of the α'-hydrogen not only controls the rate of the rearrangement but also the mechanism of the rearrangement in the bicyclic haloketones 6(8).

The abstraction of the α'-hydrogen is the necessary step in the cyclopropanone mechanism, but this is not necessarily the rate determining step. One of the strong pieces of evidence for rate determining proton removal is that no deuterium was incorporated into the recovered haloketone from deuterated solvent. 9-chloro-trans-1-decalone, 2α-bromo-cholestan-3-one, 17α-bromopregnenolone and 2-bromo-4-methyl cis-4-phenylcyclohexanone have all been shown to have proton removal as the rate determining step (58, 12, 25, 73). In our bicyclic haloketones 6(8) with only one α'-hydrogen, little or no deuterium (<1%) was incorporated in the recovered haloketones in deuterated solvent and one deuterium atom was incorporated in the product. This clearly showed that the α'-hydrogen did come off the molecule and the proton removal was the rate determining step. Further

---

* The rate at 0° is estimated from the activation energy of the haloketones 6(8).

evidence for rate determining proton removal comes from the kinetic isotope effect. The bromoketones 6(8)B and chloroketone 6(8)C showed kinetic isotope effects of 6.0 and 3.1, respectively. These numbers are relatively small in comparison with that of acetone at 0°, which has a deuterium kinetic isotope effect of 13 with hydroxide ion (91). The small or lack of kinetic isotope effect is usually attributed to equilibration of the haloketone with base. But in our case, there is no exchange which excludes the possibility of equilibrium. The maximum kinetic isotope effect should occur when the bond



formation and the bond breaking occur to the same extent. The recent finding of Bordwell showed that the maximum was rather flat but the overall apparent shape of the curve was retained (92).

The extent of bond breaking of C-H bond at the transition state was more than half broken in chloroketone 6(8)C, but the extent of bond breaking in bromoketone 6(8)B was about half broken. It might be less or more than half broken at the transition state. The value 6.0 is the biggest kinetic isotope effect reported in a Favorskii rearrangement. The small value of isotope effect for chloroketone 6(8)C is also consistent with other systems as shown in Table V. Because the chlorine atom has a stronger inductive effect than the bromine atom, the small hydrogen isotope effect for the chloroketone 6(8)C implies that the bond breaking is to a greater extent in the chloroketone than in bromoketone at the transition state.

With the deuterium exchange and kinetic isotope effects at hand, we go back to our previous schemes path (C) and (D) for the rearrangement mechanism. The deuterium exchange and kinetic isotope effects are consistent with path (C) and path (D) with $k_2 > k_{-1}$. Furthermore, the Br/Cl rate ratio supports k_1 being the rate determining step. In a stepwise mechanism for a pair of haloketones the Br/Cl rate ratio depends on the nature of the rate determining step, for k_1 being the rate determining step in both haloketones, the Br/Cl rate ratio will be small or less than one. If k_2 is the rate determing step the Br/Cl rate ratio will be large. If the rate of halogen release were included in the overall rate, the nature of the halogen would have great effect on the rate according to rate equation (7). In order for the halogen to have great influence on the overall rate,the halide release should be the rate determining step. For example, the Br/Cl rate ratio in an S_N2 reaction is 50 (93). Those reactions having a large Br/Cl rate ratio occur with a preequilibrium step followed by rate determining halogen release (25). Considering the greater inductive effect that the chlorine has over the bromine atom, we would expect the α'-hydrogen of the chloroketone to be more acidic than the α'-hydrogen of the bromoketone. This conclusion is supported by the deuterium exchange studies on 4,4-dimethyl-2-halocyclohexanone as shown in Table VIII. For those rearrangements with preequilibria, the chloroketone is slower than the corresponding bromoketone as shown in Table VII because the chlorine is a poorer leaving group than bromine. But in the case where proton abstraction is the rate determining step, the chloroketone should rearrange slightly faster than the bromoketone since the α'-hydrogen is more acidic in chloroketone.

TABLE VIII

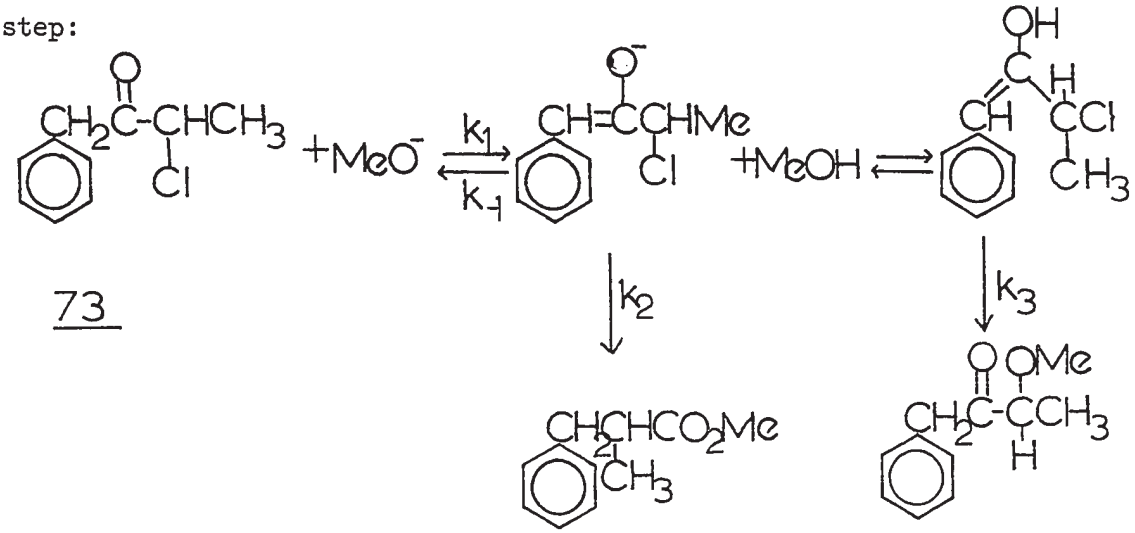
Hydrogen-Deuterium Exchange of Haloketones during Reaction*

	Before Reaction	After Reaction
4,4-dimethyl-2-bromocyclohexanone	0.7 d_0, 10.9 d_1, 47.6 d_2, 40.8 d_3	8.0 d_0, 33.1 d_1 49.5 d_2, 9.4 d_3
4,4-dimethyl-2-chlorocyclohexanone	3.2 d_0, 24.7 d_1, 60.5 d_2, 11.6 d_3	96.7 d_0, 3.3 d_1
2α-bromocholestan-3-one	2.67 D	1.82 D
2α-chlorocholestan-3-one	2.80 D	1.50 D
1-bromobicyclo[5.3.1]undecan-11-one	0	99.2% d_0, 0.8% d_1
1-chlorobicyclo[5.3.1]undecan-11-one	0	98.7% d_0, 1.3% d_1

* References 25, 12.

This is borne out in the case of 3-chloro-1-phenylbutan-2-one and the Br/Cl rate ratio is equal to 0.9. This fact is entirely consistent with proton removal being the rate determining step. But in the bicyclic haloketones 6(8) the rate ratio is 2. In similar cases, the Br/Cl rate ratio is proportional to the extent of deuterium exchange (25). The case where k_1 is the rate determining step for the bromoketone and k_2 for the chloroketone the Br/Cl rate ratio is not compatible with our case of k_1 being rate determining step for both haloketones. This may imply that other stepwise mechanisms are in operation. They are considered below.

Firstly, Bordwell has reported the rearrangement of 3-chloro-1-phenyl-butan-2-one 73 which has similarity with our bicyclic haloketones 6(8) in Br/Cl rate ratio and deuterium exchange. By careful studies in acidic and basic conditions with 73, Bordwell had arrived at the following mechanism where k_1 was the rate determining step:



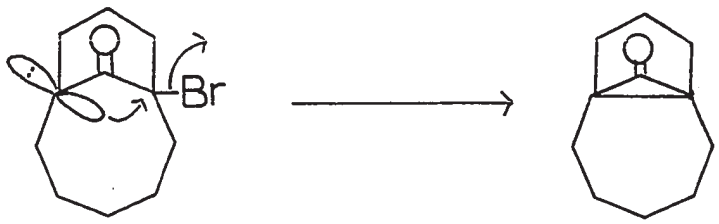
The rearrangement product arose from the enolate allylic halide and the substitution product from the enol allylic halide. The ratio of

the products is base concentration dependent. The higher base concentration favours the rearranged product formation. This enolate allylic halide intermediate is not consistent with our Br/Cl rate ratio because it will predict a Br/Cl rate ratio nearly equal to one or slightly less than one if k_1 is the rate determining step for both ketones. The difference between 0.9 and 2 might not be great enough to exclude the enolate allylic halide intermediate in our case. But the reported entropy of activation for an enolate allylic halide intermediate is +16 eu (25), which is inconsistent with our case as shown in Table V. Therefore, the enolate allylic halide intermediate is excluded.

Secondly, the oxyallyl mechanism is unfavourable for bicyclic haloketones 6(8), since there is no driving force for oxyallyl formation for the system cannot obtain full delocalization due to the rigidity of the rings. But it was found that the haloketones 6(8) racemized in acid condition (Chapter V) and not in basic condition. The racemization presumably proceeds through an enol allylic halide and if the oxyallyl is formed in basic condition at all, it will be formed irreversibly. Furthermore, similar reactions that occur by a carbanion intermediate like Ramberg-Backlund reaction and Favorskii rearrangement of 1-chloro-3-phenyl propanone show positive entropy of activation (94). Therefore, the oxyallyl mechanism is unlikely. At the same time, the oxyallyl as intermediate for the formation of α-methoxy ketones was rejected by Bordwell on the ground of acid and base catalyzed alcoholsis of haloketones to give α-methoxyketone (36).

The final stepwise mechanism is the direct S_N2 displacement

by the carbanion to form the cyclopropanone. This type of internal S_N2 displacement was challenged on geometric grounds in the 2-chlorocyclohexanone case and has been excluded in α-chlorobenzyl



94

methyl ketone case by the large Br/Cl rate ratio and ρ value (-2.37). The large degree of positive charge developed at the benzylic carbon excluded the S_N2 displacement, but favoured the ionization of the chloride ion with the aid of "π-participation" of the enolate ion. The S_N2 type displacement was demonstrated to occur in the α-halobenzyl

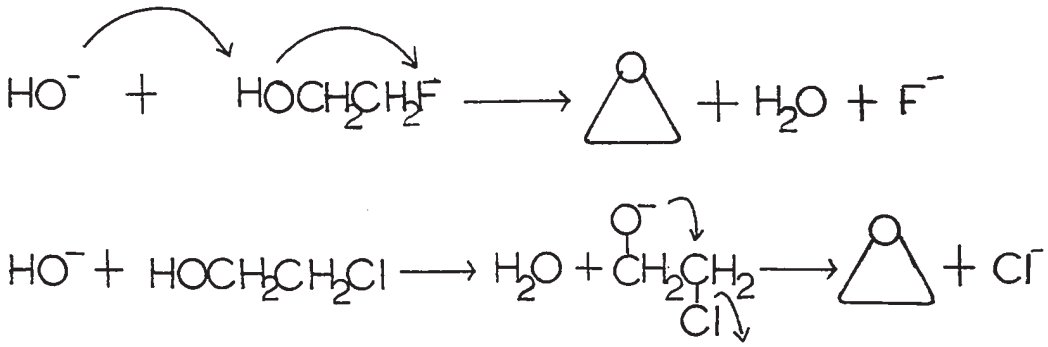
sulfones. This type of internal S_N2 displacement was said to be "σ-participation." The α-sulfonyl carbanion is more sp^3-like than sp^2-like and our 6(8) bicyclic α-carbonyl carbanion is also comparable for the carbanion is not completely planar. σ-participation might be possible in this case also. The geometry of the molecule favours the back lobe of the sp^3 orbital in σ-participation because of the proximity of the bridgehead carbon atoms in haloketones 6(8)

(the C_1-C_5 distance in bicyclo[3.3.1]nonane itself is 2.50A), the presence of even a fraction of a negative charge in the rear lobe of the bridgehead carbanion orbital might well lead to considerable transannular repulsive forces which would be relieved by departure of the bromide ion (62a). Furthermore, the activation entropy for the α-chlorobenzylsulfone was positive, whereas the entropies of the present bicyclic haloketones 6(8) are negative. Since the rate determining step in the bicyclic haloketone reaction is the proton removal, if the S_N2 type displacement occurred, the chloroketone would be expected to rearrange faster than bromoketone 6(8)B. Therefore, the S_N2 type displacement is not likely. By excluding all the possible stepwise mechanisms, we are left with the concerted mechanism.

In a concerted 1,3-elimination mechanism, the C-H and C-X bonds are broken with the simultaneous formation of C-C bond. The concerted mechanism might predict a great rate difference between the haloketones due to difference in bond energy of C-X if we assume same bond energy for C-H in both haloketones. But only a factor of 2 in rate difference was observed in the bicyclic haloketones. The α'-hydrogen of the chloroketone 6(8)C is more acidic than that of the bromoketone because of the greater inductive effect of the chlorine atom, but the chlorine itself is a poorer leaving group. The activation effect of the chlorine atom on the α'-hydrogen could be large enough to level off the difference in energy needed to break the C-Br and C-Cl bonds causing only slight differences in rate between chloroketone 6(8)C and bromoketone 6(8)B to be observed.

The concerted mechanism is consistent with the lack of deuterium exchange, the kinetic isotope effect, the Br/Cl rate ratio

and the activation parameters. In a concerted mechanism some degrees of freedom of the molecule are lost in the transition state and a negative change in entropy would be anticipated. The ethylene oxide formation from 2-fluoroethanol is 910-times slower than from 2-chloroethanol at 50° yet the activation energy for the 2-fluoroethanol reaction is 2 kcal/mole lower as shown in Table IX.



The slower rate for the 2-fluoroethanol reaction is due to the great loss of entropy compared to 2-chloroethanol which reacts in a stepwise mechanism. The ethylene oxide formation from 2-fluoroethanol has been suggested to occur by a concerted mechanism (94).

Another point merits further consideration. If the concerted mechanism is in operation, does it fit the stereochemistry of the product? The concerted mechanism is a concerted 1,3-elimination reaction. The stereochemistry at C_6 of the 1,3-elimination in norbornane system has been found to be both inversion and retention, but with more retention (95). There is no evidence to indicate that the reaction

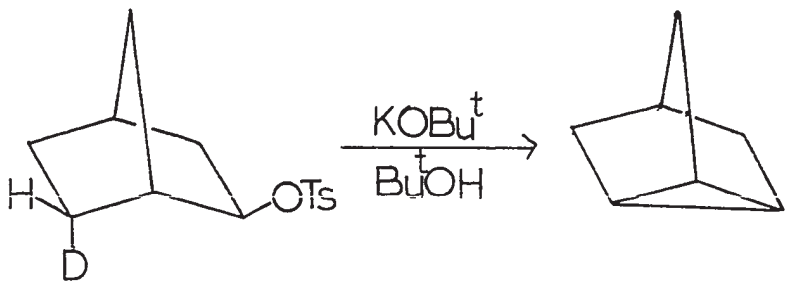


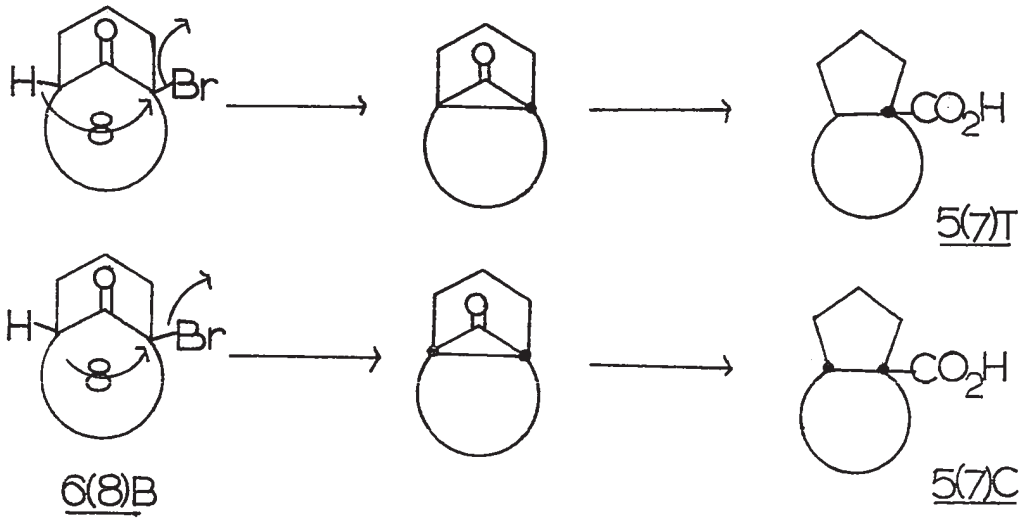
TABLE IX

Activation Parameters of Reaction of Halohydrins*

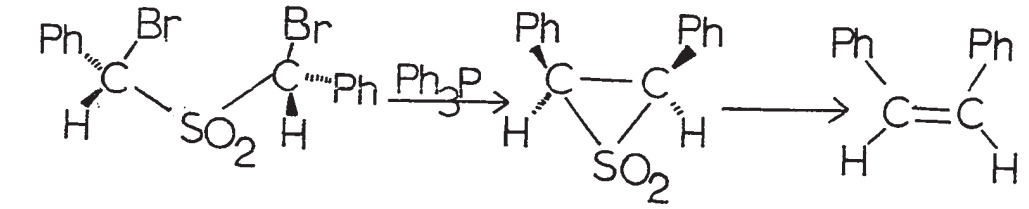
	Temp.	k(min^{-1})	Ea(Kcal/mole)	$\Delta S^{\ddagger}$ (e.u)
CH_2OHCH_2F	30°	1.5×10^{-3}	21.5	-6
CH_2OHCH_2Cl	0°	1.67×10^{-2}	23.3	+11
	35°	2.17		
CH_2OHCH_2Br	0°	9.87×10^{-1}	21.9	+9

* Reference 94

is concerted or not concerted. Bordwell had studied 1,3-eliminations in dihalosulfone and monohalosulfones and the results were all consistent with a double invevsion mechanism or a double retention mechanism (96). But this double retention mechanism is ruled out for steric reasons in the Ramberg-Backlund reaction with 1-chloro-8-thiabicyclo[3.3.1]nonane 91 (62a). It is clear in these reaction that 1,3-elimination proceeds with double inversion. The double inversion in the Ramberg-Backlund reaction was shown by Bordwell to be stepwise. For a concerted 1,3-elimination in the bicyclic haloketones 6(8), the configuration at the α'-carbon could be inverted or retained, followed by ring opening of the cyclopropanone with retention which gives different configurations of the final product. Because of the geometry of the bicyclic system, the double inversion mechanism is the only one possible. Furthermore, the retention mechanism would give trans acid which was not observed in the rearrangement. Therefore, the

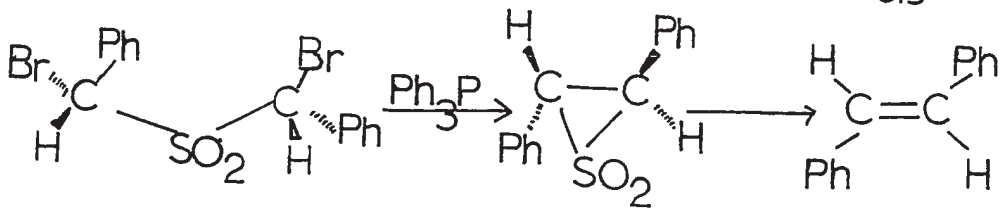


concerted 1,3-elimination for cyclopropanone formation is consistent with the stereochemistry of the product.



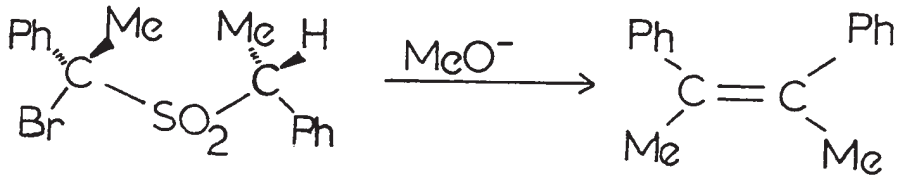
meso

cis



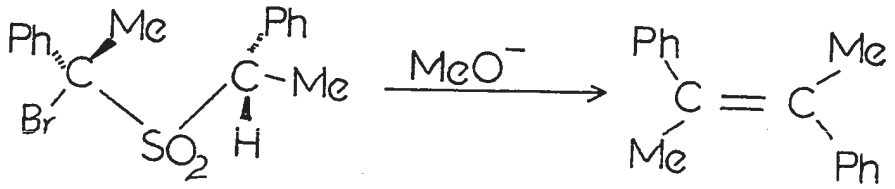
dl

trans



erythro

cis

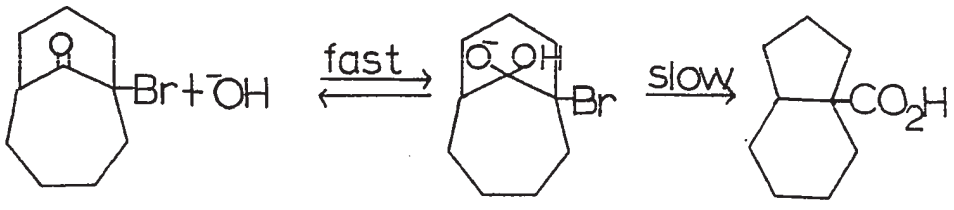


threo

trans

CONCLUSION

In the present studies, the mechanism of rearrangement of optically active bromoketone 6(7)B was shown to go by a semibenzilic mechanism in further confirmation of the previous findings based on deuteration studies. There is a noted decrease in semibenzilic mechanism rate from bromoketones 6(6)B to 6(7)B and 6(8)B. The decrease in rate may be attributed to the higher strain energy in the lower bicyclic bromoketone 6(6)B than in the higher bicyclic haloketone 6(8) and the decrease in reactivity of the carbonyl groups as seen from the reduction of six membered to eight membered ketones. From kinetic studies the reaction is first order in both substrate and base. By analogy with the benzilic acid rearrangement and ester hydrolysis, the first step is the reversible fast addition of base to the carbonyl group to form a tetrahedral intermediate which collapses to give the product in the rate determining step. The mechanism is not solvent



6(7)B 5(6)C

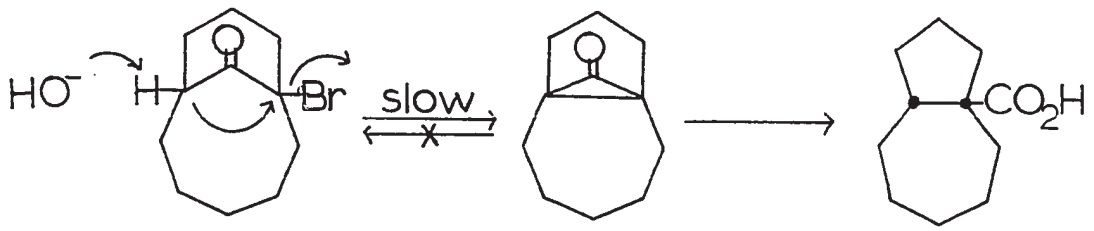
dependent. But the mechanism is related to the base strength. There was a change of mechanism from semibenzilic to cyclopropanone mechanism with stronger bases. The change in mechanism is rationalized on the acidity of the α'-hydrogen of the bromoketone 6(7)B.

In the bromoketone 6(8)B, the reactivity of the carbonyl group is reduced and the α'-hydrogen becomes more acidic; therefore, the cyclopropanone mechanism occurs with most of the bases. But when a more nucleophilic but weaker base such as hydroperoxide is used, the semibenzilic mechanism reappears. The change in mechanism is due to the faster rate of the stronger nucleophiles toward the carbonyl group and lower rate of hydrogen removal. Making use of the optically active bromoketone 6(8)B and chloroketone 6(8)C, we were able to determine quantitatively the extent of the two mechanisms in competition. The chlorine has the stronger inductive effect than bromine, the effect of the chlorine has reversed the mechanism to cyclopropanone pathway at least 80% with the strongest nucleophile, hydroperoxide.

The kinetic studies on the haloketones 6(8) showed that the reaction is second order with first order in the substrate and base. By the use of kinetic isotope effect, Br/Cl rate ratio, deuterium exchange technique and activation parameters of the haloketones 6(8), a concerted mechanism for the formation of cyclopropanone is proposed*. The oxyallyl intermediate is not favoured in this bicyclic system. Other stepwise mechanisms for cyclopropanone formation are excluded. The rate determining step is probably the concerted 1,3-elimination

---

* A concerted mechanism with multiple bonds forming and breaking might no longer be a myth (97).



6(8)B 5(7)C

of hydrogen halide. Attempts to detect or isolate the cyclopropanone were in vain. The stereochemistry of the two asymmetric carbons is inverted during the formation of cyclopropanone by 1,3-elimination. The cis configuration of the acid 5(7)C was confirmed by comparison with authentic cis acid 5(7)C obtained by unambiguous synthesis. The exclusive formation of cis acid 5(7)C during the rearrangement indicates that the ring opening of the cyclopropanone with retention of configuration.

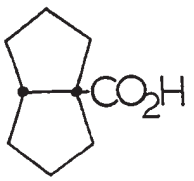
The present findings and related studies in the literature prove that the mechanism of the Favorskii rearrangement is dependent on the acidity of the α'-hydrogen, the nature of the halogen, the reactivity of the carbonyl group and the basicity and nucleophilicity of the base.

CHAPTER V

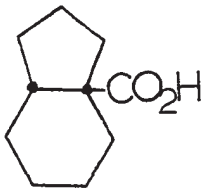
Synthesis of Compounds

(A) cis-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C

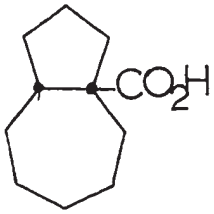
The acid obtained from Favorskii rearrangement of haloketones 6(8) was a bicyclo[5.3.0]decane-1-carboxylic acid which could have cis or trans fusions at the ring junctions. The stereochemistry of the lower homologous acids 5(5) and 5(6) obtained from the bromoketones 6(6)B and 6(7)B was shown to be cis by unambiguous



5(5)C



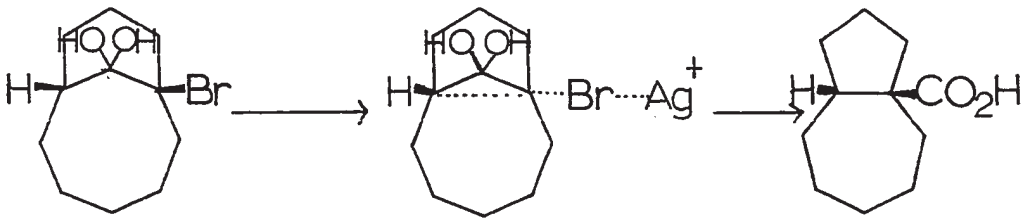
5(6)C



5(7)C

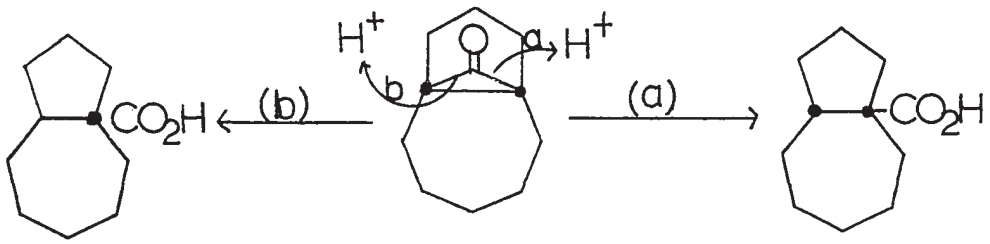
synthesis or comparison with authentic samples (98). The silver nitrate reaction with the haloketones 6(8) was shown to occur by a semibenzilic mechanism with the stereochemical requirement that a cis acid should be formed. This is because the attack of the solvent such as water or methanol on the carbonyl group atom will result in the formation of an intermediate 6(8)I which on rearrangement (S_N2 displacement) gives species 6(8)S which now has partial C-Br and

C-C bonds. This species 6(8)S will produce a cis configuration product after ejecting the bromine atom. But the rearrangement of



6(8)I 6(8)S 5(7)C

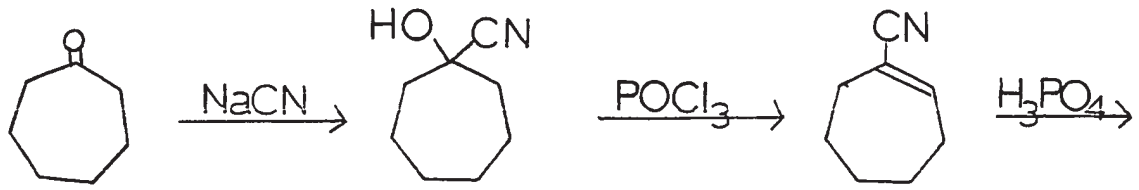
haloketone 6(8) with base occurred by a cyclopropanone pathway from which a cis or trans acid might be obtained. In order to prove the stereochemistry of the ring junction of the acids from silver nitrate

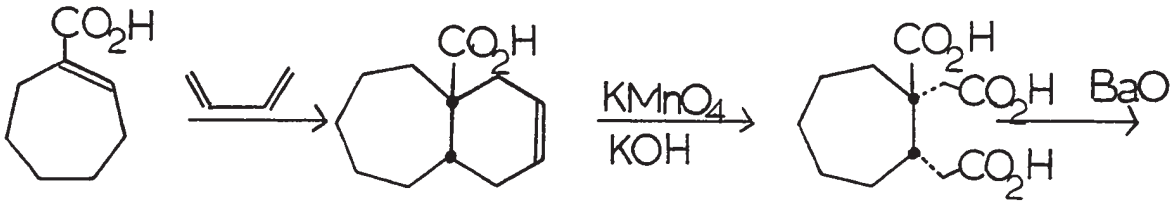


5(7)T 94 5(7)C

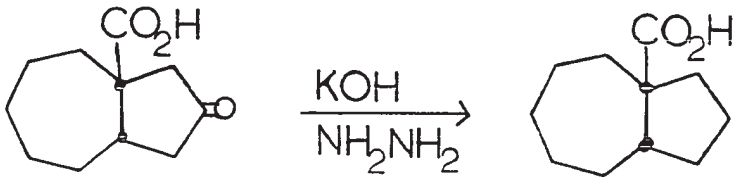
and base reactions with haloketone 6(8), both cis and trans acids 5(7)C and 5(7)T were synthesized for comparison.

The cis acid 5(7)C consists of an azulenic skeleton with cis ring fusion. In order to get a cis ring fusion the Diels-Alder reaction will be a good choice, for the Diels-Alder reaction always gives cis product. A Diels-Alder cycloaddition of cyclohept-1-ene carboxylic acid 109 with butadiene gives the required stereochemistry of a



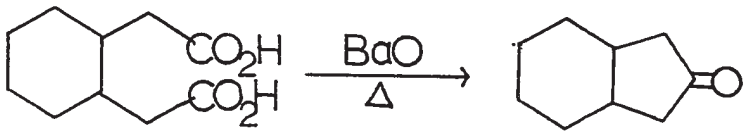


109 110 111



112 5(7)C

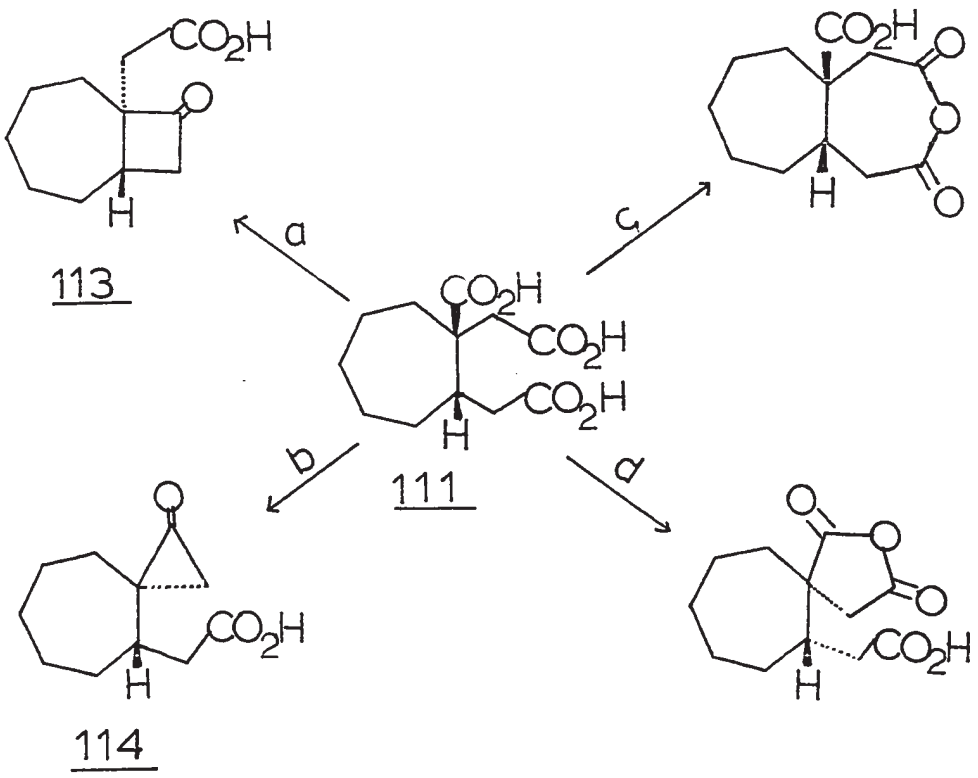
carboxyl group at the ring junction. The acid 110 can be oxidized to give a triacid 111 without disturbing the original cis configuration. It is well known that a diacid can be contracted into a cyclic ketone with ease when the ring size is five, six and seven membered (99). The yield is high with five membered ketones as seen for the 2-hydrindanone. Therefore, the triacid 111 could be converted in the



80%

γ-keto acid 112 which can then be reduced to the final cis acid 5(7)C by the Wolff-Kishner reduction.

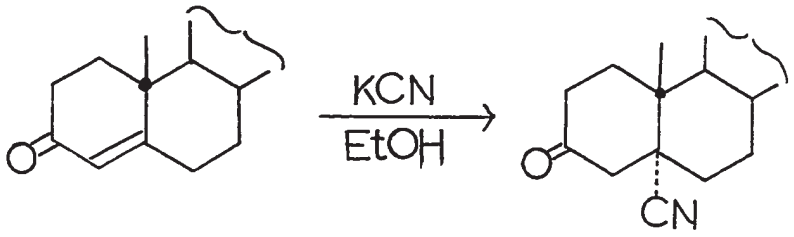
The starting cyclohept-1-ene carboxylic acid 109 was prepared according to Wheeler from cycloheptanone in three steps with overall yield 39% (100). The Diels-Alder reaction was carried out in a sealed tube at 170° with the acid 109 and excess of butadiene with a yield of 42%. Oxidation of the acid 110 with alkaline potassium permanganate to give the triacid 111 in 31% yield. The triacid 111 was converted into γ-keto acid 112 when heated with barium oxide at 200° in 52% yield. There are four other possible ways in which the three carboxyl groups can react as shown. The path (a) and (b) both give cyclobutanone 113 and cyclopropanone 114. The formation of cyclobutanones or cyclopropanones is less favourable than cyclopentanone in terms of strain energy. The path (c) and (d) give seven and five membered anhydrides which could then react further to give

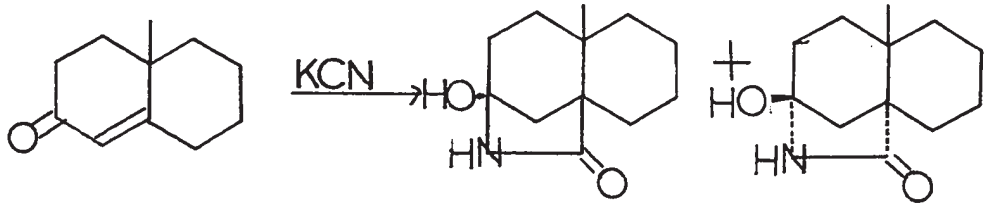


ketonic products. The above four paths did not occur to a detectable extent for the product obtained did not show IR absorption at 1820, 1780, 1865 and 1785 cm^{-1}, which are the absorptions of cyclopropanone, cyclobutanone and acid anhydride. The product obtained was quite pure as shown by TLC plate. The γ-keto acid 112 showed IR absorption at 1745 cm^{-1} characteristic of five membered ketones. The final step was to reduce the ketone group to methylene group. This was accomplished by Huang-Minlon reduction of the γ-keto acid 112 in 100% yield. The acid has mp and mixed mp 57.5-58.5° with the acid 5(7)C obtained from rearrangement of bromoketone 6(8)B. The IR spectrum is superimposable with that of the rearranged acid 5(7)C. Finally the GLPC retention times of the methyl esters of the two acids were equal. Therefore, the configuration of the acid 5(7)C obtained from rearrangement is cis.

(B) trans-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)T

The bicyclo[5.3.0]decen-9-ene-4-one 115, one of the intermediates in total synthesis of azulene, was used as starting material. There have been several reports on the 1,4-conjugate addition of hydrogen cyanide to α,β-unsaturated ketones (101, 102). The stereochemistry of the addition reveals that the trans is more favoured than the cis, although there is a case in which the cis is formed predominantly over the trans (101b). Therefore, hydrocyanation seemed a potential





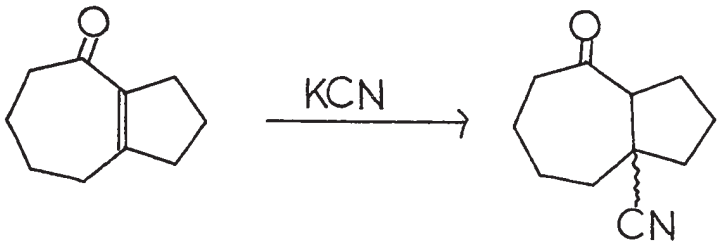
121 122

method for introducing a functional group at the angular position to give the trans configuration. The hydrocyanation of unsaturated ketone 115 followed by reduction and hydrolysis would give the trans acid 5(7)T.

The unsaturated ketone 115 was prepared according to the method of Anderson and Nelson (103). The 2-hydroxy-decalin was dehydrated with phosphoric acid and then isomerized to $\Delta^{9,10}$-octalin.

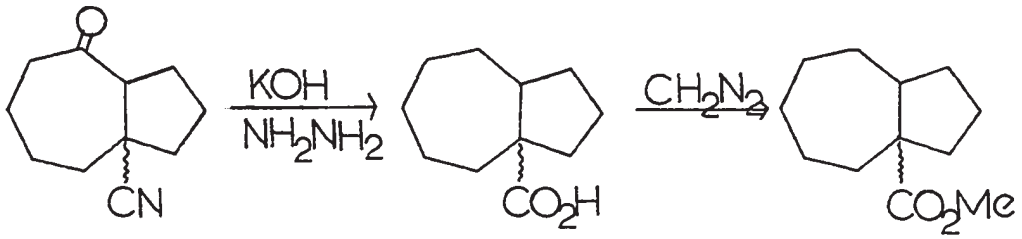
The $\Delta^{9,10}$-octalin was ozonized in acetic acid to give the 1,6-cyclodecanedione which was condensed to bicyclo[5.3.0]decen-9-ene-4-one 115.

When a solution of unsaturated ketone 115 and potassium cyanide was refluxed for 5 hours, 1-cyanobicyclo[5.3.0]decan-6-one 116 was obtained in 57% yield. A TLC plate showed two isomers in nearly equal amount. The keto nitrile mixture 116 was inseparable in column chromatography and it seemed to be epimerized by enolization on selica gel. The crude keto nitrile 116 was subjected to Huang-Minlon



115 116

reduction to give 35% of acid. GLPC analysis of the methyl ester of

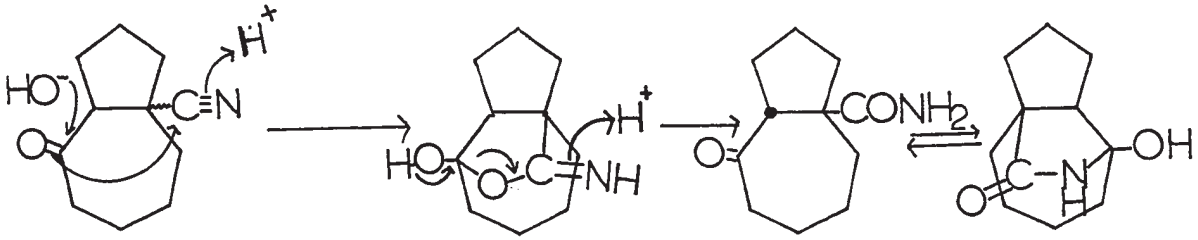


116

the crude acid showed 88% of methyl cis-bicyclo[5.3.0]decane-1-carboxylate 5(7)E and 12% of presumably the trans isomeric ester. The acidic hydrolysis of the keto nitrile 116 in 85% phosphoric acid or concentrated hydrochloric acid gave a poor yield of recovered keto-nitrile. Only a trace of acid was detected with considerable loss of

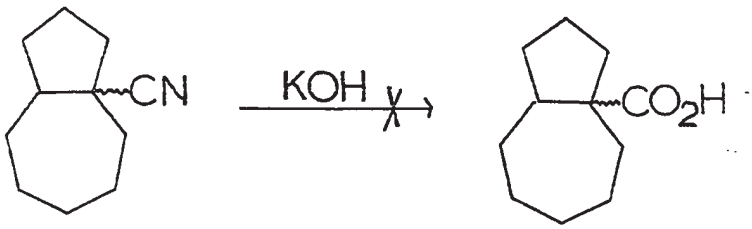
keto nitrile. The hydrolysis of the ketonitrile 116 was not investigated further.

In another attempt to prepare more ketonitrile to our surprise a solid, mp 141-142°, was obtained in 77% yield with the same conditions. The compound showed OH, NH and amide I band IR absorptions and no amide II band absorption at 1600-1650 cm^{-1}. PMR spectrum showed absorptions at 4.47 and 7.10 ppm for OH and NH and both are exchangable with deuterium oxide. The compound was identified as the lactamol 117 which was consistent with the spectroscopic data. The structure 117

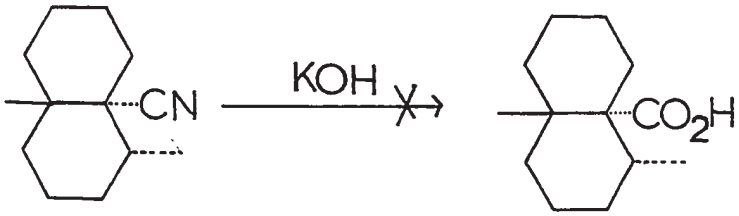


116 118 117

is in accordance with the reported observation by Nagato, Bower, Johnston and Weyer that lactamols were sometimes the major products(102). It was observed that the hydrocyanation is reversible and under mild conditions the keto nitrile was converted to lactamol with the participation of the carbonyl group due to its close proximity. In the absence of the carbonyl group, the nitriles 119 and 120 are inert to aqueous potassium hydroxide (102b). It is noteworthy that lactamols 121 and 122 can be formed in cis and trans configurations and they were isolated by the above workers. But in our case only the trans isomer can be formed, the cis isomer is too highly strained according to Drieding models and the non-cyclic keto amide 118, would predominate. In fact, only one spot was detected by TLC plate. In

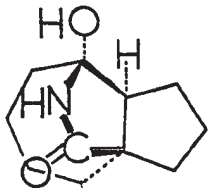


119

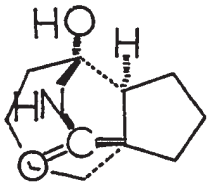


120

view of the fact that the keto amide 118 and the lactamol 117 are in equilibrium, if the carbonyl group could be reduced without epimerization of the ring junction the trans acid would necessarily be obtained by

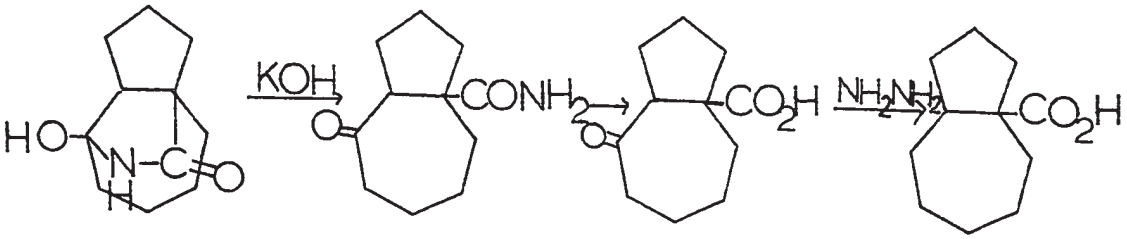


trans 117



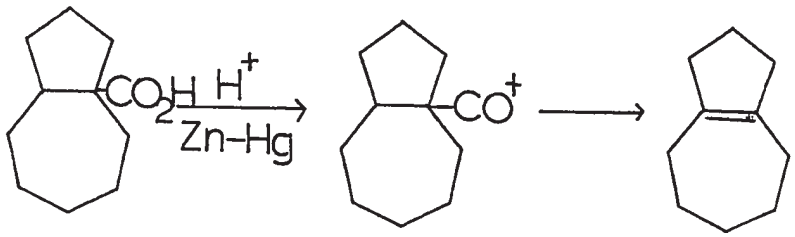
cis 117

hydrolysis of the resulting amide. Therefore, the lactamol 117 was subjected to reduction conditions. The lactamol 117 was first exposed to Huang-Minlon reduction to give 59% of acid which was identical in IR and PMR spectra with those of the cis acid 5(7)C. Furthermore,there was no depression in mp on admixture with the cis-acid. The Huang-Minlon conditions were too drastic for the keto acid intermediate which epimerized to the cis acid. The second attempt was the Clemmensen reduction. The GLPC analysis of the methyl ester of the



117 5(7)C

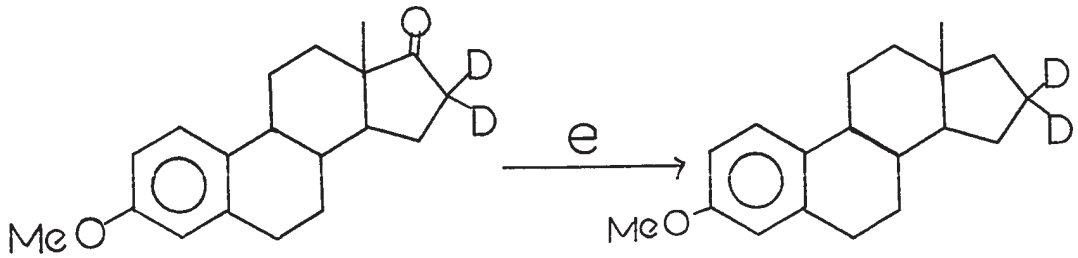
acid showed 25% of methyl cis-bicyclo[5.3.0]decan-1-carboxylate and 75% of presumably methyl trans-bicyclo[5.3.0]decan-1-carboxylate. However, only 2% yield of acid was obtained, the rest of the material may have been resinified or else the acid product was not stable in



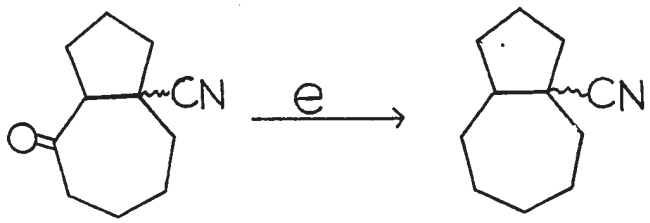
5(7)C

the strongly acidic conditions possibly forming hydrocarbon which was lost during work up. In view of much material loss in the reaction, the reaction was not investigated further.

During the course of looking for mild conditions to reduce a carbonyl group, a paper on electrolytic reduction of ketones in acidic conditions appeared. The reduction of estrone-16,16-d_2 methyl ester, 5% d_1, 95% d_2 to 3-methoxy-1,3,5 (10) estratriene-16,16-d_2, 6% d_1, 94% d_2 showed that there was little or no deuterium loss during electrolytic reduction even though in acidic medium. Furthermore, the



yield of reduction product was excellent 85%-97% (10[illegible]). The electrolytic reduction was first applied to the ketonitrile 116 with cis and trans isomers in acid condition. The yield of the nitrile 119

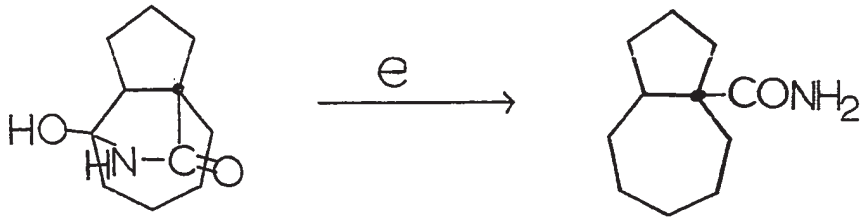


116 119

was excellent.

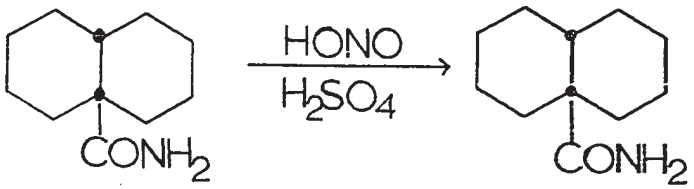
Judging from the TLC and IR spectrum, the product was quite pure and probably consisted of a mixture of cis and trans isomers. Several attempts were made to hydrolyze the nitrile 119 without success. The alkaline hydroperoxide condition gave back starting nitrile. The acidic hydrolysis in 85% phosphoric acid gave decomposition product which showed no nitrile or carboxyl group absorption in IR spectrum. Not surprisingly, the tertiary nitrile at the ring junction was too hindered to hydrolyze. This was in marked contrast to the keto nitrile 116 which was hydrolyzed in mild conditions with the participation of the keto group. The same observation was noted by

Johnston in hydrolyzing 120 (102b). The inertness of nitrile 119 caused much frustration and no further attempt was carried out to hydrolyze the nitrile 119. The electrolytic reduction on the lactamol 117 gave the corresponding amide 123 in 46% yield. Its IR spectrum



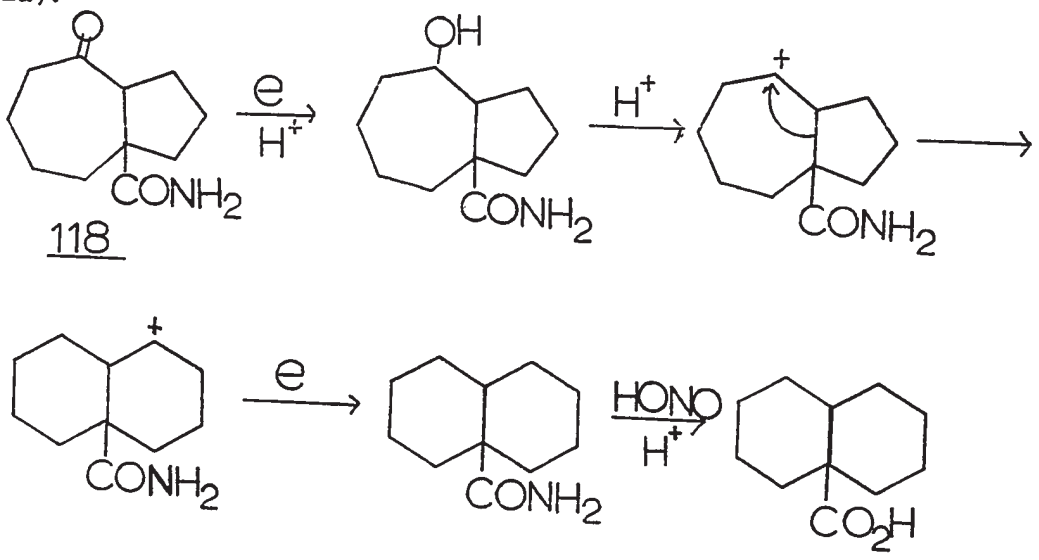
117 123

showed 3500, 3400, 3100 cm^{-1} for NH stretching, 1625 and 1575 cm^{-1} for amide I and II bands. Since the TLC plate showed it was quite pure, the amide was treated with sodium nitrite in sulfuric acid. The acid was precipitated in 38% yield. GLPC analysis of its methyl ester showed only one peak with retention time 4.4 mins. and mixed GLPC analysis with the cis-methyl ester 5(7)E showed two peaks at 4.4 mins. and 5.2 mins. The pure acid has mp 100.5-101.5°, depressed to 47-100° when mixed with the cis-acid 5(7)C. The acid obtained was trans-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)T for the following reasons: the rate of enolization was slow in the electrolytic reduction condition and the diazotization step cannot permit epimerization as shown in the case of 124 (102a). It is to be noted that the GLPC analysis gave only one peak which showed no epimerization.



124

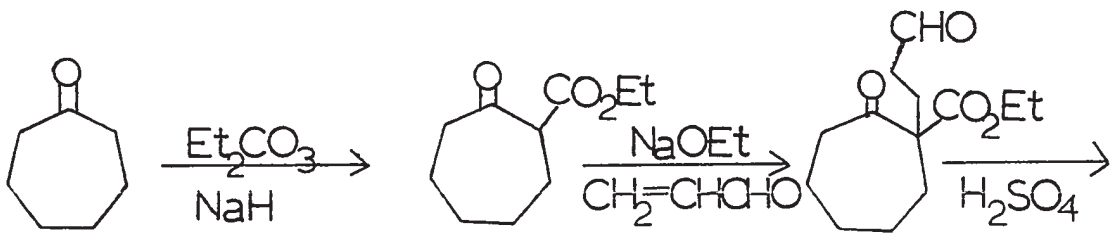
Moreover, the possible isomerization to decalin-9-carboxylic acid during electrolytic reduction was also excluded for the cis and trans decalin-9-carboxylic acids have mp 123-124° and 136-137° respectively (102a).

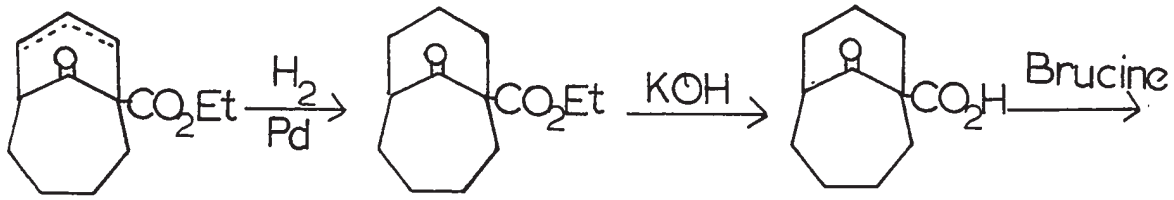


The haloketones 6(6), 6(7) and 6(8) were prepared according to previously well studied methods. Discussions are only focussed on special observations and improvements.

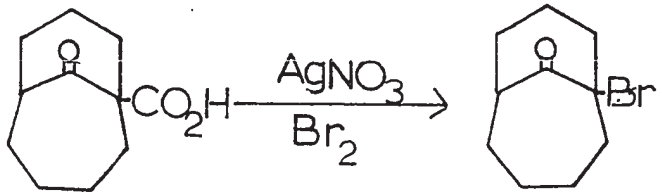
(C) Optically Active 1-bromo-bicyclo[4.3.1]decan-10-one 6(7)A

The optically active 1-bromo-bicyclo[4.3.1]decan-10-one 6(7)A was synthesized according to the procedure of Cope modified by Warnhoff, Wong and Tai as outlined (88). The lowest yield of the synthesis was the cyclization of the Michael adduct to the unsaturated ester (24%). The keto acid 6(7)A was first resolved with brucine in wet acetone. The brucine did not work very well with the keto acid 6(7)A although it worked very well with the keto acid 6(8)A. The salt did not crystallize readily at room temperature. The more dilute solutions gave





6(7)A



6(7)A 6(7)B

Optically active

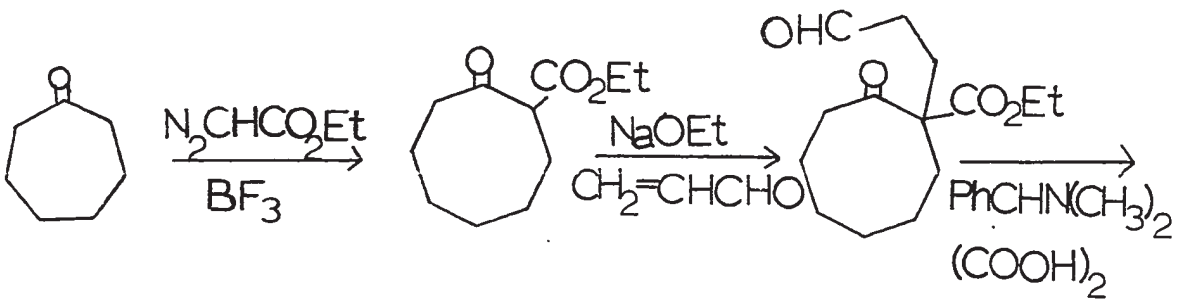
better resolution. The first five crystallizations did not show any increase in rotation at all. It took nine crystallizations to give a rotation $[\alpha]_D$-32.1° with a yield of 8%. So the resolving agent was changed to ephedrine which worked better than brucine. For example, the keto acid with $[\alpha]_D$+16.0° after two crystallizations with ephedrine gave acid with rotation $[\alpha]_D$+37.4°. A combined keto acid 6(7)A with rotation $[\alpha]_D$+32.8° was converted to bromoketone 6(7)B $[\alpha]_D$+12.4° in 60% yield.

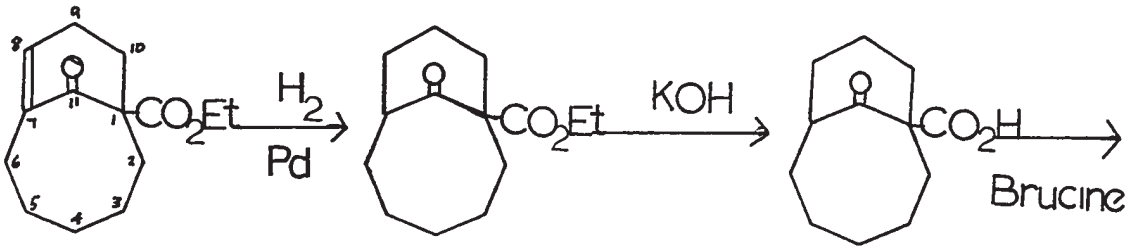
(D) Optically Active 1-chloro-bicyclo[4.3.1]decan-10-one 6(7)C

The pure chloroketone 6(7)C has not been obtained. The Hundsiecker method did not work very well. The yield was low (17%) and considerable amount (70%) of keto acid 6(7)A was recovered. The product isolated was contaminated presumably with the parent ketone 6(7) judged from the GLPC analysis. The modified Hunsdiecker method and the halo-decarboxylation method with lead tetraacetate also did not give satisfactory result with the keto acid 6(7)A.

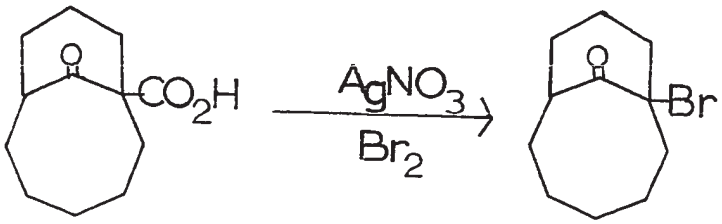
(E) Optically Active 1-bromo-bicyclo[5.3.1]undecan-11-one 6(8)B

The optically active 1-bromo-bicyclo[5.3.1]undecane-11-one 6(8)B was synthesized according to the procedure of Warnhoff, Wong and Tai as outlined below (88). The yield of the first step was high when equivalents of cycloheptanone and ethyl diazoacetate was used. The finding that the ethyl 11-oxobicyclo[5.3.1]undec-7-ene-1-carboxylate 6(8)D was a distorted enone by UV data has been confirmed by X-ray crystallographic analysis (105). The carbonyl group is twisted about the C_7-C_{11} bond by





6(8)D 6(8)E 6(8)A



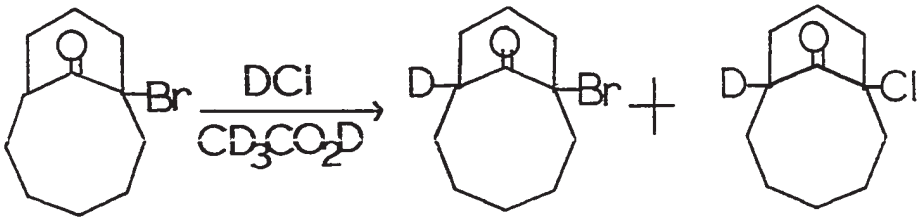
6(8)A
Optically active

6(8)B

37°. The C_7-C_8 double bond is also twisted by 8.6°. The angle of twist of the carbonyl group was further confirmed by ^{13}C NMR spectroscopy to be 35° which was very close to the X-ray result. Furthermore, the whole distorted enone is an asymmetric chromophore which should have remarkable chiroptical properties (106). The β-keto acid 6(8)A was resolved $[\alpha]_D^{21}$-45.5° by using brucine and was converted into the bromoketone 6(8)B, $[\alpha]_D$-41.1°, by the Hunsdiecker method. It was observed by Dr. C. Bonnice that a few drops of water would give better results for the resolution of the keto acid 6(8)A. The water may be required as water of crystallization in the salt.

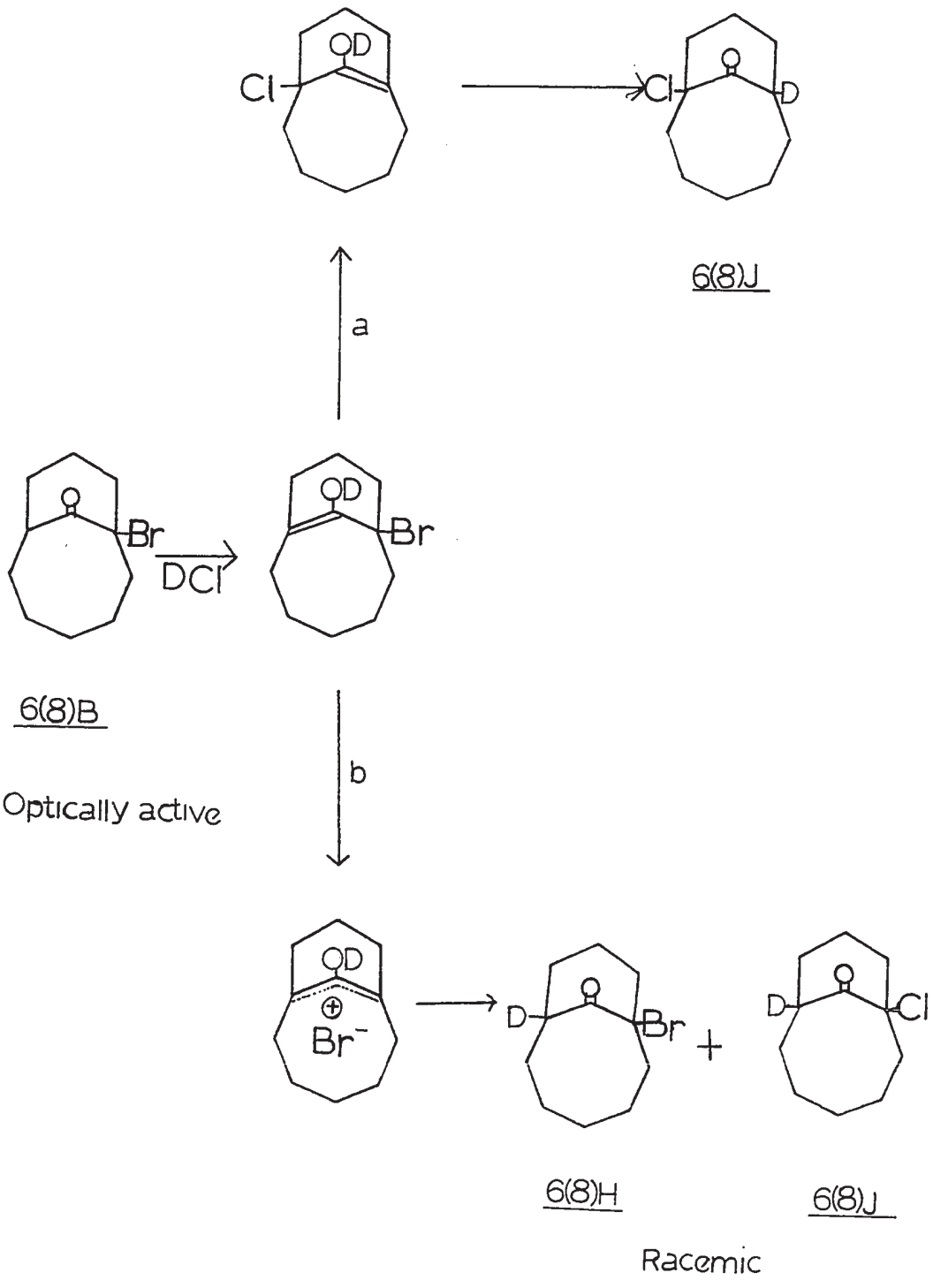
(F) 1-Bromobicyclo[5.3.1]undecan-11-one-7-d_1 6(8)H

The most common way to introduce deuterium into the position in a carbonyl compound is to exchange the hydrogen in acidic or alkaline deuterated solvent. Since the haloketone would react with base, our choice of exchange was limited to acidic catalysis. Moreover, since the hydrogen to be exchanged is at the bridgehead and the carbonyl group is less basic than in the parent ketone by 10^2-10^3, it will be anticipated that the rate will be slow, the exchange was done in acetic acid-d_4 with added deuterium chloride at 90°. The exchange after four days was only 64% d_1 and 36% d_0. It was to our surprise that the mass spectrum showed strong peaks at 201, 203 and 245, 247 which were the parent ions from 1-chlorobicyclo[5.3.1]undecan-11-one-7-d_1 and 1-bromobicyclo[5.3.1]undecan-11-one-7-d_1 respectively. The formation of chloroketone 6(8)J could be rationalized by formation of the enol in the medium, then S_N2 attack of the chloride ion at the α'-carbon to give the chloroketone 6(8)J or, perhaps more likely, ionization of the



6(8)B 6(8)H 6(8)J

enol bromide to an enol allylic cation which was then attacked by chloride or bromide to give the observed product. The above two possible mechanisms could be distinguished by using an optically active bromide if the formation of chloroketone were irreversible. By path (a) an optically active chloroketone 6(8)C would result whereas path (b) would give racemized haloketones. As a test for the above reasoning, a sample of bromoketone 6(8)B $[\alpha]_{320}$-549° was treated in the above condition for 36 hours to give a yield of 62% of haloketone whose IR spectrum was superimposable with the chloroketone 6(8)C . GLPC analysis shows 83% of chloroketone 6(8)C and 13% of bromoketone 6(8)B and 4% of unidentified product. The ORD of the distilled product had a rotation $[\alpha]_{320}$-64°. The small rotation may come from optically active bromoketone with racemic chloroketone, 13% of bromoketone 6(8)B will give a rotation $[\alpha]_{320}$-71.4° which is very close to the value observed. Another possibility is the chloroketone is optically active but with opposite rotation to the bromoketone so that a small rotation was observed. But the fact that the optically active chloroketone 6(8)C $[\alpha]_{310}$-138° was partially racemized in


OD
Cl
Cl
D
6(8)J
a
Br
DCl
OD
Br
6(8)B
Optically active
b
OD
Br⁻
D
Br
+
D
Cl
6(8)H
6(8)J
Racemic

hydrochloric acid and acetic acid to $[\alpha]_{310}$-17.8° at 90° for 72 hours showed that the chloroketone and bromoketone would racemize under these conditions. The optical activity result of the halide exchange in acetic acid medium* did not differentiate path (a) and path (b). Since the optically active chloroketone 6(8)C was partially racemized, if path (a) was followed, it was reversible.

Since the direct deuteration of the bromoketone 6(8)B gave so many complications, direct bromination of bicyclo[5.3.1]undecan-11-one-1,7-d_2 6(8)M was attempted. The bicyclo[5.3.1]undecan-11-one obtained as a byproduct of the hydrolysis of ethyl bicyclo[5.3.1]undecan-11-one-1-carboxylate 6(8)E was treated with deuterium oxide and sodium deuteroxide in dioxane at reflux for two successive exchanges. There was only about 10% exchange judged by the PMR spectrum. In view of the fact that the bromoketone 6(8)B was very reactive in base, it was surprising to see that there was only ca. 10% exchange for 60 hours in sodium deuteroxide. Therefore acidic conditions (DCl-D_2O-dioxane) were used for the exchange. The dideuterated ketone was obtained in 91% yield with 90% d_2, 7% d_1, 4% d_o. The deuterated bromoketone 6(8)B 95.5% d_1, 4.5% d_o, was obtained in 22% yield along with 1,7-dibromo-bicyclo[5.3.1]undecan-11-one by acid catalysis.

(G) 1-Chloro-bicyclo[5.3.1]undecan-11-one 6(8)C

The Hunsdiecker method was used. The reaction did not give as

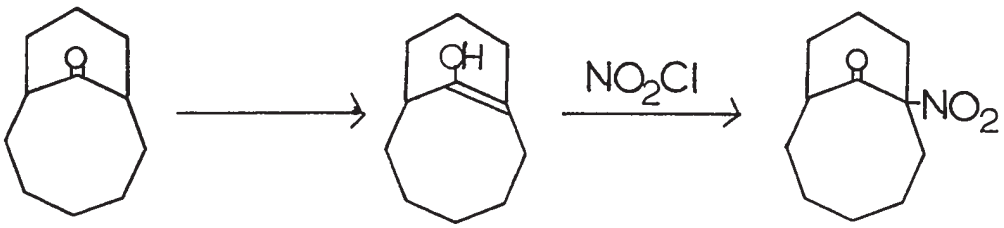
---

* The experiment was done in a flask and a syringe needle was used for introducing the deuterium chloride. The system might conceivably contain some metallic ion from the syringe needle. If so, the ions might have some effect on the exchange.

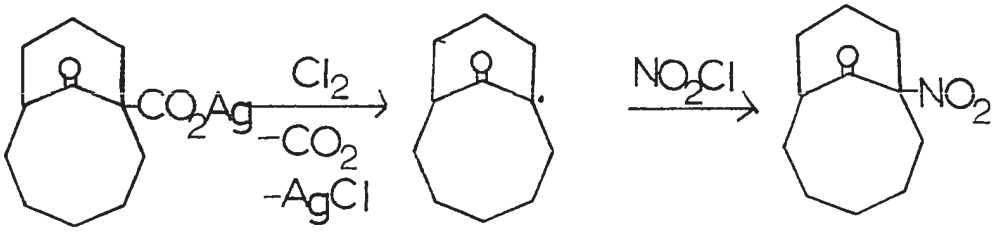
satisfactory a result as for the bromination. Usually there were considerable amounts of keto acid recovered even though great pains had been taken to avoid moisture. In one experiment about 40% of the starting keto acid was recovered. This amount of acid recovered did not seem to come from the moisture in the system. Furthermore some parent ketone 6(8)K was also detected. The chlorine gas was dried by passing through water, concentrated sulfuric acid and then dissolved in carbon tetrachloride. Recently, it was found that a stream of nitrogen passing through the above system changed litmus paper red. This showed that some sulfuric acid vapor was carried over into the carbon tetrachloride solution. This may be the reason so much keto acid 6(8)A was recovered. There was an additional compound obtained with empirical formula $C_{11}H_{17}O_3N$. Its IR spectrum showed absorption at 1715, 1370 and 1550 cm^{-1} which corresponded to the carbonyl and nitro group absorptions. Its PMR spectrum was similar to that of the chloroketone 6(8)C. Mass spectrum showed major peaks at 165, 137, 95 and 81 with no parent ion. The compound was identified as the α-nitroketone 6(8)N which was apparently formed from the potassium nitrate in the silver salt. It has been shown that carbon tetrachloride reacted rapidly with excess silver nitrate impregnated in silicic acid at room temperature to give nitryl chloride (107) which could have reacted with either the ketone 6(8)K or the keto radical to form the α-nitro ketone 6(8)N. The 1-chloro-bicyclo[5.3.1]undecan-11-one-7-d_1 6(8)J was prepared by acid catalyzed deuterium exchange of the chloroketone with deuterium chloride and acetic acid-d_4 in 80% yield and with 91% d_1, 9% d_o.

$$CCl_4 + AgNO_3 \longrightarrow CCl_3ONO_2 + AgCl$$

$$CCl_3ONO_2 \longrightarrow COCl_2 + NO_2Cl$$



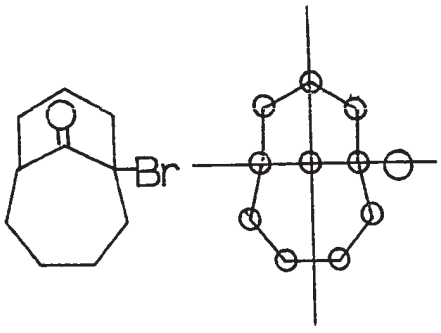
6(8)K 6(8)N



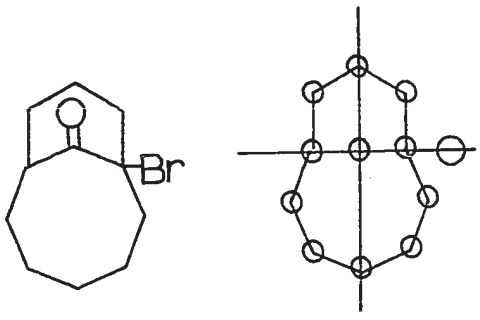
6(8)N

(H) Spectroscopic Properties of 1-Halo-bicyclo[n.3.1]alkanone

The IR absorption and λ_{max} for the carbonyl groups as well as the peak in the ORD curve of haloketones 6(6), 6(6) and 6(8) are listed in Table X. It is seen that there are bathochromic shifts in both the IR absorption and the UV absorption. According to a Drieding model all the halogens are in equatorial positions, and the amount of bathochromic shift (15-30 cm^{-1}) in IR absorption substantiates this conformation of the haloketones. On the other hand, there is a considerable bathochromic shift (11-23 nm) in the UV λ_{max} which may indicate that the conformation of the α-halogen is not exactly in the true equatorial position. For equatorial halogen there should be an hypsochromic shift of about 5-7 nm. Furthermore, inspection of the octant diagrams of the haloketones reveals that there should be no Cotton Effect for the haloketones which is contrary to the experimental observation. In the diagram the halogens lie on one of the symmetry planes of the carbonyl group and the rest of the carbon atoms are symmetrically disposed with respect to the plane bisecting the carbonyl group. The experimental observation of the Cotton Effect of the haloketone must



6(7)B



6(8)B

TABLE X

Infrared Absorption and Optical Rotatory Dispersion of 1-halobicyclo[n.3.1]alkanones

Haloketones	IR (cm^{-1})	$\Delta\nu$ (cm^{-1})	$[\theta](\lambda)^+$	λ_{max}	$\Delta\lambda$ (nm)
Cycloheptanone	1705 (CCl_4)	0	/	283*(ethanol)	0
	1700 ($CHCl_3$)	0			
6(7)C	1730 ($CHCl_3$)	30	-487 (317)	294(methanol)	11
6(7)B	1730 (CCl_4)	25	+1760(326)	306(methanol)	23
6(8)K	1695 ($CHCl_3$)	0	/	282*(ethanol)	0
6(8)C	1715 ($CHCl_3$)	20	-1248(322)	300(chloroform)	18
6(8)B	1710 ($CHCl_3$)	15	-1385(320)	302(chloroform)	20
cholestan-3-one	1715 (CS_2)#	0	+3710(309)	286(ethanol)	0
2α-bromo-cholestan-3-one	1730 (CS_2)	12	+3190(310)	282(ethanol)	-4
2α-chloro-cholestan-3-one	1735 (CS_2)	20	+3130(310)	279(ethanol)	-7

* cycloheptanone and cyclooctanone (108).

/ molecular rotation

\# Ref. (112)

result from the twisting of the carbonyl group so that the halogens are not in true equatorial positions. Even though the optical purity of the haloketones is unknown, their molecular rotations at the peaks are relatively small compared to the equatorial 2α-bromo- or 2α-chloro-cholestan-3-one. For axial haloketones the peak molecular rotation is around 10,000. Therefore the small molecular rotations of our katoketones indicates that the halogen is not axial but slightly away from equatorial.

CHAPTER VI

Experimental

General

Melting points were taken on a Reichert microscope hot stage and are corrected. Optical rotations $[\alpha]_D$ were measured with chloroform solutions, unless otherwise stated, in a 1-dm. tube on a Rudolph model 80 Polar-meter. Optical rotatory dispersion (ORD) curves were recorded on a Durrum-Jasco ORD/UV-5 spectropolarimeter with scale 20 nm. per cm. and normal speed. Infrared spectra were recorded on a Beckman IR-5A or IR-10 spectrophotometer. The ultraviolet spectra were taken on a Cary model 14 spectrophotometer. Proton magnetic resonance (PMR) spectra were determined with deuteriochloroform solutions on a Varian A-60 or T-60 spectrometer with tetramethylsilane as internal reference. Camag DF-5 silica gel with calcium sulfate binder was used for thin-layer chromatography (TLC) and thich layer chromatography (20 g. silica gel per 20 x 20 cm. plate). Sulfuric acid (30%) was used for charring. Mass spectra were run on a Varian M-66 instrument using perfloroalkane for calibration. Gas liquid partition chromatography (GLPC) was carried out on a Glowall model 400 apparatus fitted with a 1.8 m. x 3.4 m. glass column for analysis. The column was packed with 5% diethylene glycol succinate (DEGS) on non acid-washed 60-80 mesh chromasorb P.

Solutions in organic solvents were dried by washing them with saturated sodium chloride solution and then allowing them to stand with anhydrous magnesium sulfate or sodium sulfate. Removal of organic solvent was effected using a rotary evaporator under reduced pressure of the water pump on a hot water bath (60-70°). Petroleum ether refers to the fraction boiling at 60-80° unless otherwise stated.

Microanalyses were carried out in the laboratories of A.B. Gygli, Toronto, Ontario or Joseph F. Alicino, Metuchen, New Jersey.

(A) cis-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C

Cyclohept-1-ene carboxylic acid 109

The method of Wheeler and Lerner was used (100). Cycloheptanone (11.3 g., 0.10 mole) was mixed with sodium cyanide solution (12.0 g., 0.15 mole in 50 ml. of water) in a three-necked flask which was fitted with a mechanical stirrer. The solution was cooled in an ice-salt bath. A solution of 25 g. of sodium bisulfite in 60 ml. of water was added from a dropping funnel during a period of 0.5 hr. The mixture was stirred vigorously during addition and a clear solution was formed after the mixture had been stirred for 9 hrs. The aqueous solution was extracted with ether several times, and the combined ethereal extracts were dried. After removal of the solvent at reduced pressure with rotatory evaporator, 10.0 g. (72%) of crude cyanohydrin was obtained. TLC (ethyl acetatepetroleum ether 1:2) showed one spot with no starting material.

IR spectrum: $\nu_{max}^{CCl_4}$ 3400 (OH) and 2225 cm^{-1}(CN)

The crude cyanohydrin (10.0 g., 0.72 mole) in 25 m. of pyridine and 25 ml. of benzene was treated with a mixture of phosphorous oxychloride (30 ml.) and pyridine (30 ml.) in a 250-ml. flask. The solution was warmed slowly and heated under reflux in oil bath for 2 hrs. The reaction mixture was cooled and poured cautiously onto 500 ml. of ice. The aqueous solution was extracted several times with ether. The combined ethereal extracts were washed with dilute hydrochloric acid, water and then dried. The ether was removed and 8.0 g. of oily 1-cyanocycloheptene was obtained. The oil was distilled, and the fraction distilling at 54-55° (1 mm.) was collected. (7.0 g. 80%).

IR spectrum: $\nu_{max}^{CCl_4}$ 2225 (CN), 1625 cm^{-1} (C=C) no OH absorption.

The distilled 1-cyanocycloheptene (7.0 g., 0.58 mole) was hydrolyzed with 21.0 g. of 85% phosphoric acid at 160° under reflux for 10 hrs. The cooled solution was diluted with water and extracted with ether several times. The combined ethereal solution was washed with water and dried. After removal of the ether, 10.0 g. (71% overall) of solid was obtained. The crude acid after recrystallization from petroleum ether (b.p. 30-60°) gave colorless plates of cyclohept-1-ene-carboxylic acid 109. mp 50.5-51.5 [lit (115) mp 49°].

IR spectrum: $\nu_{max}^{CCl_4}$ 2500-3200 (carboxyl OH), 1675 (carboxyl C=O), 1640 cm^{-1} (C=C).

PMR spectrum: δ 7.35 (1H, t, 7 cps, = CH-[CH_2] and 11.61 ppm(1H, s, COOH).

cis-Bicyclo[5.4.0]undec-9-ene-1-carboxylic acid 110

Cyclohept-1-ene carboxylic acid 109 (3.23 g., 0.023 mole) was divided between two thick-walled Pyrex glass tubes (diameter 1.5 cm. and length 30 cm.) and cooled in a Dry Ice-acetone bath. About 4 ml. of butadiene was passed in and condensed over the acid in each tube. The tubes were sealed and heated at 170° for 24 hrs. After the tubes were cooled in a Dry Ice-acetone bath, the tubes were opened. The contents of the tubes were extracted several times with 10% aqueous sodium hydroxide. Masses of polymer were precipitated during the extraction. The alkaline extracts were further washed with benzene and ether. The aqueous layer was then acidified to pH~2, and the precipitated acid (2.0 g.) was filtered, mp 73-76°. The crude acid was recrystallized from acetic acid-water to give colorless plates, mp 76-77.5°.

IR spectrum: $\nu_{max}^{CCl_4}$ 3500-2400 (carboxyl OH) and 1675 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 5.60 (2H, s, CH=CH) and 11.58 ppm (1H, s, COOH)

Anal. Calcd. for $C_{12}H_{18}O_2$ (194.26): C, 74.18; H, 9.34

Found: C, 74.39; H, 9.43.

Oxidation of cis-bicyclo[5.4.0]undec-9-ene-1-carboxylic acid 110

The unsaturated acid 110 (1.0 g., 5.1 mmoles) was dissolved in potassium hydroxide solution (0.50 g. in 10 ml. of water) and 2.40 g. of potassium permanganate was added in portions. The solution turned green at once and heat was evolved. The solution was stirred with a magnetic bar for 0.5 hr. and was then acidified with dilute sulfuric acid and filtered through a sintered glass funnel. The filtrate was

concentrated to about 30 ml. and kept in the refrigerator for crystallization. The solid was filtered and dried under vacuum to yield 0.40 g. (31%) of the triacid 111. Three recrystallizations from water gave colorless plates, mp. 172-173°.

IR spectrum: ν_{max}^{Nujol} 2250-3500 (carboxyl OH) and 1750-1700 cm^{-1} (superimposed carboxyl C = O)

Anal. Calcd. for $C_{12}H_{18}O_6$ (2.58.26): C, 55.76; H, 7.02

Found: C, 55.65; H, 7.04

cis-9-oxobicyclo[5.3.0]decane-1-carboxylic acid 112

The triacid 111 (342 mg., 1.32 mmoles) was mixed well with 10 mg. of barium oxide in a glass tube (8 mm. x 30 cm.). About half of the length of the tube was inserted in a heating block and the rest of the tube was cooled with a current of air. The tube was heated at 150° (150 mm.) for 3 hrs. and then at 240° (60 mm.) until no further product distilled over. The yield amounted to 135 mg. of yellow oil (52%). TLC (acetic acid chloroform, 6:94) showed only traces of an impurity. Stort-stem distillation at 133° (1 mm.) gave an analytical sample.

IR spectrum: $\nu_{max}^{CCl_4}$ 2400-3500 (carboxyl OH), 1745 (ketone C=O) and 1700 cm^{-1} (carboxyl C=O)

PMR spectrum: δ^{CCl_4} 10.8 ppm (1H, s, COOH)

Anal. Calcd. for $C_{11}H_{16}O_3$ (192.24): C, 67.32; H, 8.22

Found: C, 67.29; H, 8.18

cis-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C

To a solution of 191 mg. (0.98 mmole) of keto acid 112 in 6 ml. of triethylene glycol were added 1.5 ml. of hydrazine hydrate (85%) and 0.5 g. of potassium hydroxide pellets. The mixture was refluxed in an oil bath at 140° for 1.5 hrs. after which time the excess hydrazine hydrate was distilled out. The temperature of the oil bath was then raised to 200° and maintained at that temperature for 22 hrs. The cooled reaction mixture was diluted with water and extracted with chloroform. The aqueous layer was acidified with concentrated hydrochloric acid and extracted again with chloroform. Evaporation of the dried chloroform extracts left 180 mg. (100%) of crude product. TLC (petroleum ether-ethyl acetate, 65:35) showed some of the unreacted keto acid. The crude acid was separated on a thick plate with the above solvent system using alcoholic methyl red indicator for spraying solution. The purified product after two recrystallizations from petroleum ether gave colorless plates, mp 57.5-58.5°. The infrared spectrum of the pure acid was identical with that of the acid obtained from the Favorskii rearrangement of 1-bromobicyclo[5.3.1]undecan-11-one 6(8)B and the acid showed no depression in mp with the acid from the Favorskii reaction, mp 57-58°.

IR spectrum: $\upsilon_{max}^{CS_2}$ 2300-3400 (carboxyl OH) and 1680 cm^{-1} (carboxyl C=O)

Anal. Calcd. for $C_{11}H_{18}O_2$ (182.25): C, 72.48; H, 9.95

Found: C, 72.40; H, 9.75.

(B) trans-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)T

$\Delta^{9,10}$-Octalin

$\Delta^{9,10}$-Octalin was prepared in 65% yielded by phosphorus pentoxide catalyzed dehydration of β-decalol according to the method of Campbell and Harries (109). It is a colorless liquid, bp 44-46° (2mm)[lit. (109) bp 190-192° (760 mm)]. The PMR spectrum showed that the product contained 20% of a mixture of $\Delta^{1,2}$-octalin and $\Delta^{2,3}$-octalin.

IR spectrum: $\nu_{max}^{CCl_4}$ 2900 (CH stretching) and 1450 cm^{-1} (CH_2 deformation)

1,6-Cyclodecanedione

1,6-Cyclodecanedione was prepared in 30% yield by ozonolysis of $\Delta^{9,10}$-octalin in aqueous acetic acid solution at 0° according to the method of Plattner and Hulstkamp (111). The dione is a colorless crystal, mp 101-102° [lit. (111) mp 100°].

IR spectrum: $\nu_{max}^{CCl_4}$ 1710 cm^{-1} (ketone C=O)

PMR spectrum: δ^{CCl_4} 1.6-2.0 (8H, bm, ketone α-H) and 2.0-2.4 ppm (8H, bm ketone β-H)

$\Delta^{9,10}$-Bicyclo[5.3.0]decen-4-one 115

The unsaturated ketone 115 was synthesized in 86% yield by sodium bicarbonate catalyzed intramolecular condensation of 1,6-cyclodecanedione at reflux according to the method of Anderson (103). It is a colorless liquid bp 111-112° (6.7 mm.) [lit (103) 126-128° (15 mm.)].

IR spectrum: $\nu_{max}^{CCl_4}$ 1640 cm^{-1} (conjugated C=O)

PMR spectrum: δ^{CCl_4} 1.5-2.0 (1H, bm, methylenes) and 2.2-2.4 ppm (8h, bm, ketone α-H and allylic H).

1-Cyanobicyclo[5.3.0]decan-6-one 116

A solution of the unsaturated ketone 115 (1.5 g., 0.010 mole) in methanol (5 ml.) was added to a solution of potassium cyanide (0.02 mole in 4 ml. of water and 20 ml. of methanol). The solution was refluxed for 5 hrs. The solvent was removed and the residue was taken up in water. The water solution was extracted several times with chloroform. The chloroform extracts were washed with water and dried. Removal of the solvent left 1.0 g. (57%) of oily product. TLC showed two spots. The product (11.5 mg.) was developed on a thick plate and 30 mg. of product was obtained from the lower band. Short-stem distillation at 100° (0.1 mm.) gave an analytical sample. There was no change in the IR spectrum after distillation.

IR spectrum: $\nu_{max}^{CCl_4}$ 2225 (CN) and 1725 cm^{-1} (ketone C=O)

Anal. Calcd. for $C_{11}H_{15}NO$ (177.24): C, 74.53; H, 8.53; N, 7.91

Found: C, 74.35; H, 8.45; N, 7.73.

Lactamol 117 of trans-1-carboxamidobicyclo[5.3.0]decan-6-one 118

A solution of 6.0 g. (0.04 mole) of enone 115, 5.2 g. (0.09 mole) of potassium cyanide, 200 ml. of methanol and 16 ml. of water was heated under reflux for 5.5 hrs. The cooled solution was

neutralized with acetic acid and the solvent was removed. The residue was taken up in water and extracted with chloroform. The chloroform extracts were washed with water and dried. On removal of the solvent, 6.0 g. (77%) of solid product was obtained. Three crystallizations from petroleum ether-methanol gave fine needles of lactamol 117, mp 141-142°.

IR spectrum: $\nu_{max}^{CCl_4}$ 3000-3500 (OH), 1675 cm^{-1} (amide C=O)

PMR spectrum: δ 4.47(1H, s, OH) and 7.10 ppm (1H, b, NH)

Anal. Calcd. for $C_{11}H_{17}NO_2$ (195.25): C, 67.66; H, 8.78; N, 7.13

Found: C, 67.12; H, 8.90; N, 7.46

Attempted Preparation of trans-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)T

(a) Huang-Minlon Reduction of Lactamol 117

To a solution of 2.12 g. (0.011 mole) of lactamol 117 in 30 ml. of triethylene glycol were added 6.0 g. of potassium hydroxide pellets and 20 ml. of hydrazine hydrate. The mixture was refluxed for 1 hr. at 140°, after which time the temperature of the oil bath was raised to 210° and maintained for 5 hrs. The excess hydrazine was distilled out at 210°. The cooled reaction mixture was diluted with water and washed with chloroform. The aqueous solution was acidified with hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water and dried. Evaporation of the solvent left 1.07 g. (59%) of crude acid. The acid had the same infrared spectrum, PMR spectrum and Rf on TLC as authentic cis-bicyclo[5.3.0]-

decane-1-carboxylic acid 5(7)C. Three recrystallizations from petroleum ether gave colorless plate, mp 58-59.5, undepressed on admixture with the cis-acid 5(7)C.

IR spectrum: $\nu_{max}^{CCl_4}$ 2225-3400 (carboxyl OH) and 1680 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 2.50-3.0 ppm (1H, tertiary-H at ring junction)

Anal. Calcd. for $C_{11}H_{18}O_2$ (182.25): C, 72.48; H, 9.91

Found: C, 72.06; H, 9.95

(b) Huang-Minlon Reduction of Ketonitrile 116

To a solution of 803 mg. (4.70 mmoles) of keto nitrile 116 in 20 ml. of triethylene glycol were added 3 g. of potassium hydroxide pellets and 4.5 ml. of hydrazine hydrate. The mixture was refluxed for 1 hr. at 140° after which the temperature of the oil bath was raised to 210° and maintained for 5 hrs. while the excess hydrazine was distilled out. The reaction was worked up as for the Huang-Minlon reduction of lactamol 117 in (a). Evaporation of the solvent left 295 mg. (35%) of acid. TLC (ethyl acetate-petroleum ether, 35:65) of the crude product showed three products with Rf 0.68, 0.55 and 0.36. The acid was chromatographed on two thick-plates with the above solvent system to give 163 mg. of acid (Rf: 0.68) whose PMR spectrum was identical to that of authentic cis-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C. Gas chromatography of the methyl ester of the acid at 120° showed two peaks which corresponded to methyl ester of cis (88%) and trans-bicyclo-[5.3.0]decane-1-carboxylic acid (12%).

(c) Clemmensen Reduction of Lactamol 117

A mixture of 10 g. of mossy zinc, 1.0 g. mercuric chloride, 0.5 m. of concentrated hydrochloric acid and 10 ml. of water was stirred for 5 mins. in a 250-ml. round bottom flask. The aqueous solution was decanted and the amalgamated zinc was covered with 7.5 ml. of water and 10 ml. of concentrated hydrochloric acid.

A sample of 2.0 g. (0.01 mole) of the lactamol 117 in 10 ml. of benzene was added to the amalgamated zinc and refluxed briskly for 48 hrs. during which time a 3-ml. portion of concentration hydrochloric acid was added every 4 hrs. The solution was cooled to room temperature and 50 ml. of ice was added. The aqueous solution was extracted with ether. The ether extracts were washed with water and dried. Removal of the solvent left 197 mg. of product which was dissolved in 10% potassium hydroxide solution. The alkaline solution was extracted with ether. The ether extracts were washed with water and dried. After removal of the solvent, 97 mg. (2%) of acid was obtained. The crude acid was chromatographed on 5 g. of selica gel (B.D.H. 60-120 mesh). Elution with petroleum ether-benzene (90:10) gave 10 mg. of acid which was converted into methyl ester with diazomethane. GLPC analysis of the methyl ester at 120° showed 75% cis- and 25% trans-methyl bicyclo[5.3.0]decane-1-carboxylate.

1-Cyanobicyclo[5.3.0]decane 119

The electrolytic procedure of Throop and Tokes was used (104).

The electrolytic cell used for reduction consisted of two

lead electrodes each with a surface area of 12 cm^2 in an H-shaped cell with cathode and anode compartments which were divided by a sintered glass partition. Each compartment was of 40 ml. capacity. The electrodes were polished with sand-paper and cleaned with distilled water and acetone. The cathode was coated with lead dioxide before use so that during electrolytic reduction a fresh lead surface was formed.

The reduction was done by dissolving 400 mg. (2.26 mmoles) of the ketonitrile 116 in a mixture of 20 ml. of 10% sulfuric acid and 20 ml. of peroxide free dioxane in the cathode compartment which was stirred with a magnetic stirrer. The same electrolyte was used in the anode compartment. The cell was kept at room temperature. A direct current of 1.5 amp. at 18 volts was used for the reduction and it was produced from a D.C. generator Model 855 B, Harrison Laboratory, Inc., New Jersey. After 20 hrs. the cathode solution was extracted with ether. The ether extracts were washed with water and then dried. Removal of the solvent left 370 mg. (100%) of 1-cyanobicyclo[5.3.0]decane. The product was quite pure for hydrolysis.

IR spectrum: $\nu_{max}^{CCl_4}$ 2225 cm^{-1} (C≡N)

PMR spectrum: δ^{CCl_4} 1-2.4 ppm (17H, bm)

Attempted Hydrolyses of 1-cyanobicyclo[5.3.0]decan-6-one 116

(a) In Phosphoric Acid

The keto nitrile 116 (150 mg., 0.85 mmole) was refluxed with 5 ml. of 85% phosphoric acid for 4 hrs. The cooled solution was diluted with water and extracted with chloroform. The chloroform extracts were

washed with water and dried. Removal of solvent gave 50 mg. (20%) of recovered keto nitrile 116 identical with starting material.

(b) In Concentrated Hydrochloric Acid

The keto nitrile 116 (170 mg., 0.96 mmole) was refluxed with 2 ml. of concentrated hydrochloric acid for 8 hrs. The cooled solution was made alkaline with sodium hydroxide and extracted with chloroform. The alkaline solution was acidified with hydrochloric acid and extracted again with chloroform. The chloroform extracts were washed with water and dried. Removal of solvent left 30 mg. (20%) of recovered 116 whose infrared spectrum showed traces of acid.

Attempted Hydrolyses of 1-cyanobicyclo[5.3.0]decane 119

(a) In Hydrogen Peroxide and Potassium Hydroxide

A mixture of the crude nitrile 119 (350 mg., 2.0 mmoles), 6 ml. of 30% hydrogen peroxide, 6 ml. of 10% potassium hydroxide and 6 ml. of ethanol was heated on a water bath at 80° for 5 hrs. and then refluxed on steam bath for 1 hr. Another 2 ml. of hydrogen peroxide was added and the reaction mixture was refluxed further for 12 hrs. The cooled solution was acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water and dried. After removal of the chloroform, the infrared spectrum of the residue (370 mg.) showed strong C≡N absorption and very weak C=O absorption.

(b) In 85% Phosphoric Acid

The nitrile 119 recovered from (a) was treated with 10 ml. of 85% phosphoric at 180° for 40 hrs. The black reaction solution was diluted with 50 ml. of ice. The aqueous solution was extracted with ether. The combined ethereal extracts were washed with water and dried. A dark brown residue (165 mg.) was obtained after removal of the solvent. Infrared spectrum of the residue showed no C=N or C=O absorptions and it was a spectrum of hydrocarbon. PMR spectrum showed broad multiplet between 0.60-2.70 ppm. Further attempts to hydrolyze to nitrile 119 were abandoned.

trans-Bicyclo[5.3.0]decane-1-carboxaminde 123

The electrolytic reduction of lactamol 117 was carried out as described for the ketonitrile 116. A solution of 746 mg. (3.9 mmoles) of lactamol 117 in 20 ml. of 10% sulfuric acid and 20 ml. of peroxide free dioxane was electrolyzed in the cathode compartment with a current of 1.5 amperes and 18 volts. After 135 hrs. the cathode solution was extracted with ether. The ethereal extracts were washed with water and dried. Removal of ether left 633 mg. of product. TLC (acetic acid-chloroform, 6:94) showed three spots. The crude product was chromatographed on 25 g. of selica gel (B.D.H. 60-80 mesh). From the fractions eluted by benzene-ether (75:25), 172 mg. of solid amide 123 was obtained. TLC (acetic acid-chloroform, 6:94) showed one spot, Rf = 0.70. Another 18 mg. of solid was obtained from benzene-ether (50:50) fractions. One recrystallization from chloroform-petroleum ether gave 5 mg. m.p. 154-157°, TLC (acetic acid-chloroform 6:94) one spot. Further elution

with benzene-ether (33:67) gave 300 mg. starting lactamol. The total yield of amide was 46% based on reacting lactamol.

IR spectrum: $\nu_{max}^{CHCl_3}$ 3500, 3400, 3100 (NH), 1625 (amide I band, C=O) and 1575 cm^{-1} (amide II band, NH_2)

PMR spectrum: δ 5.72 ppm (2H, b, $CONH_2$)

Mass spectrum: m/e 181 (M^+)

trans-Bicyclo[5.3.0]decane-1-carboxylic acid 5(7)T

The amide 123 (132 mg., 0.73 mmole) was added to a solution of 0.7 ml. of concentrated sulfuric acid and 2 ml. of 20% sodium nitrite. Upon addition brown fumes were evolved and precipitation occurred immediately. The solution was shaken for 3 hrs. after which it was made alkaline with dilute potassium hydroxide. The solution was extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid and extracted again with ether. The ethereal extracts were washed with water and dried. On removal of solvent, 50 mg. (38%) of acid was obtained, m.p. 100.5-101.5° after sublimation at 50-60° (0.1 mm.). The melting point was depressed to 47-100° when mixed with cis-acid 5(7)C. GLPC at 120° of the methyl ester from crude product showed only one product with retention time 4.4 minutes. The methyl ester of the cis-bicyclo[5.3.0]decane-1-carboxylic acid at the same condition had retention time at 5.2 minutes. Mixed GLPC showed two peaks distinctly.

IR spectrum: $\nu_{max}^{CCl_4}$ 2225-3300 (carboxyl OH) and 1680 cm^{-1} (carboxyl C=O)

PMR spectrum: δ^{CCl_4} 1.0-2.8 (17H, OM) and 12.1 ppm (1H, s, COOH)

Anal. Calcd. for $C_{11}H_{18}O_2$ (182.25): C, 72.49; H, 9.95

Found: C, 72.88; H, 9.89.

Basic Decomposition of m-Chloroperbenzoic Acid

A stock solution of m-chloroperbenzoic acid was prepared by dissolving 2 gm. of the peracid (Aldrich) in 100 ml. of 95% ethanol. A solution of 6 ml. of peracid solution and 2 ml. of 5% of sodium hydroxide was refluxed for 20 mins. The solution was then acidified with dilute hydrochloric acid and excess of potassium iodide solution (4 gm. of potassium iodide in 100 ml. of water) was added. The iodine liberated was titrated with 0.1 N sodium thiosulfate with starch as indicator and 0.5 ml. of solution was used. A second run was done with 4 ml. of the peracid with 15 mins. reflux and 0.8 ml. of thiosulfate solution was used. A parallel titration was performed with 2 ml. of the peracid without heating and 2.65 ml. of sodium thiosulfate was consumed.

(C) 1-Halobicyclo[n.3.1]alkanones

11-Oxobicyclo[5.3.1]undecane-1-carboxylic acid 6(8)A

The procedure of Warnhoff, Wong and Tai was followed (88). A solution of 95 g. (0.85 mole) of cycloheptanone in 100 ml. of ether was treated with freshly distilled boron trifluoride etherate (122 g., 0.85 mole) and 105 g. (0.90 mole) of ethyl diazoacetate at -60°. The reaction gave 14.1 g. of recovered cycloheptanone and 126 g. (89%) of 2-carbethoxycycloactanone, bp 92-112° (1-1.25 mm.). [lit (88) 102-125°

(2.5 mm.)].

IR spectrum: $\nu_{max}^{CCl_4}$ 1750 (ester C=O), 1710 (ketone C=O), 1645(ester C=O of enol) and 1615 cm^{-1} (C=C of enol)

The 2-carbethoxycyclooctanone (126 g., 0.65 mole) was subjected to Michael addition with 45.2 g. (0.81 mole) of freshly distilled acrolein with sodium ethoxide (0.042 mole) as base in 283 ml. of absolute ethanol at -70°. The reaction was worked up to give 68 g. (41%) of Michael adduct, bp, 137° (1.75 mm.) [lit (88), 134-139° (0.58 mm.)].

IR spectrum: $\nu_{max}^{CCl_4}$ 2710 (aldehyde CH), 1730 and 1712 cm^{-1} (superimposed aldehyde, ester and ketone C=O)

PMR spectrum: δ^{CCl_4} 1.25 (3H, t, J = 7 cps, $CH_3[CH_2O]$, 4.12 (2H,q, J = 7 cps, $OCH_2[CH_3]$, and 9.66 ppm (1H, t, J = 7 cps, CHO).

The distilled Michael reaction adduct (68 g., 0.268 mole) was heated with 340 ml. of N,N-dimethyl benzylamine to which 34 g. of anhydrous oxalic acid was added to 170° for 48 hrs. The water formed from the reaction was drained off with a takeoff condenser during the reaction. The excess amine was distilled off and then worked up as reported to give 52.0 g. (82%) of crude conjugate keto ester. The IR spectrum of the crude product showed no hydroxyl absorption. The crude product (52 g. 0.221 mole) in 220 ml. of 95% ethanol was hydrogenated at 3-atm. initial pressure and room temperature on a Parr series 1309 shaker in the presence of 10.4 g. of 5% palladium supported on barium carbonate. Hydrogen uptake was 18 lbs. (100% of the theoretical 17.9 lbs.). Filtration of the catalyst and evaporation of

the solvent gave 49.1 g. (93%) of ethyl-11-oxo-bicyclo[5.3.1]undecane-1-carboxylate.

IR spectrum: $\nu_{max}^{CCl_4}$ 1735 (ester C=O) and 1700 cm^{-1} (ketone C=O)

PMR spectrum: δ^{CCl_4} 1.26 (3H,t, J = 7 cps, $CH_3[CH_2O]$), 2.2-2.6 (1H, bm, ketone α-H) and 4.12 ppm (2H, q, J = 7 cps, $OCH_2[CH_3]$).

The keto ester 6(8)E, 49.1 g. (0.208 mole) in 250 ml. of methanol was hydrolyzed with 175 ml. of 10% sodium hydroxide at 90° for 48 hrs. The reaction afforded 12.0 g. of 11-oxo-bicyclo[5.3.1]-decane 6(8)K and 28 g. (60%) of 11-oxo-bicyclo[5.3.1]undecane-1-carboxylic acid 6(8)A, mp 131-133° after recrystallization from ethyl acetate. The overall yield was 17% from cycloheptanone.

IR spectrum: $\nu_{max}^{CHCL_3}$ 2500-3500 (carboxyl OH), 1680-1750 cm^{-1} (superimposed carboxyl and ketone C=O)

PMR spectrum: δ 2.40-2.90 (1H, bm, ketone α-H) and 9.90 ppm (1H, s, COOH)

Optically Active 11-Oxobicyclo[5.3.1]undecane-1-carboxylic acid 6(8)A

To a solution of 1.87 g. (0.0089) of keto acid 6(8)A in 10 ml. of acetone was added 3.13 g. (0.0075 mole) of brucine (B.D.H.). A few drops of water was added. The mixture was warmed on a steam bath until a clear solution was obtained. No precipitation of crystals occurred at room temperature for 3 hrs. The solution was cooled in the refrigerator overnight. A yield of 2.50 g. of solid was obtained and 0.70 g. of the solid was treated with dilute hydrochloric acid. The aqueous solution was extracted with ether, the ethereal extracts were washed

with water and dried. Removal of solvent afforded 182 mg. of white solid mp 137-138° with decarboxylation. The optical rotation of this acid was $[\alpha]_D^{20}$ - 33.1° (c, 5.64 in chloroform).

The same procedure was used for a larger scale resolution. To a solution of 60.54 g. (0.29 mole) of keto acid 6(8)A in 320 ml. of reagent acetone was added 113.5 g. (0.29 mole) of brucine. An additional 50 ml. of acetone was used to wash all the brucine into the solution, and 2.5 ml. of water was added. The mixture was warmed on a steam bath and the final volume of the amber solution was about 350 ml. A few crystals of the above briscine salt was added to the cooled solution at room temperature. The solution was kept in the refrigerator for 2 days to give first crop of solid, 44.15 g. The acid, 124 mg., recovered from 474 mg. of salt had $[\alpha]_D^{21}$ - 45.5°. The mother liquid was further concentrated to give a second crop of 24.12 g. of solid which was decomposed to give 7 g. of acid $[\alpha]_{308}$ - 518.4°. The first crop of salt was decomposed to give 13 g. of acid, $[\alpha]_{308}$ - 756°, mp 111-115° (dec.).

ORD: (c, 0.595 in chloroform) $[\alpha]_{450}$ - 121°, $[\alpha]_{400}$ - 182°, $[\alpha]_{350}$ - 350°

$[\alpha]_{308}$ - 756° $[\alpha]_{274}$ + 505°

Optically Active 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

To a solution of optically active β-keto acid 6(8)A, $[\alpha]_D^{21}$ - 45.5°, 12.69 g. (0.0605 mole) in 80 ml. of methanol was added a solution of 3.39 g. (0.06 mole) of potassium hydroxide in 50 ml. of methanol. The resulting solution showed pH~7. The solution was made slightly alkaline pH~8-9 by a drop of dilute potassium hydroxide. A

solution of silver nitrate, 10.30 g. in 10 ml. of water and 50 ml. of methanol was added with stirring. The silver salt formed immediately and was collected on a sintered-glass funnel. The crude silver salt was washed with methanol and dried in a vacuum desiccator at 60° (1 mm.) for 40 hrs. The dried grey silver salt weighed 23.72 g. (124%) and contained some potassium nitrate. The dried silver nitrate salt in 25-ml. Erlemeyer flask was fitted to one of the side necks of a 250 ml. three-necked flask with Tygon tubing. The flask was fitted with a mechanical stirrer and condenser with drying tube. The silver salt was added in small portions to a solution of 12.24 g. (0.64 mole) of dry bromine (washed with concentrated sulfuric acid and distilled from phosphorus pentoxide) in 80 ml. of spectral grade carbon tetrachloride for 0.5 hr. Bubbles of carbon dioxide evolved and yellow silver bromide precipitated. The reaction mixture was further stirred for 1.5 hrs. at 50-60°. The silver bromide was filtered and washed well with water and ether. The filtrate was concentrated and taken up in 150 ml. ether. The ether solution was washed with sodium bisulfite solution to remove the excess bromine and with sodium bicarbonate solution. Finally, the solution was washed with water and dried. Removal of solvent gave 10.0 g. (70%) of bromoketone which was recrystallized once from petroleum ether, mp, 55-65°. TLC in petroleum ether-ethyl acetate (3:1) showed single spot.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (ketone C=O)

ORD: (c, 0.68 in chloroform) $[\alpha]_{450}$ - 35°, $[\alpha]_{400}$ - 65°, $[\alpha]_{350}$ - 214°, $[\alpha]_{321}$ - 564° $[\alpha]_{290}$ + 290°

Optically Active 1-Chlorobicyclo[5.3.1]undecan-11-one 6(8)C

A solution of 2.86 g. (0.051 mole) of potassium hydroxide in 50 ml.of methanol was added to a solution of 10.70 g. (0.051 mole) of optically active β-keto acid 6(8)A $[\alpha]_{308}$ + 492° in 80 ml. of methanol. The resulting solution had pH~8. A solution of 8.65 g. (0.051 mole) of silver nitrate in 8 ml. of water and 40 ml. of methanol was added to the basic solution with stirring. The silver salt formed immediately and was collected on a sintered glass funnel. The salt was washed several times with methanol and dried in a vacuum desiccator at 70° (2 mm.) for 39 hrs. The filtrate was acidified with dilute nitric acid and extracted with ether to give 414 mg. of recovered acid. The dry silver salt, 17.89 g. (110% presumably containing some potassium nitrate) was added to 55 ml. of chlorine solution in carbon tetrachloride (1.98 N, 0.54 mole) in a three-necked flask which was fitted with a mechanical stirrer and condenser with drying tube. Bubbles of carbon dioxide were evolved and heat was released. The addition time was 30 mins. and the mixture was further warmed at 60° with stirring for 45 mins. The reaction mixture was filtered and the filtrate was concentrated. The concentrated filtrate was taken up in ether and extracted with sodium bicarbonate solution. The ethereal solution was then washed with water until neutral and dried. Removal of solvent afforded 4.603 g. of oil. The bicarbonate wash were acidified with dilute hydrochloric acid to give 4.25 g. starting acid after extraction with ether and drying. TLC analysis of the oil showed two products. (Rf = 0.58, 0.69). The more polar product was UV visible. The crude product was chromatographed on 140 g. of silica gel (B.D.H. 60 - 120

mesh). Elution with benzene-petroleum ether (45:55) afforded 1.46 g. of semisolid product. (Rf. 0.69, TLC single spot). Recrystallized from petroleum ether gave long needles mp 68.5-69.5°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1715 cm^{-1} (ketone C=O)

PMR spectrum: 2.70-3.00 ppm (1H, bm, ketone-αH)

ORD: (c, 0.980 in chloroform) $[\alpha]_{450}$ + 46°, $[\alpha]_{400}$ + 76°, $[\alpha]_{350}$ + 189°, $[\alpha]_{320}$ + 479°

Anal. Calcd. for $C_{11}H_{17}OCl$ (200): C, 66.14; H, 8.63

Found: C, 65.38; H, 8.47

Further elution with benzene-petroleum ether (50:50) and (60:40) afforded no separation. The whole column was washed out with ether and the products were separated on thick layer chromatography eluting with petroleum ether-ethyl acetate (70:30) to give 758 mg. of chloroketone (Rf = 0.69) and 1.30 g. of 1-nitrobicyclo[5.3.1]undecan-11-one 6(8)N (Rf = 0.58), as needles from petroleum ether, mp 95-96°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1715 (ketone C=O), 1370 and 1550 cm^{-1} (NO_2)

PMR spectrum: δ 2.20-3.00 ppm (5H, bm, ketone α-H and CH_2-C-NO_2-CH_2)

ORD: (c, 0.375 in chloroform) $[\alpha]_{400}$ + 187.0°, $[\alpha]_{350}$ + 507.0, $[\alpha]_{318}$ + 2110°, $[\alpha]_{300}$ 0, $[\alpha]_{290}$ - 2700°

Anal. Calcd. for $C_{11}H_{17}O_3N$ (211): C, 62.54; H, 8.11; N, 6.63

Found: C, 68.08; H, 8.22; N, 6.41

Mass spectrum: m/e 165 ($M-NO_2$), 137, 95, 81.

Bicyclo[5.3.1]undecan-11-one,7-d_2 6(8)M

Metallic sodium 114.7 mg. (5.0 miliatoms) was dissolved in 17 ml. of purified anhydrous dioxane and 3.5 ml. (175 mmoles) of deuterium oxide. To the cooled basic solution was added 2.15 g. (13 mmoles) of bicyclo[5.3.1]undecan-11-one 6(8)K. The solution was refluxed with stirring for 12 hrs. The excess dioxane and deuterium oxide were distilled off at atmospheric pressure and residue dissolved in ether. The ether solution was dried with magnesium sulfate. Removal of solvent afforded 2.15 g. (100%) of recovered ketone. The PMR spectrum of the crude product showed only about 10% exchange.

The recovered ketone was further subjected to the same treatment again with 110 mg. (4.8 miliatoms) of sodium, 5 ml. of deuterium oxide and 20 ml. of dioxane for 48 hrs. The PMR spectrum was taken after distilling off the solvent and no increase in deuterium exchange was noted. The residue was worked up to give 1.65 g. (77%) recovered ketone.

Since there was no appreciable exchange in basic condition, an acid catalytic condition may help. A stream of deuterium chloride, generated by mixing 2 ml. of deuterium oxide and 1 ml. of phosphorous trichloride, was passed into a solution of 1.65 g. (10 mmoles) of ketone 6(8)K in 4 ml. of deuterium oxide and 20 ml. of dioxane for about 5 minutes. The solution turned brown and two phases separated. It seemed that the deuterium chloride reacted with the metal needle used for passing the gas. The mixture was refluxed for 48 hrs. and the excess dioxane was distilled off. The residue was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent gave 1.50 g. (91%) of deuterated ketone.

PMR spectrum showed no ketone α-H absorption. GLPC analysis showed single product. The crude product was further purified by bulb-to-bulb distillation, 75-90° (0.4 mm) to give 1.37 g. of bicyclo[5.3.1]undecan-11-one 6(8)M. Deuterium analysis by mass spectroscopy gave 89.5% d_2, 6.9% d_1 and 3.6% d_0.

Mass spectrum: m/e 168.2 (M^+).

1-Bromobicyclo[5.3.1]undecan-11-one-7-d_1 6(8)H

To a solution of 1.37 g., (8.3 mmoles) of dideuterated ketone 6(8)M in 14 ml. of carbon tetrachloride containing a few drops of acetic acid-d_4 was added 12.8 ml. of bromine solution (0.85 N in carbon tetrachloride) dropwise for a period of 1.5 hrs. The solution was washed with aqueous sodium sulfite and water until neutral and dried. Removal of solvent gave 1.55 g. of yellow oil. The crude oil was subjected to bulb-to-bulb distillation at 70-80° (0.4 mm.) to give 519 mg. of liquid and 931 mg. of residue which solidified when cooled. Two crystallizations of the residue from petroleum ether gave 480 mg. grey needle, mp 69-74°C. A sample of 373 mg. of needles was sublimed at 60° (0.4 mm.) to give 240 mg. of pure deuterated bromoketone 6(8)H mp 71-76° and 128 mg. of 1,7-dibromo[5.3.1]undecan-11-one 6(8)F. The mother liquid of the crystallization and the distillate were combined and distilled again at 60-75° (0.4 mm.) to give 420 mg. of pure recovered ketone 6(8)M and 348 mg. of residue which was recrystallized twice to give 63 mg. of monobromoketone 6(8)H mp 68-75°. The total isolated yield of monobromoketone was 303 mg. (22% based on reacting ketone).

IR spectrum: $\nu_{max}^{CHCl_3}$ 1720 cm^{-1} (ketone C=O)

PMR spectrum: no absorption at 2.7-2.9 ppm for ketone α-H

Mass spectrum: m/e 245, 247, (M^+), 95.5% d_1 and 4.5% d_o.

1-Chlorobicyclo[5.3.1]undecan-11-one-7-d_1 6(8)J

To a solution of 404 mg. (2 mmoles) of chloroketone 6(8)C in 4 ml. of acetic acid-d_4 was passed a stream of deuterium chloride generated by mixing 2 ml. of phosphorus trichloride and 2 ml. of deuterium oxide in a 10-ml. flask capped with a rubber septum. A 20-cm. length of rubber tubing with a needle at both ends conveyed the gas to the chloroketone solution. The gas was passed in for 10 mins. and the solution was then heated at 95° for 18 hrs. The excess solvent was evaporated off and the last traces of acetic acid was removed at 70° (2 mm.). The black residue was dissolved in 3.5 ml. of acetic acid-d_4, deuterium chloride passed again and refluxed for 24 hrs. The acetic acid was taken off as before. The black residue was taken up in ether and washed with water until neutral. After being dried, the solvent was removed to give 322 mg. (80%) of black oil. The black oil was distilled at 50° (0.2 mm.) to give 110 mg. of solid which was recrystallized from petroleum ether to yield 68 mg. of needles. The residue was recrystallized from petroleum ether to give 97 mg. of grey solid which was sublimed at 50° (0.2 mm.) to give 53 mg. of colorless solid. The combined solid was resublimed again to yield 110 mg. of pure chloroketone-7-d_1 6(8)J, mp 64-67°. Deuterium analysis by mass spectroscopy gave 91% d_1 and 9% d_o.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1715 cm^{-1} (ketone C=O)

Mass spectrum: m/e 201, 203 (M^+)

Deuteration of 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

A stream of deuterium chloride, which was generated by mixing 2 ml. of phosphorus trichloride and 2 ml. of deuterium oxide in a 10-ml. flask, was passed into a solution of 370 mg. (1.5 mmoles) of bromoketone 6(8)B in 0.5 ml. of chloroform-d and 0.5 ml. of acetic acid-d_4. The exchange was followed by running the PMR spectrum at suitable intervals. The exchange seemed complete after four days. The solvent was evaporated to give 300 mg. (81% recovery) of black residue. The residue was distilled at 90° (1 mm.) to give 61 mg. of solid, mp 74-77°. Deuterium analysis by mass spectroscopy gave 64% d_1 and 36% d_0.

The partially deuterated bromoketone (98 mg., 0.4 mmole) was treated with 1 ml. of acetic acid-d_4, deuterium chloride and heated at 90° for 9 hrs. The reaction was worked up as before to give 74 mg. (76%) of solid. Mass spectrum showed strong peaks at 201, 203 and 245, 247, parent ions for 1-chlorobicyclo[5.3.1]undecan-11-one-7-d_1 and 1-bromobicyclo[5.3.1]undecan-11-one-7-d_1. Judging from the peak intensities in the mass spectrum, there were 58% of chloroketone and 42% of bromoketone.

Racemization of 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

A stream of hydrogen chloride, generated by mixing 2 ml. of phosphorus trichloride and 2 ml. of water in a 10-ml. flask, was passed

into a solution of 32 mg. (0.13 mmoles) of bromoketone 6(8)B ($[\alpha]_{321}$ - 549.0°) in 2 ml. acetic acid for 5 mins. using a Tygon tube fitted with needles. The solution was heated at 90° for 24 hrs. GLPC analysis of the solution at 170° showed about 50% of the bromoketone converted into chloroketone. Hydrogen chloride was further passed into the solution for 3 mins. and the solution was heated for another 12 hrs. The excess acetic acid was evaporated and taken up in ether. The ethereal solution was washed with water until neutral and dried. Evaporation of the solvent gave 20 mg. (62%) solid. IR spectrum of the solid was identical to that of the chloroketone 6(8)C. The crude product was evaporatively distilled to give 14 mg. solid, mp 65-68°. GLPC analysis of the distilled product at 170° showed 82.6% chloroketone 6(8)C, 13.1% bromoketone 6(8)B and 4.3% unidentified product. A sample of the distilled haloketones (5.4 mg.) was treated with sodium methoxide in methanol and GLPC analysis at 170° of the solution showed only methyl cis-bicyclo[5.3.0]decane-1-carboxylic and no haloketones. The ORD of the haloketone had a rotation $[\alpha]_{321}$ - 64°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1715 cm^{-1} (ketone C=O)

ORD: (c, 0.54 in chloroform) $[\alpha]_{450}$ - 9.1°, $[\alpha]_{400}$ - 17°, $[\alpha]_{350}$ - 26°, $[\alpha]_{321}$ - 64°

1,7-Dichlorobicyclo[5.3.1]undecan-11-one 6(8)G

A sealed tube containing bicyclo[5.3.1]undecan-11-one 6(8)K (472 mg., 3.02 mmoles), 2 ml. of acetic acid, chlorine solution in carbon tetrachloride (12.5 ml., 9.15 mmoles) and 2 drops of concentrated hydrochloric acid was heated on a steam bath overnight. The colorless

solution was concentrated and taken up in ether which was washed with water, diluted sodium bicarbonate and brine. Removal of the solvent left 641 mg. (55%) of white solid which was six times recrystallized from petroleum ether to give colorless needles, mp 156-157.5°. An analytical sample, mp 157-158° was prepared by subliming the crystals at 90° (0.1 mm.).

IR spectrum: $\nu_{max}^{CHCl_3}$ 1735 cm^{-1} (ketone C=0)

Anal. Calcd. for $C_{11}H_{16}OCl_2$ (23.5.1): C, 56.21; H, 6.76

Found: C, 56.01; H, 6.99.

10-Oxobicyclo[4.3.1]decan-1-carboxylic acid 6(7)A

The procedure of Warnhoff, Wong and Tai was used (88).

Cycloheptanone (180 g., 1.61 moles) was treated with 157 g of sodium hydride (56.2% dispersed in oil), 432 g. (3.92 moles) of diethyl carbonate in 1 l. of dry ether to give 223.9 g. of 2-carbethoxycycloheptanone (77%) after distillation at 82-106° (2.5-3.0 mm.). [lit (88) bp 111-112 (9 mm.)].

IR spectrum: ν_{max} 1740 (ester C=0), 1710 (ketone C=0) and 1640 cm^{-1} (conjugated C=0)

PMR spectrum: δ^{Neat} 1.18 (t, J = 7 cps) and 1.33 (t, J = 7 cps) (3H total, $CH_3[CH_2O]$), 1.70 (b, ring CH_2), 2.46 (b, CH_2-C=0 and CH_2-C=C), 3.53 (b, 0=C-CH-C=0), 4.12 and 4.19 (2H doubled quartet, J = 7 cps, $O-CH_2-[CH_3]$), 11.75 ppm (1H, s, enolic OH).

The 2-carbethoxycycloheptanone (219.7 g., 1.20 moles) was subjected to Michael addition with 73 g. (1.44 moles) of freshly distilled acrolein and sodium ethoxide (0.61 mole) as base in 420 ml. of absolute ethanol. The Michael adduct (101 g.) was obtained in 35% yield after distillation at 136° (0.8 mm). [lit. (88) bp 142-145° (1.0 mm].

IR spectrum: $\nu_{max}^{CCl_4}$ 2720 (aldehyde CH), 1730 and 1715 cm^{-1} (superimposed aldehyde, ester, ketone C=O)

PMR spectrum: δ^{CCl_4} 1.25 (3H, t, J = 7 cps, $CH_3[CH_2O]$), 4.14 (2H, q, J = 7 cps, $OCH_2[CH_2]$, and 9.64 ppm (1H, s,CHO).

The Michael adduct (101g., 0.42 mole) was cyclized in two portions to ethyl-10-oxobicyclo[4.3.1]dec-7-ene-1-carboxylate in 35 ml. of concentrated sulfuric acid. A total yield of 22.1 g. (24%) of the unsaturated ester was obtained, bp 116-118° (1.25 mm.). [lit. (88) bp 99-101° (0.15 mm.)].

IR spectrum: $\nu_{max}^{CCl_4}$ 3040 (C=CH), 1745 (ester C=O) and 1715 cm^{-1} (ketone C=O)

PMR spectrum: δ^{CCl_4} 1.26(3H, t, J = 7 cps, CH_3 $[CH_2O]$), 4.15 (2H, q, J = 7 cps, $OCH_2[CH_3]$) and 5.17 ppm (2H, complex pattern, CH=CH).

The unsaturated ester (22.1 g., 1.0 mole) was hydrogenated over 4.6 g. of 5% palladium supported on charcoal in ethanol. A total yield of 19.75 g. (80%) of ethyl-10-oxobicyclo[4.3.1]decane-1-carboxylate was obtained. TLC analysis (petroleum ether - ethyl acetate 65:35) showed a single spot.

IR spectrum: $\nu_{max}^{CCl_4}$ 1740 (ester C=O), 1705 cm^{-1} (ketone C=O)

PMR spectrum: δ^{CCl_4} 1.24 (3H, t, J = 7 cps, CH_3 [CH_2O]), 2.5-2.8 (1H, bm, ketone α-H) and 4.12 ppm (2H, q, J = 7 cps, OCH_2 [CH_3]).

The saturated ketoester 19.75 g. (0.8 mole) was hydrolyzed with 60 ml. of 10% potassium hydroxide and 30 ml. of ethanol in an oil bath at 100° for 24 hrs. to give 15.25 g. (97%) of 10-oxobicyclo[4.3.1]decan-1-carboxylic acid 6(7)A. The overall yield of acid 6(7)A from cycloheptanone was 4.7%. The acid, mp 95-100°, was quite pure as shown by TLC in petroleum ether-ethyl acetate (50:50), single spot.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2500-3500 (carboxyl OH), 1750-1660 (broad C=O)

PMR spectrum: δ 2.85(1H, bm, ketone α-H) and 11.61 ppm (1H, s, COOH).

Optically Active 10-Oxobicyclo[4.3.1]decane-1-carboxylic acid 6(7)A

To a solution of 13.0 g. (0.066 mole) of keto acid 6(7)A in 40 ml. of reagent grade acetone and 0.5 ml. of water was added 26.4 g. (0.066 mole) of brucine. The mixture was warmed on the steam bath until a clear solution was obtained. The solution was cooled in the refrigerator overnight. The solid salt was filtered and dried. Twenty eight grams of crystal was obtained and a sample of 500 mg. of the solid was decomposed into acid with dilute hydrochloric acid. After work up as before, 120 mg. of acid was obtained. The optical rotation of this acid was $[\alpha]_D$ - 5.1°. (c, 4.76 in chloroform). The solid crystal was

successively recrystallized in wet acetone and 1.12 g. (8%) mp 90-99°, of acid was obtained with rotation $[\alpha]_D$ - 32.1° (c, 6.39 in chloroform) after nine crystallizations.

In view that the brucine gave poor resolution with the acid, 3.39 g. of the acid, $[\alpha]_D$ + 16, was resolved with 2.85 g. of ephedrine in 13 ml. of acetone. The salt crystallized out in room temperature and two successive crystallizations gave 1.07 gm. of salt which was decomposed with dilute hydrochloric acid as before to give 540 mg. (16%) of acid, mp 88-94°. The acid had rotation $[\alpha]_D$ + 37° in chloroform.

Optically Active 1-bromobicyclo[4.3.1]decan-10-one 6(7)B

The procedure of preparing 1-bromobicyclo[5.3.1]undecan-11-one 6(8)B was followed. A sample of β-keto acid 6(7)A ($[\alpha]_D$ - 34.1°) 1.988 gm. (0.010 mole) in 20 ml. of methanol was neutralized with 0.580 gm. of potassium hydroxide. To the solution was added a solution of 1.74 gm. (0.010 mole) of silver nitrate. The silver salt was filtered and dried. The dry salt was added slowly to a solution of bromine (1.63 gm., 0.010 mole) in 20 ml. of carbon tetrachloride for a period of 1 hr. It was worked up as before. The bromoketone 6(7)B (1.75 gm.) was obtained in 71% yield and evaporatively distilled at 80° (0.1 mm.). TLC analysis (petroleum ether-ethyl acetate, 65:35) showed one spot. The bromoketone solidified in the refrigerator, mp 25-35°, $[\alpha]_{325}$ - 896°.

ORD: (c, 0.915 in CH_3OH) $[\alpha]_{400}$ - 87.4°, $[\alpha]_{350}$ - 180.5°, $[\alpha]_{325}$ - 896.2°.

IR spectrum: $\nu_{max}^{CS_2}$ 1725 cm^{-1} (ketone C=O)

Optically Active 1-Chlorobicyclo[4.3.1]decan-10-one 6(7)C

The procedure of preparing 1-chloro-bicyclo[5.3.1]undecan-11-one 6(8)C was followed. A sample of β-keto acid 6(7)A (2.112 gm., 0.010 mole) in 10 ml. of methanol was neutralized with 630 mg. (0.011 mole) of potassium hydroxide in 3 ml. of water and 5 ml. of methanol. To the solution was added a solution of 1.87 gm. (0.011 mole) of silver nitrate in 2 ml. of water and 5 ml. of methanol. The dry salt (2.648 gm., 90%) was added slowly to a chlorine solution (1.74N) in carbon tetrachloride (13 ml., 0.011 mole) for a period of 40 mins. It was worked up as before to give 1.49 gm. (70%) of keto acid 6(7)A and 0.323 gm. (16%) of neutral product. The crude product was purified by thick layer chromatography and evaporative distillation at 80-100° (0.2 mm.). GLPC and TLC (petroleum ether-ethyl acetate 70:30) showed one peak.

IR spectrum: $\nu_{max}^{CHCl_3}$ 1730 cm^{-1} (ketone C=0)

ORD: (c, 0.25 in chloroform) $[\alpha]_{450}$ - 24°, $[\alpha]_{400}$ - 40°, $[\alpha]_{350}$ - 100°, $[\alpha]_{320}$ - 254°, $[\alpha]_{300}$ - 0°, $[\alpha]_{270}$ + 360°

Mass Spectrum: m/e 186, 188 (M^+)

PMR spectrum: δ 4.35 (1H, b, tertiary hydrogen at rings junction)*
1.00-3.4 ppm (14H, b, methylene hydrogens).

---

* The chemical shift of the tertiary hydrogen is considerably lower than those of the bicyclic haloketones so far studied, the assignment is entirely based on the integration of the spectrum.

(D) Favorskii Rearrangement of Optically Active 1-Halobicyclo[4.3.1]-decan-10-one 6(7)

(1) Rearrangement of 1-Bromobicyclo[4.3.1]decan-10-one 6(7)B

Aliquots of the same batch of bromoketone 6(7)B $[\alpha]_D$+ 12.4° were used in each of the experiments below except for (e) in which the specific rotation is specified.

(a) With Silver Nitrate in Aqueous Ethanol

Bromoketone 6(7)B (201 mg., 0.87 mmole) was dissolved in 4 ml. of absolute ethanol, and a solution of 148 mg. (0.87 mmole) of silver nitrate in 4 ml. of distilled water was added. A cloudy appearance was observed immediately. The flask was protected from light by wrapping with aluminum foil and was shaken at room temperature for 2 hours. The yellow silver bromide precipitate was filtered and washed well with ether. The silver bromide weighed 143 mg. (88%) after it was dried in oven at 90° for several hours.

The filtrate was made alkaline with dilute sodium bicarbonate solution and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent left 22 mg. of a mixture of recovered bromoketone 6(7)B and two other neutral materials which were detected by TLC analysis.

The basic aqueous solution was acidified with concentrated hydrochloric acid, and extracted with ether. The ethereal solution was washed with water, dried and concentrated to leave 90 mg. (61%) of yellow rearranged cis-bicyclo[4.3.0]nonane-1-carboxylic acid 5(6)C. The IR and PMR spectra were identified with those of the authentic

acid. TLC (ethyl acetate-petroleum ether, 50:50) showed mainly one product with traces (<5%) of more polar products. The crude product was evaporatively distilled at 80° (0.1 mm.) to give 63 mg. of colorless solid, m.p. 44-46°, $[\alpha]_D^{20}$ - 10.7 (c, 3.50 in chloroform).

ORD: (c, 1.21 in methanol), $[\alpha]_{450}$- 11.1°, $[\alpha]_{400}$- 14.0°, $[\alpha]_{350}$- 19.8°, $[\alpha]_{300}$- 31.4°

Half a mililiter of thionyl chloride was added to 25 mg. of the above acid and the solution was heated on the steam bath to expell all the hydrochloric acid and sulfur dioxide. Half a mililiter of isopropyl alcohol was added to the solution which was further heated for 20 mins. The excess alcohol was removed by distillation. The residue was distilled at 56° (0.2 mm.) to give 9 mg. of sweet smelling isopropyl ester. GLPC analysis at 120° (1% SE 30) showed that the product containing less than 1% isopropyl alcohol. ORD spectrum was run on the distilled product.

ORD: (c, 0.77 in methanol) $[\alpha]_{450}$- 5.7°, $[\alpha]_{400}$- 7.2°, $[\alpha]_{350}$- 11.7°, $[\alpha]_{300}$- 18.5°

Another similar experiment was done with a sample of bromoketone 6(7)B of different optical purity. A sample of 223 mg. (0.96 mmole) of bromoketone 6(7)B($[\alpha]_{325}$- 896°) in 4 ml. of absolute ethanol was treated with a solution of 173 mg. (0.96 mmole) of silver nitrate in 4 ml. of water. The reaction mixture was shaken for 2 hrs. Work up as before afforded 130 mg. (75%) of acid 5(6)C which was evaporatively distilled at 100° (0.2 mm.) for ORD measurement.

ORD: (c, 1.91 in methanol), $[\alpha]_{450}$+ 12.5°, $[\alpha]_{400}$+ 15.6°, $[\alpha]_{350}$+ 22.9°, $[\alpha]_{300}$+ 35.5°

(b) With Potassium t-Butoxide in Dimethoxyethane

A solution of 275 mg. (1.19 mmoles) of bromoketone 6(7)B in 6 ml. of dry dimethoxyethane (freshly distilled from sodium hydride and then from lithium aluminum hydride) was added through a dropping funnel to a mixture of 5 ml. of the same dimethoxyethane and 214 mg. (1.88 mmoles) of twice sublimated potassium t-butoxide. The reaction mixture became turbid immediately on addition of the bromoketone. The reaction mixture was stirred with a magnetic bar at 40° for 1 hr. and then refluxed for 5.5 hrs. at 100°. The cooled solution mixture was diluted with water and extracted with ether. The combined ethereal extracts were washed with ether and dried. Removal of solvent left 194 mg. (70%) of sweet smelling liquid t-butyl cis-bicyclo[4.3.0]nonane carboxylate 5(6)B. The crude t-butyl ester was purified by column chromatography on 5 g. of silica gel and 75 mg. of pure product was obtained from petroleum ether-benzene (70:30) fractions. TLC-analysis (petroleum ether-ethylacetate, 90:10) showed one spot. IR and PMR spectra of the purified product were identical with those of the authentic sample.

ORD: (c, 1.05 in chloroform) of the purified product showed that it was racemic (no rotation from 700 to 300 nm.).

IR spectrum: $\nu_{max}^{CHCl_3}$ 1725 cm^{-1} (ester C=0)

PMR spectrum: δ 1.44 (9H, s, t-butyl), 2.15-2.60 ppm (1H, bm, tertiary-H at bridgehead).

Attempted Hydrolysis of t-Butyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)B

The purified ester 5(6)B (22.5 mg., 0.096 mmole) was refluxed with a mixture of 2 ml. of t-butanol and 1 ml. of 10% aqueous potassium hydroxide for 6 hrs. at 110°. The solution was diluted with 3 ml. of water and extracted with ether. The ethereal extracts were washed and dried. Removal of solvent left 16 mg. (71%) of oil whose infrared spectrum and TLC behaviour were identical with those of the starting ester.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether extracts were washed with water and dried. There was no acidic material after the solvent was removed.

(c) With Sodium Methoxide in Dimethoxyethane

To a solution of 60.7 mg. (11.3 mmoles) sodium methoxide in 10 ml. of dry dimethyoxyethane (freshly distilled over sodium), was added dropwise a solution of 240 mg. (1.04 mmoles) of bromoketones 6(7)B in 10 ml. of dimethoxyethane. The solution was stirred with a magnetic bar. Turbidity was observed immediately on addition and the solution was then refluxed for 10 hrs. at 100° in an oil bath. The solution was diluted with 10 ml. of water and the basic solution (pH~10) was extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of solvent left 118 mg. (62%) of colorless liquid methyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)E. TLC analysis in petroleum ether-ethyl acetate (65:35) and GLPC at 125° of the crude product showed only one product, $[\alpha]_D^{19}$ - 6.51 (c, 4.46 in

chloroform).

ORD: (c, 1.20 in methanol), $[\alpha]_{400}$- 13.7°, $[\alpha]_{350}$- 26.4°, $[\alpha]_{300}$- 32.3°

IR spectrum: $\nu_{max}^{CHCl_3}$ 1725 cm^{-1} (ester C=O)

PMR spectrum: δ 2.45 (1H, b, tertiary-H at bridgehead) and 3.70 ppm (3H, s, COOMe).

The pure ester (61 mg., 0.336 mmole) in 2 ml. of methanol was refluxed with 2 ml. aqueous potassium hydroxide (10%) at 90° for 22 hrs. The solution was diluted with 5 ml. of water and washed twice with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent left 46 mg. of acid (82%). The acid was distilled at 80° (0.8 mm.) to give a colorless oil. ORD curve showed that the rotations at various wavelengths were almost equal that of the silver nitrate reaction.

ORD: (c, 1.20 in methanol) $[\alpha]_{450}$- 11.0°, $[\alpha]_{400}$- 14.0°, $[\alpha]_{350}$- 19.8°, $[\alpha]_{300}$- 31.4°

(d) With Sodium Hydroxide in Xylene

Finely powdered sodium hydroxide (420 mg., 10.5 mmoles) which had been dried at 130° (1 mm.) for 10 hrs. was added to a solution of 206 mg. of bromoketone 6(7)B, (0.89 mmole) in 6 ml. of dried xylene (freshly distilled over sodium) and the reaction mixture was refluxed at 150° for 10 hrs. The cooled solution was diluted with water and extracted with ether. The ether extracts were washed with water and dried. Evaporation of the solvent left 15 mg. of oil. TLC (acetic acid-chloroform, 3:97) showed at least three spots and no recovered

bromoketone.

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent afforded 115 mg. (77%) acid 5(6)C whose IR and PMR spectra were identical with those of the authentic cis-bicyclo[4.3.0]nonane-1-carboxylic acid 5(6)C. TLC (acetic acid-chloroform, 3:97) showed one major spot and traces of a more polar spot. The crude product was purified on a column of 4 g. of silica gel (B.D.H. 60-120 mesh) to yield 50 mg. of pure acid 5(6)C from petroleum ether-benzene (65:35) fractions. The optical rotation of the pure acid at various wavelengths was slightly greater than those of the silver nitrate reaction product.

ORD: (c, 1.39 in methanol), $[\alpha]_{450}$- 13.0°, $[\alpha]_{400}$- 16.6°, $[\alpha]_{350}$- 24.4°, $[\alpha]_{300}$- 39.1°

(e) With Potassium t-Butoxide in t-Butyl Alcohol-d_1 and Deuterium Oxide

A 0.5-dram vial containing a solution of 480 mg. (2.08 mmoles) bromoketone 6(7)B($[\alpha]_{325}$- 896°) in 1 ml. of t-butyl alcohol-d_1 was dropped into a solution of doubly sublimed potassium t-butoxide (875 mg., 8.0 mmoles) in deuterium oxide (88 mg., 4.4 mmoles) and t-butyl alcohol-d (10 ml.). The solution was well shaken and the reaction was then refluxed for 3.5 hrs.

The basic reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. No neutral material remained after the solvent was evaporated.

The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent left 131 mg. (37%) of cis-bicyclo-[4.3.0]nonane-1-carboxylic acid 5(6)C which was evaporatively distilled at 100° (0.2 mm.). IR, PMR and mass spectra showed no deuterium incorporation. ORD curve of the purified acid was superimposable on that of the silver nitrate reaction product.

PMR spectrum: 2.2 - 2.7 (1H, b, tertiary-H at bridgehead) and 11.9 ppm (1H, b, COOH).

ORD: (c, 0.8 in methanol) $[\alpha]_{450}$+ 12.5°, $[\alpha]_{400}$+ 15.6°, $[\alpha]_{350}$+ 22.9°, $[\alpha]_{300}$+ 35.5°

Mass spectrum: m/e 168, 99.5% d_0, 0.5% d_1.

(f) With Potassium t-Butoxide in t-Butyl Alcohol-d and Deuterium Oxide

To a sample of doubly sublimed potassium t-butoxide (365 mg., 2.8 mmoles) in a 25-ml. stoppered flask were added deuterium oxide (32µl, 36 mg., 1.4 mmoles) and t-butonol-d_1 (4.5 ml.). The mixture was warmed to dissolve all the potassium t-butoxide. A solution of 160 mg.(0.69 mmole) of bromoketone 6(7)B in 1.5 ml. of t-butanol-d was added. White solid precipitated immediately from the yellow solution. The reaction mixture was refluxed at 110° for 4.5 hrs. after which it was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 5 mg. of oil whose TLC (petroleum ether-ethylacetate, 65:35) showed some t-butyl ester plus some other more polar spots.

The aqueous layer was acidified with nitric acid and extracted with ether. The ethereal extracts were washed with water and dried.

Removal of solvent left 85 mg. (74%) of cis-bicyclo[4.3.0]nonane-1-carboxylic acid which was purified by evaporative distillation.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2235-3500 (carboxyl-OH) and 1700 cm^{-1} (carboxyl C=O)

Mass spectrum: m/e 168, 95.5% d_o, 4.5% d_1

ORD: (c, 2.44 in methanol) $[\alpha]_{400}$ - 11.0°, $[\alpha]_{350}$ - 18.5°, $[\alpha]_{300}$ - 31.2°

(g) With Sodium Isopropoxide in Isopropyl Alcohol-d

Freshly cut sodium (193 mg., 8.4 matoms) was dissolved in 3.4 g. of isopropyl alcohol-d (98% D). A sample of bromoketone (250 mg., 1.08 mmoles) was weighed out in a small tube which was quickly dropped into the flask. The flask was well shaken and the reaction mixture was refluxed for 5 hrs. at 110°. The solution was diluted with water and extracted with ether. The combined ether extracts were washed with water and dried. Removal of solvent afforded 40 mg. of liquid whose TLC (petroleum ether-ethyl acetate, 65:35) showed traces of bromoketone. The crude product was chromatographed on 1.5 g. of silica gel. From the petroleum ether-benzene (90:10) fractions were obtained 20 mg. of pure (TLC) isopropyl ester 5(6)I. IR and PMR spectra showed no deuterium incorporation.

IR spectrum: $\nu_{max}^{CCl_4}$ 1725 cm^{-1} (ester C=O)

PMR spectrum: 1.22 (6H, d, $[(CH_3)_2]$C H), 2.1 - 2.7 (1H, bm, tertiary-H at bridgehead) and 5.05 ppm (1H, heptet, $CH[CH_3]_2$)

Mass spectrum: m/e 210, 7.9% d_1, 92.1% d_o

ORD: (c, 0.64 in chloroform) $[\alpha]_{400}$- 10.2°, $[\alpha]_{350}$- 15.0°, $[\alpha]_{300}$- 24.4°

(c, 1.16 in methanol) $[\alpha]_{400}$- 6.8°, $[\alpha]_{350}$- 9.9° $[\alpha]_{300}$- 15.2°

The aqueous solution was worked up as in (f) to give 91 mg. of acid 5(6)C. PMR and IR spectra showed no deuterium incorporated and ORD curve showed 100% retention.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2250-3500 (carboxyl OH), 1700 cm^{-1} (carboxyl C=0)

PMR spectrum: δ 2.1-2.7 (1H, bm, tertiary-H at bridgehead) and 11.3 ppm (1H, s, COOH)

ORD: (c, 1.2 in methanol) $[\alpha]_{400}$- 15°, $[\alpha]_{350}$- 20°, $[\alpha]_{300}$- 32.3°

In a similar run, only acid 5(6)C was obtained. IR, PMR and mass spectra showed no deuterium incorporated.

Attempted Hydrolysis of Isopropyl cis-bicyclo[4.3.0]nonane-1-carboxylate 5(6)I

A solution of 54 mg. (0.26 mmole) of isopropyl ester 5(6)I in 1.5 ml. of 10% aqueous potassium hydroxide and 1 ml. of isopropyl alcohol was refluxed at 110° for 4 hrs. after which time the solution was diluted with 4 ml. of water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 35 mg. (65%) of oil whose TLC behaviour was identical with that of the starting ester.

The aqueous layer was acidified and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent

left 2 mg. of residue whose TLC showed it contained the cis-bicyclo-[4.3.0]nonane-1-carboxylic acid and two more polar products.

(h) With Potassium Acetate in Acetic Acid

The bromoketone 6(7)B (150 mg., 0.70 mmole) was refluxed in a mixture of 3.2 ml. of acetic acid and 127 mg. of potassium acetate at 140° for 46 hrs. The cooled solution was diluted with water and extracted with ether. The combined ether extracts were washed with water and dried. Removal of solvent left 126 mg. (84%) of residue whose TLC behaviour, optical purity, infrared and PMR spectra were identical to those of the starting bromoketone.

(2) Rearrangement of 1-chlorobicyclo[4.3.1]decan-10-one 6(7)C

Metallic sodium, (90 mg., 4 matoms), was dissolved in 4 ml. of freshly prepared ethanol-d (99%) and 2 ml. of deuterium oxide (99.5% D). A solution of 73 mg. (0.43) of semisolid chloroketone 6(7)C ($[\alpha]_{320}$- 254°) in 3 ml. of ethanol-d was added to the alkaline solution. The solution was refluxed overnight. The excess ethanol was distilled and the residue was taken up in water. It was worked up as in (g) to give 53 mg. of oil. PMR and IR spectra of the crude product showed no deuterium incorporation. The crude product was chromatographed on 2 gm. of silica gel (BDH 60-120 mesh) to yield 32 mg. of cis-bicyclo[4.3.0]-nonane-1-carboxylic acid 5(6)C from petroleum ether-benzene (75:25) fractions. It was further purified by evaporative distillation at 60-72° (0.2 mm.) for ORD measurement. The pure acid melted at 44-46° and showed no depression on admixture with authentic acid 5(6)C. The GLPC retention of the methyl ester was equal to that of the authentic

ester 5(6)E. The mass spectrum of the acid showed no deuterium incorporation.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2500-3500 (carboxyl OH) and 1690 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 2.2-2.7 (1H, b, tertiary-H at bridgehead) and 11.9 ppm (1H, b, COOH)

ORD: (c, 1.08 in chloroform) $[\alpha]_{450}$+ 3.7°, $[\alpha]_{400}$+ 5.1°, $[\alpha]_{350}$+ 7.9°, $[\alpha]_{300}$+ 13.0°

Mass spectrum: m/e 168.1, 99.1% d_o, 0.9% d_1

(E) Favorskii Rearrangement of Optically Active 1-Halobicyclo[5.3.1]-undecan-11-one 6(8)

(1) Rearrangement of 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

Aliquots of the same batch of bromoketone 6(8)B $[\alpha]_{321}^{21}$- 564° (chloroform) were used in each of the experiments below except for $a_{ii}e_{ii}$ and h_{ii} in which the specific rotation is specified.

(a) With Silver Nitrate

(i) In Aqueous Methanol

To a solution of 456 mg. (186 mmoles) of bromoketone 6(8)B in 5 ml. of methanol was added a solution of 317 mg. (1.86 mmoles) of silver nitrate in 7 ml. of methanol and 3 ml. of water. Precipitation of silver bromide occurred immediately. The reaction mixture was refluxed on a steam bath and the reaction was followed by TLC. After 3.5 days the reaction mixture was filtered, the silver bromide was

washed well with ether and dried to constant weight (347 mg., 100%).

The acidic filtrate was extracted with ether and the ether extracts were extracted with aqueous sodium bicarbonate. The ether layer was washed with water and dried. Removal of solvent left 290 mg. of oil which was evaporatively distilled at 60-70 (0.6 mm.) to give 87 mg. of colorless product. GLPC analysis of the distilled product showed the major product was methyl cis-bicyclo[5.3.0]decane-1-carboxylate 5(7)C. Attempts to purify the ester by preparative GLPC resulted in much loss of material. The residue from the distillation was subjected to chromatography on 5 g. of alumina. (Woelnr, neutral, activity II). Elution with benzene-petroleum ether (10:90 and 30:70) afforded 50 mg. (14%) of pure ester. GLPC at 150° and TLC showed single compound. ORD showed a positive plain curve.

ORD: (c, 1.22 in chloroform) $[\alpha]_{450}$+ 54.0°, $[\alpha]_{400}$+ 75.0°, $[\alpha]_{350}$+ 108°, $[\alpha]_{300}$+ 150°

(ii) In Aqueous Ethanol (Done by Dr. C. Bonnice)

Bromoketone 6(8)B $[\alpha]_D$- 17.6°, 500 mg., 2.04 mmoles) was weighed into a 10 ml. Erlemeyer flask and was dissolved in 4 ml. of absolute ethanol. To this solution was added 0.525 g. (3.1 mmoles) of silver nitrate in 4 ml. of absolute ethanol and 5 ml. of distilled water.

A slight turbidity resulted. The flask was warmed to 60-70° in a water bath for 4 days and the whole set up was protected from light by aluminum foil. The silver bromide was filtered through a preweighed sintered glass funnel and washed well with water and ether. The precipitate was dried to constant weight, 0.3792 g. (98%). The filtrate was acidified with dilute nitric acid and extracted with ether. The

ethereal extracts were further extracted with 3% aqueous sodium hydroxide. The ether layer was washed with water and dried. Removal of solvent afforded 161 mg. of neutral product. TLC analysis in petroleum ether-ethyl acetate (65:35) showed mostly starting bromoketone. The basic aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent gave 175 mg. of acid (70%). The crude acid, containing three spots as revealed by TLC, was purified by evaporative distillation at 75-90° (0.1 mm.) and column chromatography on 3 g. of silica gel (B.D.H., 60-120 mesh). Elution with petroleum ether-benzene (75:25 and 50:50) gave 174 mg. of pure acid for ORD measurement.

ORD: (c, 0.373 in chloroform) $[\alpha]_{450}$+ 56.1°, $[\alpha]_{400}$+ 78.2°, $[\alpha]_{350}$+ 114°, $[\alpha]_{300}$+ 178°

ORD: (c,0.620 in methanol) $[\alpha]_{450}$+ 57.7°, $[\alpha]_{400}$+ 80.6°, $[\alpha]_{350}$+ 117°, $[\alpha]_{300}$+ 188°

ORD: (c, 0.600 in methanol) $[\alpha]_{450}$+ 60°, $[\alpha]_{400}$+ 76.6°, $[\alpha]_{350}$+ 112° $[\alpha]_{300}$+ 177°

(b) With Potassium Bicarbonate in Aqueous Methanol

To a solution of 245 mg. (1.0 mmole) of bromoketone 6(8)B in 8 ml. of methanol was added a solution of 2.46 mg. (2.46 mmoles) of potassium bicarbonate in 2.5 ml. of water. The solution was refluxed on a steam bath for 20 hrs. The solution was diluted with water and extracted with ether. The ethereal extracts were washed and dried. Removal of solvent left 76 mg. (39%) of methyl cis-bicyclo[5.3.0decane-1-carboxylate 5(7)E whose PMR spectrum, TLC and GLPC were identical to

those of an authentic sample. The ORD curve was run on the distilled sample.

PMR spectrum: δ 2.5-3.0 (1H, b, bridgehead-H), 3.7 ppm (3H, s, COOMe)

ORD: (c, 1.86 in chloroform) $[\alpha]_{450}$+ 32°, $[\alpha]_{400}$+ 43°, $[\alpha]_{350}$+ 7.5°, $[\alpha]_{300}$+ 14.0°

The aqueous layer was acidified with hydrochloric acid and extracted with ether. The extracts were washed and dried. Evaporation of the solvent afforded 78 mg. (43%) of acid. The acid was chromatographed on 5 g. of silica gel (B.D.H., 60-120 mesh). Elution with petroleum ether-benzene (65:35) and (50:50) gave 40 mg. of pure acid which was converted into methyl ester by reaction with diazometane. TLC analysis (petroleum ether-ethyl acetate, 65:35) and GLPC analysis at 140°C of the ester showed to be pure.

ORD: (c, 2.32 in chloroform) $[\alpha]_{450}$+ 9.8°, $[\alpha]_{400}$+ 13.0°, $[\alpha]_{350}$+ 18.8°, $[\alpha]_{300}$+ 27.2°

(c) With Potassium Cyanide in Methanol

A solution of 249 mg. (1.02 mmoles) of bromoketones 6(8)B in 2 ml. of methanol was added to a mixture of sodium cyanide (161 mg., 3.1 mmoles) in 10 ml. of methanol. The reaction mixture was refluxed in an oil bath for 15 hrs. at 89°. The cooled solution was diluted with water and extracted with ether. The ether extracts were washed with water and dried. Removal of solvent afforded 189 mg. of semisolid. TLC analysis (petroleum ehter-ethyl acetate, 65:35) showed mostly starting bromoketone plus another compound. The IR spectrum showed absorption at 3100-3600 cm^{-1} (OH) and 2240 cm^{-1} (CN). The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The

ether extracts were washed with water and dried. Evaporation of the solvent left 7 mg. of acid whose TLC showed complex mixtures.

The neutral fraction was further subjected to reflux with 155 mg. of sodium cyanide in 10 ml. of methanol for 2 days. The reaction was worked up as above to give 140 mg. (71%) of neutral product and 8 mg. (4%) of acidic product. The neutral product was evaporatively distilled at 60-75° (0.8 mm.) to give a colorless liquid. GLPC analysis at 135° showed one major peak with the same retention time as the authentic methyl ester 5(7)E and two minor peaks.

IR spectrum: $\nu_{max}^{CCl_4}$ 1710 cm^{-1} (ester C=O)

ORD: (c, 1.38 in chloroform) $[\alpha]_{400}$+ 27.2°, $[\alpha]_{350}$+ 40.4°, $[\alpha]_{300}$+ 65.2°

(d) With Sodium Ethoxide in Ethanol-d

Metallic sodium, 24.8 mg. (1.08 matoms), was dissolved in 5 ml. of freshly prepared ethanol-d (99%-D) and 1 ml. of deuterium oxide (99.5%) under nitrogen. A solution of 344 mg. (1.4 mmoles) of dry bromoketone 6(8)B in 2 ml.of ethanol-d was added to the alkaline solution. The solution was refluxed for 2.5 hrs. The solution was diluted with 5 ml. of deuterium oxide and extracted with anhydrous ether. The combined ethereal extracts were washed with six 1-ml-portion of deuterium oxide and dried.

Removal of solvent afforded 144 mg. of oil. The crude product was evaporatively distilled at 60-90° (0.2 mm.) to give a colorless solid. GLPC analysis showed to be pure starting bromoketone. The ORD curve was recorded and the recovered bromoketone was found to have retained all its optical activity. The mass spectrum showed no deuterium incorporation at

all.

ORD: (c, 0.505 in chloroform $[\alpha]_{450}$- 36°, $[\alpha]_{400}$- 84.0°, $[\alpha]_{350}$- 202.0°, $[\alpha]_{320}$- 594.1°, $[\alpha]_{300}$- 118.0°

Mass spectrum: m/e 244, 246. 99.2% d_o, 0.8% d_1.

The basic aqueous solution was acidified with a few drops of phosphorus trichloride and extracted with ether. The ethereal extracts were washed with four 1 ml.-portion deuterium oxide and dried. Removal of solvent left 67 mg. (34%) of cis-bicyclo[5.3.0]decane-1-carboxylic acid 5(7)C. PMR spectrum showed no tertiary hydrogen absorption. The acid was chromatographed on 5.5 g. of silica gel (B.D.H.60-120 mesh). Elution with benzene-petroleum ether (35:65) afforded 57 mg. of pure acid. The ORD curve of the pure acid showed that it was 92% racemized by comparing the calculated rotation of its methyl ester with (a_i) as shown in Table III.

PMR spectrum: no absorption at 2.5-3.1 ppm for the tertiary hydrogen at ring junction

Mass spectrum: m/e 183, 19.5% d_o, 80.5% d_1

ORD: (c, 2.11 in chloroform) $[\alpha]_{450}$+ 5.4°, $[\alpha]_{400}$+ 7.1°, $[\alpha]_{350}$+ 10°, $[\alpha]_{300}$+ 14.7°

(e) With Sodium Hydrosulfide in Aqueous Ethanol

i) To a solution of bromoketone 6(8)B (304 mg., 1.24 mmoles) in 6 ml. of ethanol was added a solution of sodium hydrosulfide prepared by saturation of sodium hydroxide (100 mg., 2.5 mmoles) in 2 ml. of water with hydrogen sulfide for 1 hr. The solution was refluxed at 90° for 40 hrs. The cooled solution was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal

of solvent left 1 mg. of oil which was discarded.

The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent gave 61 mg. (27%) of acid. The PMR spectrum of the crude acid was identical with that of the authentic cis-bicyclo[5.3.0]decane-1-carboxylic acid. The crude acid was chromatographed on 4.5 g. of silica gel (B.D.H. 60-120 mesh). Elution with benzene-petroleum ether (30:70 and 40:60) afforded 22 mg. of solid, m.p. 50-54°. TLC analysis in petroleum ether-ethyl acetate (65:35) showed one spot. The ORD curve was recorded with the acid and its methyl ester. The GLPC analysis of the methyl ester showed one peak which had the same retention time as the authentic ester.

PMR spectrum: δ 2.5-2.9 (1H, b, tertiary-H at ring junction) and 11.9 ppm (1H, s, COOH)

ORD: (acid, c, 2.03 in chloroform) $[\alpha]_{450}$+ 21.7°, $[\alpha]_{400}$+ 21.7°, $[\alpha]_{350}$+ 42.4°, $[\alpha]_{300}$+ 64.1°

ORD: (ester, c, 1.76 in chloroform) $[\alpha]_{450}$+ 18.2°, $[\alpha]_{400}$+ 24.0°, $[\alpha]_{350}$+ 33.0°, $[\alpha]_{300}$+ 51.2°

ii) To a solution of 40 mg. (0.16 mmole) of bromoketone 6(8)B ($[\alpha]_D$- 17.6°) in 1 ml. of absolute ethanol was added a solution of sodium hydrosulfide which was prepared by passing hydrogen sulfide into a solution of sodium hydroxide (12 mg., 0.3 mmole in 1 ml. of water) for 1 hr. The solution was refluxed for 24 hrs. TLC showed the reaction was incomplete and another solution of sodium hydrosulfide (50 mg. of sodium hydroxide in 1 ml. of water and hydrogen sulfide passed for 1 hr.), was added. The solution was refluxed further for 3 hrs. The cooled solution was diluted with water and extracted with

ether several times. The aqueous solution was acidified with dilute hydrochloric acid and extracted again with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 17 mg. (59%) of acid whose TLC behaviour in petroleum ether-ethyl acetate (65:35), infrared spectrum and GLPC retention time at 130° of its methyl ester were identical with those of the authentic cis-bicyclo[5.3.0]-decane-1-carboxylic acid. ORD was taken with the distilled sample at 90° (0.1 mm.).

IR spectrum: $\nu_{max}^{CHCl_3}$ 2240-3500 cm^{-1} (carboxyl OH), 1700 cm^{-1} (carboxyl C=O)

ORD: (c, 0.66 in methanol), $[\alpha]_{450}$+ 26.8°, $[\alpha]_{400}$+ 36.7°, $[\alpha]_{350}$+ 52.67°, $[\alpha]_{300}$+ 75°

(f) With Sodium Phenoxide in Dioxane

A mixture of dry phenol (5.4 g., 0.056 mole)(freshly distilled from sodium) and 1.0 g. (0.044 g. atom) of metallic sodium in 20 ml. of peroxide-free dioxane (freshly distilled twice from sodium and tested with potassium iodide starch paper) was refluxed for 4 hrs. The dioxane and the excess phenol were distilled out. The white residue was dried at 150° (20 mm.) overnight and further at 150° (0.1 mm.) for 2 hrs. To a mixture of 183 mg. (1.57 mmoles) of sodium phenoxide in 5 ml. of dry dioxane was added 240 mg. (0.98 mmole) of predried bromoketone 6(8)B. The mixture was swirled well to get all the bromoketone in solution, and a cloudy appearance developed immediately. The reaction mixture was refluxed for 19 hrs. A light brown solution containing white solid resulted after reflux. The solution (pH~9) was diluted

with water and extracted with ether. The combined ethereal extracts were washed with water and dried. Removal of solvent left 220 mg. (87%) of oil. GLPC analysis of the crude product showed mainly one product with some phenol. The phenol did not separate on silica gel TLC but separated well on alumina TLC, (petroleum ether-ethyl acetate, 70:30). The crude product was chromatographed on 5 g. of alumina (Woelm, neutral, Grade II). Elution with petroleum ether and benzene-petroleum ether (3:97) afforded 137 mg. (54%) of pure phenyl-cis-bicyclo[5.3.0]-decane-1-carboxylate 5(7)P. A sample of the ester was evaporatively distilled at 110° (0.3 mm.) for elemental analysis and ORD measurement. It was racemic.

IR spectrum: $\nu_{max}^{CCl_4}$ 1740 cm^{-1} (ester C=O)

PMR spectrum: δ 2.5-2.9 ppm (1H, bm, tertiary-H at ring junction),
6.8-7.3 ppm (5H, m, phenylic protons)

ORD: (c, 1.02 in chloroform), no detectable rotation from 700-300 nm.

Anal. Calcd. for $C_{17}H_{22}O_2$ (258.40): C, 79.03; H, 8.58

Found: C, 78.96; H, 8.66.

A solution of 122 mg. (0.34 mmole) of phenyl cis-bicyclo-[5.3.0]decan-1-carboxylate and 100 mg. of sodium methoxide (Fisher) in 10 ml. of methanol was refluxed at 100° for 5 days. The excess methanol was then removed and water was added. The aqueous solution was extracted with ether for several times. The combined ethereal solutions were washed and dried. Removal of solvent left 50 mg. of neutral material. The aqueous solution was acidified with dry-ice and extracted again with ether. Work up as before gave 40 mg. of acid. A sample of 25 mg. of the crude acid was evaporatively distilled at 85° (1 mm.) for ORD measurement. It was entirely racemic and melted at 55-58°.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2300-3500 cm^{-1} (carboxyl OH) and
1680 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 2.5-3.0 ppm (1H, b, tertiary-H at bridgehead)
8.6 ppm (1H, s, COOH)

ORD: (c, 0.75 in chloroform) no rotation from 300 to 700 nm.

(g) With Sodium Cyanide in Acetonitrile

To a solution of 258 mg. (1.05 mmoles) of bromoketone 6(8)B in 10 ml. of dry acetonitrile was added 71 mg. (1.45 mmoles) of sodium cyanide. The reaction mixture was refluxed for 60 hrs. The solution was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent left 206 mg. starting bromoketone whose identity was confirmed by IR, PMR spectra, ORD and TLC behaviour.

The aqueous layer was acidified with hydrochloric acid and worked up as before to give 11 mg. of oil whose TLC showed at least six spots. The acidic material was not investigated.

(h) With Sodium Hydroxide in Aqueous Hydrogen Peroxide and t-Butyl Alcohol

i) To a solution of sodium hydroxide (153 mg., 4.0 mmoles) in 3 ml. of water and 2 ml. of 70% hydrogen peroxide was added a solution of bromoketone 6(8)B (122 mg., 0.50 mmole) in 1 ml. of t-butyl alcohol. Oxygen evolved vigorously, and the flask was occasionally cooled with water. There were two phases in the solution. The reaction mixture was refluxed and the reaction was complete after 1.5 hrs. judging from TLC. The reaction mixture was diluted with water and extracted with ether.

The ethereal extracts were washed with water and dried. Removal of solvent gave 3 mg. of product whose TLC showed at least six products. The neutral product was not investigated further. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ether extracts were washed with water and dried. Removal of solvent afforded 73 mg. (80%) of cis-bicyclo[5.3.0]decane-1-carboxylic acid. A sample of the crude acid was purified by evaporative distillation for ORD measurement. A mixed GLPC of the methyl ester of the purified acid and authentic methyl cis-bicyclo[5.3.0]decane-1-carboxylate at 140° showed one peak.

ORD: (acid, c, 5.80 in chloroform), $[\alpha]_{450}$+ 46.5°, $[\alpha]_{400}$+ 98.3°, $[\alpha]_{300}$+ 150°

ii) A solution of sodium hydroxide (160 mg., 4.0 mmoles) in 2 ml. of water and 2 ml. of 70% hydrogen peroxide was added to a solution of bromoketone ($[\alpha]_D$- 17.6°, 122 mg., 0.50 mmole) in 1 ml. of t-butyl alcohol. The solution was refluxed on the steam bath for 4 hrs., diluted with water (20 ml.) and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 10 mg. of oil whose TLC in petroleum ether-ethyl acetate showed at least 5 spots. It was not investigated further.

The aqueous solution was worked up as in h_i to give 74 mg. (80%) of cis-bicyclo[5.3.0]decane-1-carboxylic acid. TLC (petroleum ether - ethyl acetate, 65:35) showed two other minor products. The crude product was chromatographed on 2.5 g. of silica gel (B.D.H. 60-120 mesh). Elution with petroleum ether-benzene, (60:40) fractions gave 13 mg. of pure acid. The ORD of the acid was a positive plain curve. The specific rotation at various wavelength was nearly equal to those of the silver

nitrate reaction.

ORD: (c, 1.25 in methanol), $[\alpha]_{400}$ + 76.8°, $[\alpha]_{350}$ + 115.2°, $[\alpha]_{300}$ + 171.2°.

iii) Bromoketone 6(8)H with Sodium Hydroxide in Aqueous Hydrogen Peroxide and Ethanol

To a solution of bromoketone-7-d_1 6(8)H (138 mg., 0.56 mmole, 85.3% d_1) dissolved in 1.5 ml. of 95% ethanol was added a solution of sodium hydroxide (121 mg., 3.0 mmoles) in 1 ml. of water, 0.5 ml. of ethanol and 2 ml. of hydrogen peroxide (70%). Oxygen was evolved immediately. The solution was warmed cautiously so that the oxygen evolution was not too vigorous. After the oxygen evolution had subsided, the solution was refluxed on a steam bath for 23 hrs. At the fourth hour, 1 ml. of hydrogen peroxide was added. The solution was diluted with 5 ml. of water and extracted with ether. The ethereal extracts were washed with brine water and dried. Removal of solvent left 3 mg. oil whose TLC (petroleum ether-ethyl acetate 65:35) showed at least 6 spots. The aqueous solution was acidified with dilute hydrochloric acid and extracted again with ether four times. The ethereal extracts were washed with brine water and dried. Removal of solvent afforded 58 mg. (57%) of acid. Two crystallizations from petroleum ether gave colorless crystals, m.p. 58-60°. The GLPC retention time of the methyl ester at 130° was identical to that of the authentic sample of methyl cis-bicyclo[5.3.0]-decane-1-carboxylate 5(7)E.

PMR spectrum: δ no absorption at 2.50-3.00 ppm.

Mass spectrum: m/e 182, 183, 37.3% d_o, 62.7% d_1

IR spectrum: $\nu_{max}^{CHCl_3}$ 2300-3500 (carboxy OH) and 1700 cm^{-1} (carboxy C=O).

(2) Attempt to Detect the Cyclopropanone 94

(a) In Potassium Bromide Dish

A potassium bromide dish was made by pressing a mixture of 2 mg. of bromoketone 6(8)B 7 mg. of sodium hydroxide and 147 mg. of potassium bromide. The transparent dish was directly attached to the infrared spectrometer. The region of 1900-1600 cm^{-1} was scanned. The absorption at 1810 cm^{-1} for reported cyclopropanone did not show up for several hours.

(b) With Sodium 3-ethyl-3-pentoxide

A mixture of 50 mg. of freshly cut sodium in 8 ml. of freshly distilled 3-ethyl-3-pentanol was refluxed at 150° for 24 hrs. To 24 mg. of bromoketone 6(8)B was added 1 ml. of the alkoxide solution. Infrared spectrum was run with the solution and no band around 1800 cm^{-1}, appeared for several hours. TLC analysis of the solution showed no reaction.

(c) With Sodium Methoxide under Irradiation

To a solution of 119 mg. (2 mmoles) of sodium methoxide in 10 ml. of methanol in a Pyrex tube under irradiation with a 450 watts mercury lamp was added dropwise a solution of 247 mg. (1 mmole) of bromoketone 6(8)B. The solution was diluted with water and extracted with ether after 132 hours. The combined ethereal extracts was washed with water and dried. After removal of solvent left 200 mg. of neutral material which was subjected to short stem distillation at 100-110° (20 mm.) to give 25 mg. colorless liquid. GLPC analysis at 90° showed retention time corresponding to $\Delta^{9,10}$-octalin, but TLC analysis showed at least eight compounds. Due to the complexity of the reaction, the

reaction was not investigated further.

(d) With Metals

To a solution of 108 mg. of 1,7-dibromobicyclo[5.3.1]undecan-11-one 6(8)F in 10 ml. of dry tetrahydrofuran was added 16 mg. magnesium ribbon. TLC analysis of the solution showed no reaction after 1 hr. A piece of lithium ribbon was added to the solution and further stirred for 7 hrs. The solution was filtered. After removal of the solvent, there was 138 mg. of solid left. TLC analysis showed one more polar product with the starting material. IR spectrum showed an absorption at 1720 cm^{-1} and no absorption at 1810 cm^{-1}.

(3) Rearrangement of 1-chlorobicyclo[5.3.1]undecan-11-one 6(8)C

Aliquots of the same batch of chloroketone 6(8)C, $[\alpha]_{320}$ + 479.4° were used in each of the experiments below except for (e) in which the specific rotation is specified.

(a) With Silver Nitrate in Aqueous Methanol

To a solution of chloroketone 6(8)C (144 mg., 0.70 mmole) in 5 ml. of methanol was added a solution of silver nitrate (334 mg., 1.97 mmoles in 2 ml. of water). Cloudiness appeared immediately and the solution was refluxed on the steam bath for 20 hrs. The silver chloride was filtered, washed well with ether and dried to constant weight, 33.7 mg. (33%). The filtrate was extracted with ether. The combined ethereal layer was extracted with dilute sodium bicarbonate solution. The ethereal layer was washed with water and dried. Removal of solvent left 107 mg. of oil. GLPC analysis showed 90% of recovered chloroketone and

about 10% of methyl-cis-bicyclo[5.3.0]decane-1-carboxylate 5(7)E. The bicarbonate washes were acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 30 mg. of acid (69% based on reacted chloroketone). The acid was identified as cis-bicyclo[5.3.0]decane-1-carboxylic acid by the IR spectrum and TLC. The crude acid was chromatographed on 1.5 g. of silica gel. Elution with benzene-petroleum ether (30:70) gave 12 mg. of pure acid which was evaporatively distilled at 70-100° (0.6 mm.) for ORD measurement.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2225-3500 (carboxyl OH) and 1700 cm^{-1} (carboxyl C=O)

ORD: (c, 0.655 in chloroform), $[\alpha]_{450}$ - 30.6°, $[\alpha]_{400}$ - 463°, $[\alpha]_{350}$ - 59.5°, $[\alpha]_{300}$ - 91.6°

(b) With Sodium Hydroxide in Aqueous Hydrogen Peroxide and t-Butyl Alcohol

A solution of sodium hydroxide (170 mg., 4.25 mmoles in 2 ml. of water) and 2 ml. of hydrogen peroxide (70%) was added dropwise to a solution of chloroketone (134 mg., 0.67 mmole in 1 ml. of t-butyl alcohol). Oxygen evolved vigorously and the reaction mixture was refluxed on the steam bath. The reaction was nearly complete after 2 hrs. as shown by TLC. Another 2 ml. of hydrogen peroxide was added and only small amount of oxygen evolved. The reaction was worked up after 6 hrs. The reaction mixture was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent left 4.5 mg. of oil whose TLC showed 5 spots. It was

discarded. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed and dried. Removal of solvent afforded 98 mg. (80%) of solid whose PMR spectrum and TLC behaviour in petroleum ether-ethyl acetate (65:35) were identical with those of the authentic cis-bicyclo[5.3.0]decane-1-carboxylic acid. The crude acid was chromatographed on 5.5 g. of silica gel (B.D.H. 60-80 mesh). Elution with petroleum ether-benzene (70:30) gave 57 mg. of acid mp 47-57°. A sample of the acid was evaporatively distilled at 70-100 (0.4-0.6 mm.) for ORD measurement. GLPC analysis of the methyl ester at 130° showed one peak which corresponded to the methyl cis-bicyclo[5.3.0]-decane-1-carboxylate 5(7)C.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2225-3500 (carboxyl OH) and 1700 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 2.5-2.9 (1H, bm, tertiary-H at ring junction) and 10.5 ppm (1H, b, COOH).

ORD: (c, 0.835 in chloroform) $[\alpha]_{450}$- 4.8°, $[\alpha]_{400}$- 8.4°, $[\alpha]_{350}$- 12.0°, $[\alpha]_{300}$- 19.2°

The experiment was repeated with 100 mg. of chloroketone 6(8)C in 1 ml. of t-butyl alcohol and 160 mg. of sodium hydroxide in 2 ml. of water and 2 ml. of hydrogen peroxide (70%). The acid (78 mg., 86%) was purified on 2.5 g. silica gel (B.D.H., 60-80 mesh) and distilled to run ORD.

ORD: (c, 0.800 in chloroform), $[\alpha]_{450}$- 8.7°, $[\alpha]_{400}$- 10.0°, $[\alpha]_{350}$- 12.5°, $[\alpha]_{300}$- 17.5°

(c) With Sodium Hydroxide in Aqueous Ethanol

Metallic sodium (150 mg., 70 mg. atoms) was dissolved in 10 ml. of ethanol (95%). To the basic solution was added 101 mg. (0.5 mmole) of chloroketone. The solution was refluxed for 22 hrs. TLC analysis at the 10th hour showed that the reaction was incomplete. The solution was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent gave 10 mg. of sweet smelling liquid whose TLC showed starting chloroketone and one less polar component. The neutral fraction was not investigated further. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent left 66 mg. of acid (73%). The acid was chromatographed on 4.0 g. of silica gel (B.D.H. 60-120 mesh). Elution with benzene-petroleum ether (30:70) gave 22 mg. of solid which showed the same TLC behaviour and IR spectrum with the authentic cis-bicyclo-[5.3.0]decane-1-carboxylic acid 5(7)C. The ORD of the acid showed it was entirely racemic.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2230-3500 (carboxyl OH) and 1695 cm^{-1} (carboxyl C=O)

ORD: (c, 1.268 in chloroform): The solution curve superimposed exactly with the base line from 700 to 300 nm.

(d) With Potassium Bicarbonate in Methanol

To a solution of 139 mg. (0.68 mmole) of chloroketone in 5 ml. of methanol was added a solution of 187.5 mg. (1.87 mmoles) of potassium, bicarbonate in 2 ml. of methanol. Precipitation was observed immediately.

The reaction mixture was refluxed for 63 hrs. at 90°. The reaction was diluted with water and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent left 60 mg. of neutral products which were not investigated further. The aqueous solution was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Evaporation of the solvent afforded 46 mg. (37%) of acid which was chromatographed on 3 g. of silica gel (B.D.H. 60-80 mesh). Elution with benzene-petroleum ether (30:70) gave 24 mg. of pure acid 5(7)C mp 55-60° (TLC one spot) which was distilled at 100-120° (0.6 mm.) for ORD measurement. It was entirely racemic.

IR spectrum: $\nu_{max}^{CHCl_3}$ 2225-3500 (carboxyl OH) and 1695 cm^{-1} (carboxyl C=O)

ORD: (c, 1.485 in chloroform) sample and base lines were superimposed from 700 to 300 nm.

(e) With Sodium Deuteroxide in Deuterated Ethanol

Metallic sodium, 25 mg. (1.1 mg. atoms) was dissolved in 3 ml. of ethanol-d (99% D) and 3 ml. of deuterium oxide. To the base solution was added a solution of 241 mg. (1.4 mmoles) of chloroketone 6(8)C, $[\alpha]_{322}$- 674° in 2 ml. of ethanol-d. The solution was refluxed at 110° for 17 hrs. The cooled solution was diluted with 5 ml. of deuterium oxide and extracted with anhydrous ether. The ethereal extracts were washed with deuterium oxide and dried. Removal of solvent gave 237 mg. of oil. GLPC analysis showed mostly starting chloroketone with trace of presumably ethyl ester. The crude product was evaporatively distilled at 85-90° (0.1 mm.) twice for mass spectrum and ORD measurement. The

recovered chloroketone retained 90.2% of its optical activity and had incorporated only 1.3% d_1.

ORD: (c, 0.633 in chloroform), $[\alpha]_{450}$- 55.5°, $[\alpha]_{450}$- 91.0°, $[\alpha]_{352}$- 21.1°, $[\alpha]_{318}$- 598°, $[\alpha]_{265}$+ 670°.

Mass spectrum: m/e 200; 98.7% d_0, 1.3% d_1

The alkaline aqueous layer was acidified with a few drops of phosphorous trichloride and extracted with ether. The ethereal extracts were washed with deuterium oxide and dried. Removal of solvent gave 54 mg. (21%) of acid 5(7)C. PMR spectrum of the crude acid showed no absorption at 2.5-2.9 ppm. The acid was chromatographed on 5 g. of silica gel (B.D.H., 60-80 mesh). Elution with petroleum ether-benzene (30:70) and (35:65) gave 10 mg. pure acid which was evaporatively distilled at 90-100° (0.1 mm.) for mass spectrum and ORD measurement. No observable rotation for wavelength higher than 400 nm.

ORD: (c, 0.58 in chloroform), $[\alpha]_{350}$+ 6.0°, $[\alpha]_{300}$+ 8.1°

Mass spectrum: m/e 182, 183 (M+); 11.3% d_0, 88.7% d_1

Reaction of Bicyclo[5.3.1]undecan-11-one 6(8)K with Potassium Hydroxide in Carbon Tetrachloride

A mixture of the bicyclic ketone 6(8)K (580 mg., 3.7 mmoles), of t-butyl alcohol 2.18 g. of potassium hydroxide, 1 ml. of water and 6 ml. of carbon tetrachloride were warmed at 50° with vigorous stirring for 4 hrs. The reaction mixture was evaporated to dryness and water was added. The aqueous solution was extracted with ether. The ethereal solution was washed with water and dried. Removal of solvent left 478 mg. of starting ketone. The recovered ketone was further subjected

to the above condition at steam bath temperature for 24 hrs. The reaction mixture was worked up as above to give 176 mg. of recovered ketone. The aqueous layer was acidified with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 257 mg. (78%) of acid mp 58-60° which was identified to be cis-bicyclo[5.3.0]decane-1-carboxylic acid by IR and PMR spectra and mixed mp. 58-60°.

IR spectrum: $\nu_{max}^{CCl_4}$ 2250-3500 (carboxyl OH), 1700 cm^{-1} (carboxyl C=O)

PMR spectrum: δ 2.50-2.90 (1H, b, proton at ring junction) and 11.83 ppm (1H, s, COOH).

(F) Kinetic Study of Favorskii Rearrangement of Bicyclic Haloketones.

Reagents and Substrates: Methanol was Fisher Spectranalyzed grade without further purification. Distilled water was boiled for a few minutes and kept in a well-stoppered flask. Sodium methoxide solution in methanol was prepared by dissolving freshly cut sodium in methanol in a volumetric flask and make up to the desired volume with methanol. The concentration of the base was determined by titrating a known volume of the base with standard hydrochloric acid (0.0100 N, B.D.H.) using methyl red as indicator. Dioxane was purified by refluxing with sodium for several hours and distilling twice from sodium. The haloketones are recrystallized from petroleum ether and sublimed under reduced pressure. They were chromatographically pure (TLC, GLPC).

Temperature Control: A well-stirred oil bath regulated by a Fisher Thermal Regulator to give temperature control 0.01° in the range 50-100°. For lower temperatures a heavily insulated Dewar flask containing ice and water with mechanical stirring gave temperature control within ± 1°.

Determination of Halides: The halide ions concentration was determined by potentiometric titration or the Volhard method. The bromide is conveniently determined with both methods, but the end point of the Volhard method for chloride is difficult to detect visually due to low concentration of halide and higher solubility of silver chloride. Furthermore, the 1-bromobicyclo[3.3.1]nonan-9-one 6(6)B and 1-bromobicyclo[4.3.1]decan-10-one 6(7)B are quite reactive toward silver nitrate, the use of potentiometric titration with these two haloketones is preferred.

(1) Potentiometric Titration

A stock solution of standard silver nitrate solution (0.01 N, B.D.H.) was kept in an amber coloured glass bottle. The reaction solution was quenched by 2 ml. of 6N nitric acid and diluted with 10 ml. of water. The solution was stirred magnetically and titrated with silver nitrate (0.01 N) using a pH-meter. The middle of the titration curve was taken as the end point or else the end point was determined by differential method. By plotting $\log \frac{b(a-x)}{a(b-x)}$ versus time, the second order rate constant (k) was determined from the slope ($\frac{a-b}{2.303}$ k) of the best straight line, where a, b and x were the initial concentration of the base, substrate and concentration of the halide determined. The slope of the best straight line was determined by the least squares method. Control experiments were performed showing that the starting haloketones did not

react with silver nitrate solution during titration.

(2) Volhard Method

Reagent grade potassium thiocyanate (0.095 N) was stored well protected from light. The Fe^{+++} reagent was prepared by dissolving 14 g. of ferric ammonium sulfate in 40 ml. of hot water, cooling to room temperature, filtering and making up the filtrate to 50 ml. with 6 N nitric acid. For estimation of halide ions the reaction solution was quenched with 2 ml. of 6 N nitric acid and diluted with 10 ml. of water followed by 1 ml. of Fe^{+++} reagent, 2 ml. of silver nitrate solution in an Erlenmeyer flask. The mixture was stirred magnetically and titrated with potassium thiocyanate to a permanent pink color. A reagent blank omitting the halide ions was carried out under identical conditions. The difference of the two titrations gave the concentration of the halide ions in the reaction mixture.

(a) 1-Bromobicyclo[3.3.1]nonan-9-one 6(6)B

With Sodium Methoxide in Methanol

A sample of bromoketone (22.8 mg., 0.105 mmole) was dissolved in methanol in a 10 ml.-volumetric flask and the volume was made up to 10 ml. with methanol after all the bromoketone had dissolved. An empty 25 ml.-round bottomed flask fitted in the thermostat served as reactor. The bromoketone solution and the base sodium methoxide (0.0440 M) were well equilibrated in the thermostat for half an hour. Exactly 9.5 ml. of each of the solutions were pipetted into the reactor, the latter being shaken vigorously to mix the two solutions. The reaction was followed by

periodically withdrawing a 2 ml. aliquot into 2 ml. of 6 N nitric acid and 10 ml. of water. The solution was titrated with silver nitrate (0.01 N) potentiometrically. Three kinetic runs were carried out in methanol solvent. The results are tabulated in Table XI.

With Sodium Hydroxide in Dioxane-Water (60:40)

The bromoketone solution was prepared by dissolving 11.1 mg. of the material in dioxane-water (60:40) in a 10 ml. flask. The sodium hydroxide solution was prepared by diluting 20 ml. of 0.10 N sodium hydroxide (B.D.H.) with 20 ml. of water in a 100-ml. volumetric flask and making it up to the mark with dioxane. Both solutions were thermally equilibrated in the thermostat for 0.5 hr. Two ml. of each solution were mixed in a 15 mm. x 10 cm. test tube which was fitted in the thermostat and the time noted. The reaction was quenched with 2 ml. of 6 N. nitric acid at an appropriate time interval and washed into a beaker for titration silver nitrate. Three kinetic runs were carried out and the results were tabulated in Table XII.

(b) 1-Bromobicyclo[4.3.1]decan-10-one 6(7)B

With Sodium Methoxide in Methanol

In three Pyrex thick-walled glass tubes (1.5 cm. x 16 cm.) chilled in ice water were mixed exactly 1 ml. of bromoketone solution (19.5 mg., 0.0836 mmole in 10 ml. of methanol) and 1 ml. of methoxide solution (0.044 M). The tubes were sealed and then immersed all together in an oil bath adjusted to $60^{\circ} \pm 0.01^{\circ}$. At suitable time intervals a tube was taken out, quickly chilled in ice water, opened and 2 ml. of 6 N nitric acid introduced. The contents were rinsed into a beaker using

TABLE XI

Reaction of Bromoketone 6(6)B with Sodium Methoxide in Methanol at 0°

$[MeO^{--}] = a = 0.0220M$ $[MeO^{-}] = a = 0.2220M$ $[MeO^{-}] = a = 0.0442M$

[6(6)B]= b = 0.005251M [6(6)B]= b = 0.00534M [6(6)B]= b = 0.00539M

t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$	t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$	t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$
15.8	5.5	0.038	17.8	5.0	0.031	22.2	8.5	0.068
38.5	8.0	0.055	44.7	7.0	0.047	36.6	12.5	0.102
59.9	9.5	0.069	90.2	12.0	0.086	65.5	14.7	0.120
123.3	15.0	0.115	129.3	13.0	0.094	85.2	20.5	0.187
162.9	18.0	0.146	292.6	23.0	0.197	97.8	20.0	0.181
196.8	19.5	0.162	361.3	25.5	0.228	120.2	23.5	0.223
			402.3	28.5	0.286	149.1	30.0	0.341

$k = (9.62 \pm 0.19) \times 10^{-2} M^{-1} min^{-1}$ $k = (8.92 \pm 0.29) \times 10^{-2} M^{-1} min^{-1}$ $k = (9.33 \pm 0.75) \times 10^{-2} M^{-1} min^{-1}$

Average of $k = (9.29 \pm 0.41) \times 10^{-2} M^{-1} min^{-1}$

TABLE XII

Reaction of Bromoketone 6(6)B with Sodium Hydroxide in Aqueous Dioxane at 0°

$[HO^-]$ = a = 0.0105M

[6(6)B]= b = 0.00205M

t min.	X x 10^3M	log $\frac{b(a-x)}{a(b-x)}$
3.0	0.65	0.101
6.0	1.25	0.237
8.0	1.50	0.318
10.5	1.80	0.450

k = 14.1 ± 0.72$M^{-1}min^{-1}$

$[HO^-]$ = a = 0.0100M

[6(6)B]= b = 0.002625M

t min.	X x 10^3M	log $\frac{b(a-x)}{a(b-x)}$
1.5	0.8	0.196
3	1.25	0.256
5	1.63	0.388
7	1.8	0.473

k = 16.9 ± 1.27$M^{-1}min^{-1}$

$[HO^-]$ = a = 0.00500M

[6(6)B]= b = 0.002625M

t min.	X x 10^3M	log $\frac{b(a-x)}{a(b-x)}$
4	0.50	0.050
8	0.92	0.10
12	1.30	0.166

k = 14.0 ± 0.6$M^{-1}min^{-1}$

Average k = 15.0 ± 0.8$M^{-1}min^{-1}$

several small portions of water and titrated with silver nitrate potentiometrically. Kinetic runs were also done at 75° and 83° and are tabulated in Table XIII.

(c) 1-Bromobicyclo[5.3.1]undecan-11-one 6(8)B

With Sodium Methoxide in Methanol

In 9 Pyrex thick-walled glass tubes (1.5 cm x 16 cm) chilled in ice water were mixed 1 ml. of methanolic bromoketone solution (0.00994 M) and 1 ml. of methanolic sodium methoxide (0.0354 M). The tubes were sealed and then immersed at once in an oil bath adjusted at 75 ± 0.01°, marking the zero time. At suitable time intervals one tube was taken out, quickly chilled in ice water, opened and 2 ml. of 6 N nitric acid introduced. The contents were rinsed into an Erlenmeyer flask with several small portions of water and 2 ml. of silver nitrate solution (0.01 N), 3 drops of Fe^{+++} reagent were added. The mixture was titrated with potassium thiocyanate solution (0.0095 N) to a permanent pink color. A blank without halide was also carried out under the same conditions. The potentiometric method and the Volhard method gave titration values within 5%. The kinetic runs were also done at 84° and 95° and the results were tabulated in Table XIV, and Table XV.

(d) 1-Chlorobicyclo[5.3.1]undecan-11-one 6(8)C

With Sodium Methoxide in Methanol

The procedure was exactly the same as for the bromoketone 6(8)C. The kinetics were done in 1:4 and 1:7 substrate to base ratio

TABLE XIII

Reaction of Bromoketone 6(7)B with Sodium Methoxide in Methanol at 60°, 75° and 83°

$[MeO^-]$ = a = 0.0220 M

[6(7)B] = b = 0.00418 M

t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$
16.4	3.0	0.0264
34.8	5.5	0.0484
57.7	7.5	0.072

$k = (1.42 \pm 0.03) \times 10^{-1} M^{-1} min^{-1}$

$[MeO^-]$ = a = 0.01915 M

[6(7)B] = b = 0.005125 M

t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$
43.6	18.5	0.153
58.4	22.0	0.191
68.68	27.5	0.268
84.26	30.0	0.304
107.45	34.0	0.388
126.25	37.0	0.463
144.9	39.0	0.468

$k = (6.16 \pm 0.27) \times 10^{-1} M^{-1} min^{-1}$

$[MeO^-]$ = a = 0.0197 M

[6(7)B] = b = 0.00583 M

t min.	X x 10^4M	log $\frac{b(a-x)}{a(b-x)}$
10.1	12.5	0.076
21.5	22.5	0.160
32.2	31.0	0.256
44.5	35.0	0.314
55.8	40.0	0.406

$k = 1.17 \pm 0.04\ M^{-1}\ min^{-1}$

TABLE XIV

Reaction of Bromoketone 6(8)B with Sodium Methoxide in Methanol at 75°

$[MeO^-]$ = a = 0.0177 M

[6(8)B] = b = 0.00497 M

t min.	X x 10^4 M	$\log \frac{b(a-x)}{a(b-x)}$
25.5	5.23	0.032
56.6	9.97	0.073
59.4	10.93	0.078
89.4	14.73	0.116
120.8	18.3	0.154
147.9	21.38	0.189
174.2	24.7	0.234
242.7	30.40	0.299
320.09	32.77	0.379

$k = 2.33 \times 10^{-1} \pm 0.005\ M^{-1}min^{-1}$

$[MeO^-]$ = a = 0.03683 M

[6(8)B] = b = 0.00497 M

t min.	X x 10^4 M	$\log \frac{b(a-x)}{a(b-x)}$
38.6	16.15	0.152
54.10	19.0	0.186
66.9	22.8	0.240
85.1	26.6	0.299

$k = 2.37 \times 10^{-1} \pm 0.001\ M^{-1}\ min^{-1}$

TABLE XV

Reaction of Bromoketone 6(8)B with Sodium Methoxide in Methanol at 84° and 95°

$[MeO^-]$ = a = 0.0177 M

[6(8)B] = b = 0.0497 M

t min.	X x 10^4 M	$\log \frac{b(a-x)}{a(b-x)}$
34.6	11.87	0.089
60.5	19.47	0.166
96.1	25.17	0.211
119.8	29.45	0.312
143.6	30.40	0.329

$k = 5.42 \times 10^{-1} \pm 0.034\ M^{-1}min^{-1}$

$[MeO^-]$ = a = 0.0177 M

[6(8)B] = b = 0.00497 M

t min.	X x 10^4 M	$\log \frac{b(a-x)}{a(b-x)}$
10.4	9.0	0.064
20.7	14.73	0.140
27.4	22.2	0.97
29.4	21.38	0.189
40.7	26.6	0.264
47.5	30.87	0.338
63.6	35.62	0.454

$k = 1.22 \pm 0.07\ M^{-1}min^{-1}$

and at three different temperatures. The results were tabulated in Table XVI and XVII.

(e) 1-Bromobicyclo[5.3.1]undecan-11-one-7-d_1 6(8)H and 1-Chlorobicyclo[5.3.1]undecan-11-one-7-d_1 6(8)J

The second order rate constants of the deuterated bromoketone 6(8)H (95.5% d_1) and deuterated chloroketone 6(8)J (91.0% d_1) with sodium methoxide in methanol were determined exactly the same way as the undeuterated haloketones at 84° with substrate to base ratio (1:4). The results were tabulated in Table XVIII. The kinetic isotope effect (K_H/K_D) for the bromoketone and chloroketone are determined to be 6.0 and 3.1 respectively.

(G) Favorskii Rearrangement of 2α-Bromo-5α-cholestan-one with Sodium Hydroxide in Aqueous Hydrogen Peroxide and t-Butyl Alcohol

A solution of sodium hydroxide (139 mg., 3.5 mmoles) in 2 ml. of water and 2 ml. of ca. 70% hydrogen peroxide was added dropwise to a solution of 2α-bromo-5α-cholestan-3-one (215.4 mg., 0.46 mmole) in 10 ml. of t-butyl alcohol. The solution was refluxed on a steam bath for 4 hrs., diluted with water (10 ml.), and extracted with ether. The ethereal extracts were washed with water and dried. Removal of solvent afforded 14 mg. neutral material which was not investigated further. The alkaline aqueous solution was acidified and worked up as in E(h) to give 202 mg. acid. TLC (acetic acid-chloroform, 3:97) showed six spots. The main product (23%) which was isolated from thick layer chromatography with the above solvent system was shown to be diacid 102 by TLC behaviour and mix mp, 189-191°, with authentic acid [lit. (114) 191-196°].

TABLE XVI

Reaction of Chloroketone 6(8)C with Sodium Methoxide in Methanol at 75°

$[MeO^-]$ = a = 0.0177 M

[6(8)C] = b = 0.00497 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
40.5	3.32	0.021
80.9	7.12	0.046
103.9	10.9	0.074
151.6	10.9	0.074
156.6	12.67	0.088
203.6	17.57	0.132
233.5	17.57	0.132
283.4	21.37	0.170
337.6	25.17	0.216

$k = 1.09 \times 10^{-1} \pm 0.005\ M^{-1}min^{-1}$

$[MeO^-]$ = a = 0.03683 M

[6(8)C] = b = 0.00497 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
25.4	4.75	0.035
30.1	5.70	0.040
50.2	11.40	0.095
66.3	15.20	0.131
78.7	15.67	0.134
90.4	15.67	0.134
97.1	18.5	0.161

$k = 1.22 \times 10^{-1} \pm 0.001\ M^{-1}min^{-1}$

TABLE XVII

Reaction of Chloroketone 6(8)C with Sodium Methoxide in Methanol at 84° and 95°

$[MeO^-]$ = a = 0.01770 M

[6(8)C] = b = 0.005255 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
35.0	9.02	0.06
60.7	16.2	0.119
74.2	18.5	0.141
120.0	21.4	0.172
143.8	23.8	0.199
183.3	30.40	0.294
238.1	33.72	0.354

k = 2.59 x 10^{-1} ± 0.016 $M^{-1}min^{-1}$

$[MeO^-]$ = a = 0.036825 M

[6(8)C] = b = 0.005255 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
15.7	7.60	0.049
28.3	11.40	0.075
40.5	20.40	0.161
53.7	23.27	0.192
72.8	26.6	0.236
86.4	28.97	0.272
95.9	32.77	0.336

k = 6.25 x 10^{-1} ± 0.041 $M^{-1}min^{-1}$

TABLE XVIII

Reaction of Deuterated Bromoketone 6(8)H and Deuterated Chloroketone 6(8)J with Sodium Methoxide in Methanol at 84°

$[MeO^-]$ = a = 0.019700 M

[6(8)H] = b = 0.004997 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
89.2	6.50	0.049
185.5	16.50	0.136
268.9	20.50	0.182
328.3	21.00	0.188
371.9	24.50	0.236
450.0	26.50	0.266
483.9	28.00	0.290
590.4	31.50	0.357

$k = (9.08 \pm 0.41) \times 10^{-2}\ M^{-1}min^{-1}$

$[MeO^-]$ = a = 0.01915 M

[6(8)J] = b = 0.005625 M

t min.	X x 10^4 M	log $\frac{b(a-x)}{a(b-x)}$
113.1	14.0	0.083
173.8	18.0	0.123
238.6	21.0	0.152
370.1	26.0	0.206
469.0	30.0	0.257
505.1	31.0	0.272
611.2	35.0	0.335
642.7	36.0	0.355

$k = (8.41 \pm 0.18) \times 10^{-2}\ M^{-1}min^{-1}$

REFERENCES

1. A.S. Kende in Org. Reactions 11, John Wiley and Sons, Inc. (1960).
2. A. Favorskii, J. Russ. Phys. Chem. Soc., 26, 559 (1894).
3. J.G. Aston and R.B. Greenburg, J. Amer. Chem. Soc., 62, 2590 (1940).
4. A.A. Sacks and J.G. Aston, ibid., 73, 3902 (1951).
5. W.G. Dauben, C.F. Hiskey and M.A. Muhs, ibid., 74, 2082 (1952).
6. E.L. May and E. Mosettig, ibid., 70, 1077 (1948).
7. J.G. Aston, J.T. Clark, K.A. Burgers and R.B. Greenburg, ibid., 43, 300 (1942).
8. a. C.L. Stevens and A.E. Sherr, J. Org. Chem., 17, 1228 (1952).
   b. W.D. McPhee and E. Klingsberg, J. Amer. Chem. Soc., 66, 1132 (1944).
9. P.E. Eaton and T.W. Cole,Jr., ibid., 86, 962 (1964).
10. B.B. Smith and H.R. Nace, ibid, 76, 6119 (1954).
11. a. Ch. R. Engel, ibid.,78, 4727 (1956).
    b. D.E. Evans, A.C. de Paulet, C.W. Shoppee and F. Winternitz, J. Chem. Soc., 1451 (1957).
12. a. H.R. Nace and B.A. Olsen, J. Org. Chem., 32, 3438 (1967).
    b. A.S. Kende, Chem. Ind. (London), 1346 (1959).
13. R.B. Loftfield and L. Schaad, J. Amer. Chem. Soc., 76, 35 (1954).
14. R.B. Loftfield, ibid., 72, 632 (1950).
15. C.L. Stevens and E. Farkas, ibid., 74, 5352 (1952).
16. H.O. House and W.F. Gilmore, ibid., 83, 3980 (1961).

17. A.W. Fort, ibid., 84, 2625 (1962).

18. H.O. House and W.F. Gilmore, ibid., 83, 3972 (1961).

19. H.T. Nagasawa and J.A. Elberling, Tetrahedron Letters, 5395 (1966).

20. E. Breuer, T. Berger and S. Sarel, Chem. Comm., 1596 (1968).

21. G.M. Iskander and F. Stansfield, J. Chem. Soc., (C) 669 (1969).

22. O.E. Edwards and M. Lesage, Can. J. Chem., 41, 1592 (1963).

23. A. Favorskii, J. Prakt. Chem. [2], 88, 641 (1913).

24. C.L. Stevens and E. Farkas, J. Amer. Chem. Soc., 74, 618 (1952).

25.a. F.G. Bordwell, R.R. Frame, R.G. Scamehorn, J.G. Strong and S. Meyerson, ibid., 89, 6704 (1967).

b. F.G. Bordwell and Richard G. Scamehorn, ibid., 90, 6751 (1968).

c. F.G. Bordwell, R.G. Scamehorn and W.R. Springer, ibid., 91, 2087 (1969).

26. G. Richard, Compt. Rend., 197, 1432 (1933).

27. B. Tchoubar and O. Sackur, ibid., 208, 1020 (1939).

28. D. Bandry, J.P. Begue and M.C. Morize, Tetrahedron Letters, 2147 (1970).

29. E.E. Smissman and G. Hite, J. Amer. Chem. Soc., 81, 1201 (1959).

30. E.E. Smissman and G. Hite, ibid., 82, 3375 (1960).

31. D. Baudry, J.P. Begue and M.C. Morixe, Tetrahedron Letters, 4797 (1970).

32. D.A. Prins and C.W. Shoppee, J. Chem. Soc., 494 (1946).

33. K.V. Scherer, Jr., R.S. Lunt,III, and G.A. Ungefur, Tetrahedron Letters, 1199 (1965).

34. N.L. Wendler, R.P. Graber and G.G. Hazen, Tetrahedron, 3, 144 (1958).

35. J.G. Aston and J.D. Newkirk, J. Amer. Chem. Soc., 73, 3900 (1951).

36. F.G. Bordwell and M.W. Carlson, ibid., 92, 3370, 3377 (1970).

37. J.M. Conia and J. Salaun, Tetrahedron Letters, 1175 (1963).

38. E.W. Warnhoff, C.M. Wong and W.T. Tai, J. Amer. Chem. Soc., 90, 514 (1968).

39. W.B. Smith and C. Gonzalez, Tetrahedron Letters, 5751 (1966).

40. W.B. Hammond and N.J. Turro, J. Amer. Chem. Soc., 88, 2880 (1966).

41. N.J. Turro, G.W. Byers and P.A. Leermaker, ibid., 86, 955 (1964).

42. J.M. Pochan, J.E. Baldwin, W.H. Flygare, ibid., 90, 1072 (1968).

43. N.J. Turro, Acc. Chem. Res., 2, 25 (1969).

44. N.J. Turro, W.B. Hammond, J. Amer. Chem. Soc., 87, 3258 (1965).

45. J.F. Pazos and F.D. Greene, ibid., 89, 1030 (1967).

46. F.D. Greene, personal communication.

47. J.K. Crandall and W.H. Machleder, J. Amer. Chem. Soc., 90, 7292 (1968).

48. R. Breslow, J. Posner and A. Krebs, ibid., 85, 234 (1963).

49. J.G. Burr and M.J.S. Dewar, J. Chem. Soc., 1201 (1954).

50.a. A.W. Fort, J. Amer. Chem. Soc., 84, 2620 (1962).

b. A.W. Fort, ibid., 84, 2625 (1962).

51. A.W. Fort, ibid., 84, 4979 (1962).

52. R.C. Cookson, M.J. Nye and G. Subrahmanyam, J. Chem. Soc., (C), 473 (1967).

53. F.G. Bordwell, R.G. Scamehorn and A.C. Knipe, J. Amer. Chem. Soc., 92, 2172 (1970).

54. S.S. Edelson and N.J. Turro, ibid., 92, 2770 (1970).

55. R. Hoffmann, ibid., 90, 1475 (1968).

56. G. Stork and I.J. Borowitz, ibid., 82, 4307 (1960).

57. H.O. House and H.W. Thompson, J. Org. Chem., 28, 164 (1963).

58. H.O. House and F.A. Richey,Jr., ibid., 32, 2151 (1967).

59. E.E. Emissman, T.L. Lemke and O. Kristiansen, J. Amer. Chem. Soc., 88, 334 (1966).

60. A.C. Cope and E.S. Graham, ibid., 73, 4702 (1951).

61.a. F.S. Fawcett, Chem. Rev., 47, 219 (1950).

b. J.A. Marshall and H. Faubl, J. Amer. Chem. Soc., 89, 5965 (1967).

62.a. E.J. Corey and E. Block, J. Org. Chem., 34, 1233 (1969).

b. Leo A. Paquette and R.W. Houser, J. Amer. Chem. Soc., 91, 3870 (1969).

63. G.J. Karabatsos and J.L. Fry in Carbonium Ion, Vol. II, Edited by G.A. Olah and P.V.R. Schleyer, Wiley Interscience, 1970.

64. D.J. Cram, Fundamentals of Carbanion Chemistry, Academic Press, New York and London, 1965.

65. W.P. Jencks and M. Gilchrist, J. Amer. Chem. Soc., 90, 2622 (1968).

66.a. W.v.E. Doering and R.S. Urban, ibid., 78, 5938 (1956).

b. F.H. Westheimer, ibid., 58, 2209 (1936).

67. Iris Wang, Ph.D. Thesis (1971).

68. D. Chambers, M.Sc. Thesis (1968).

69. S.L. Johnson in Adv. In Phys. Org., Vol. V, Academic Press, London and New York, 1967 p. 237.

70. David B. Sclove, Jose F. Pazos, R.L. Camp and F.D. Greene, J. Amer. Chem. Soc., 92, 7488 (1970).

71. E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw-Hill, 1962.

72. J.E. Baldwin and F.H.I. Cardellina, Chem. Comm. 558 (1968).

73. R. Deghenghi, G. Schilling and G. Papineau-Couture, Can. J. Chem., 44, 789 (1966).

74. W. Treibs, Chem. Ber., 66, 610 (1933).

75. Paul D. Bartlett, J. Amer. Chem. Soc., 56, 967 (1934).

76. E.J. Corey, N.W. Gilman and B.E. Ganem, ibid., 90, 5616 (1968).

77. E. Emmet Reid, Organic Chemistry of Bivalent Sulfur, Chemical Publishing Co. Inc., New York, 1962.

78. C.Y. Meyers, A.M. Malte and W.S. Matthews, J. Amer. Chem. Soc., 91, 7510 (1969).

79. T.I. Temnikova, G.A. Ugolnikova, O.A. Netsetakaya and T. Remizova, Zhur. Obsshohei Khim., 27, 2491 (1957) [Chem. Abst. 7205 (1958)].

80. C.H. DePuy, Acc. Chem. Res., 1, 33 (1968).

81. P.G. Gassman and F.V. Zalar, Tetrahedron Letters, 3251 (1964).

82. W. Reusch and P. Mattison, Tetrahedron, 23, 1953 (1967).

83. C.D. Gutsche and T.D. Smith, J. Amer. Chem. Soc., 82, 4067 (1960).

84. H.C. Brown and K. Ichikawa, Tetrahedron 1, 221 (1957).

85. E.N. Marvell and R. Stephen Knutson, J. Org. Chem., 35, 388 (1970).

86. W.A.C. Brown, J. Martin and G.A. Sim, J. Chem. Soc., 1844 (1965).

87. C. Rappe and L. Knutson, Acta Chem. Scand., 21, 163 (1967).

88. E.W. Warnhoff, C.M. Wong and W.T. Tai, J. Org. Chem., 32, 2664 (1967).

89. A.C. Cope and M.E. Synerholm, J. Amer. Chem. Soc., 72, 5228 (1950).

90. I. Roberts and H.C. Urey, ibid., 60, 880 (1938).

91. J.R. Jones, Trans. Faraday Soc., 61, 95 (1965).

92.a. F.G. Bordwell and William J. Boyle, Jr., J. Amer. Chem. Soc., 93, 511 (1971).

b. F.G. Bordwell and William J. Boyle, Jr., ibid., 93, 513 (1971).

93. A. Streitwieser Jr., Solvolytic Displacement Reaction, McGraw-Hill Book Co. Inc., New York (1962).

94. F.G. Bordwell and J.M. Williams Jr., J. Amer. Chem. Soc., 90, 435 (1968).

95.a. Alex Nickon and N.H. Werstiuk, ibid., 89, 3914 (1967).

b. Alex Nickon and N.N. Werstiuk, ibid., 89, 3915 (1967).

c. Alex Nickon and N.N. Werstiuk, ibid., 89, 3917 (1967).

96.a. F.G. Bordwell, Burce B. Jarvis and P.W.R. Corfield, ibid., 90, 5298 (1968).

b. F.G. Bordwell, E. Doomes and P.W.R. Corfield, ibid., 92, 2581 (1970).

97. F.G. Bordwell, Acc. Chem. Res., 3, 281 (1970).

98. E.W. Warnhoff and W.T. Tai, unpublished work.

99. J.P. Schaefer in Org. Reaction, Vol. 15, John Wiley and Sons, Inc., New York, 1967.

100. O.H. Wheeler and I. Lerner, J. Amer. Chem. Soc., 78, 63 (1956).

101.a. W. Nagata, I. Kikawa and M. Fujimota, Chem. and Pharm. Bull., 11, 226 (1963).

b. W.L. Meyer and J.F. Wolfe, J. Org. Chem., 29, 170 (1964).

102.a. W.L. Meyer and N.G. Schnautz, ibid., 27, 2011 (1962).

b. O.R. Rodig and N.J. Johnston, ibid., 34, 1942 (1969).

103. A.G. Anderson Jr., and J.A. Nelson, J. Amer. Chem. Soc., 73, 232 (1951).

104. L. Throop and L. Tokes, ibid., 89, 4789 (1967).

105. G.L. Buchanan, A.F. Cameron and G. Jamieson, Chem. Comm., 1145 (1969).

106. C.W. Deutsche, D.A. Lightner, R.W. Woody and A. Moscowitz,

Ann. Rev. Phys. Chem., 20, 407 (1969).

107. J.E. Gordon, J. Org. Chem., 35, 2722 (1970).

108. Dang Quoc Quan, Compt. Rend., 261, 2374 (1965).

109. W.P. Campbell and G.C. Harris, J. Amer. Chem. Soc., 63, 2721 (1941).

110. R.E. Lyle and R.A. Covey, ibid., 75, 4973 (1953).

111. P.A. Plattner and J. Hulstkamp, Helv., 27, 211 (1944).

112. E.G. Commins and J.E. Page, J. Chem. Soc., 3847 (1957).

113. F. Daniels and R.A. Alberty, Physical Chemistry, 2nd edition, John Wiley and Sons Inc., New York, 1961.

114. E.W. Warnhoff, J. Org. Chem., 27, 4587 (1962).

115. E.A. Braude, W.F. Forbes and E.A. Evans, J. Chem. Soc., 2202 (1953).

116. J. Hine, Physical Organic Chemistry, McGraw-Hill Book Company Inc., (1962).