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TITLE OF THESIS. I. Some Aspects of Radical Anion Chemistry. Dehalogenation of Alpha-Haloketones and Reductive Cyclization of Unsaturated Ketones

UNIVERSITY.. of Alberta, Edmonton, Alberta

DEGREE FOR WHICH THESIS WAS PRESENTED..... Ph.D.

YEAR THIS DEGREE GRANTED..... 1970... 1973 + elected June (73) convocation

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DATED... May 3 1973

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THE UNIVERSITY OF ALBERTA

I. SOME ASPECTS OF RADICAL ANION CHEMISTRY DEHALOGENATION OF ALPHA-HALOKETONES AND REDUCTIVE CYCLIZATION OF UNSATURATED KETONES
II. SYNTHESIS OF ALPHA-HALOKETONES

by

© LOUISELLE GINETTE ST-LAURENT

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING, 1973

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

I. SOME ASPECTS OF RADICAL ANION CHEMISTRY. DEHALOGENATION OF ALPHA-HALOKETONES AND REDUCTIVE CYCLIZATION OF UNSATURATED KETONES.
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submitted by LOUISELLE GINETTE ST-LAURENT in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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Date. May 1, 1973

A MES PARENTS

ABSTRACT

Aromatic radical anions, such as sodium naphthalene, were found to dehalogenate simple α-haloketones to the corresponding ketones. The ethylene ketals of these α-haloketones were also dehalogenated by these reagents. Sodium trimesitylboron was shown to be a more efficient reducing agent than sodium naphthalene under the conditions of investigation.

The cyclization of simple olefinic, acetylenic, and allenic ketones into five-membered cyclic tertiary alcohols was achieved by the use of radical anions. The success of these transformations was found to be highly dependent on the choice of the appropriate reagent. Reagents investigated were sodium biphenyl, sodium trimesitylboron, and lithium trimesitylboron.

α-Haloketones were found to be readily prepared by the acylation of bistetrahydropyranyl malonates with α-haloacid halides. The method appears to be mainly advantageous in the preparation of α-haloketones of the type $RCHXCOCH_2R'$. However, the acylation of a tetrahydropyranyl ester of a monocarboxylic acid with an α-haloacid chloride was found to yield a mixture of products.

ACKNOWLEDGEMENTS

The author wishes to thank Messrs R. Swindlehurst and G. Bigam and their staff for the recording of the infrared and nmr spectra, Dr. A. Hogg and staff for running the mass spectra, and Mrs. D. Mahlow and Mrs. A. Dunn for determining the microanalyses.

Many thanks are due to fellow coworkers for much help and useful discussion, and to Mr. F. Cedar for providing a most valuable sample of trimesitylboron.

The author is indebted to the National Research Council of Canada for the awarding of a Bursary and a Postgraduate Scholarship to enable this work to be accomplished.

Finally, the author would especially like to thank Dr. J. Hooz for much patient help and stimulating discussion, and for the degree of freedom allowed in the compilation of this work.

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PART I

SOME ASPECTS OF THE CHEMISTRY OF RADICAL ANIONS

GENERAL INTRODUCTION

The transfer of one electron to a neutral molecule generates a negatively charged species possessing an odd number of electrons, called a radical anion.[1,2]

$$XY + e^- \longrightarrow XY^{\cdot -} \qquad (1)$$

The electron is usually transferred to the acceptor molecule either by chemical methods (from an alkali metal or an alkaline earth metal or an anion) or by electrolytic or photolytic reduction.[3]

Because of their dual nature (anionic and radical), radical anions are intermediates of very high reactivity in a variety of organic reactions.[4] A large number of organic compounds exhibit this capability to receive an electron with the formation of radical anions. Some examples are: aromatic hydrocarbons,[1,2,5,6] heterocyclic compounds,[3,5,7] systems containing conjugated bonds and electron withdrawing groups, such as aryl ketones,[5] enones,[8] diones[4,5] and triones,[4] nitro compounds [3,4] or tetracyanoethylene,[3] and systems containing other elements as boron,[9,10] silicon,[3,4] nitrogen,[3,4,11] phosphorus[3,4,11]

and transition metals.[3,5]

These organic radical anions are readily detected, identified, and characterised by visible and ultraviolet spectroscopy, and polarographic and electron spin resonance (ESR) methods.[1,3,5,6] Their preparation and their physical and chemical properties have been extensively reviewed by several authors.[1-6] However, within the framework of the problems investigated in the present study, we are mainly concerned with some of the chemistry of those radical anions originating from aromatic hydrocarbons. Special attention will be paid to their synthetic utility as reducing agents, either by initiating the cleavage of bonds or the formation of new bonds in a synthetically useful manner.

Of all the methods available for the formation of aromatic radical anions,[12] the most developed approach is the chemical reduction with free metals.

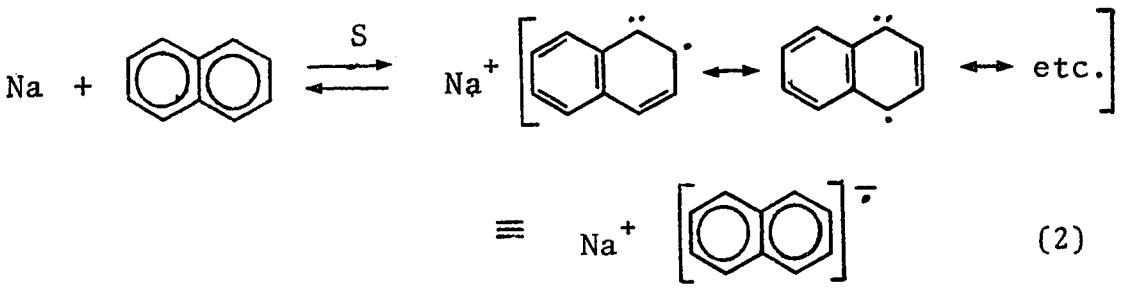
For over one hundred years, it has been known that aromatic hydrocarbons may react with alkali metals. As early as 1867, Berthelot obtained a black addition product on fusing metallic potassium with naphthalene in a closed tube.[13] But the first real comprehension of this phenomenon is attributed to Schlenk and his colleagues who studied extensively the formation and reactions of adducts from alkali metals and unsaturated hydrocarbons.[14,15]

Because of the early emphasis on the "radical"

nature of these adducts, the first structures proposed distracted the attention of earlier workers from the ionic properties of these compounds.[15,16]

In 1930, Scott and coworkers [17] obtained dark green solutions from the interaction of sodium metal with naphthalene in some specific solvents such as dimethoxyethane or dimethyl ether. Moreover, this reaction was considered a reversible process, since on addition of benzene and removal of the solvent, naphthalene and finely divided sodium were regenerated.

These observations were later followed by several detailed studies which revealed that many polycyclic aromatic hydrocarbons (for example, biphenyl, phenanthrene, anthracene, etc.) form stable, highly coloured solutions with alkali metals in ether-type solvents.[1,2,6] These solutions are conducting and paramagnetic. Thus, in terms of the modern concept of electron transfer reactions, they have been formulated as consisting of ionic substances--alkali metal cations and aromatic radical anions [1,2,6] as illustrated for sodium naphthalene.

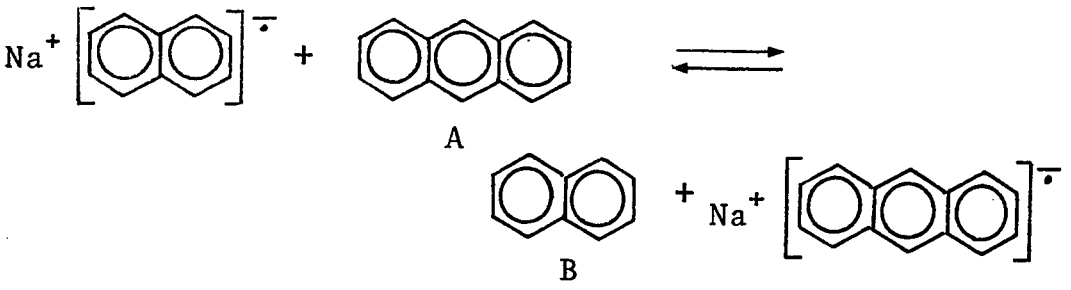


(2)

where S = ether-type solvent

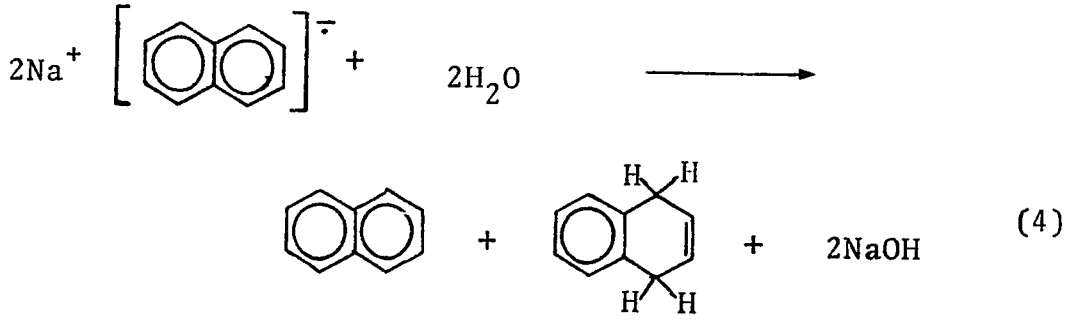
These alkali metal-aromatic hydrocarbon complex solutions are very reactive towards a wide variety of substances, such as oxygen, water,[18-20] carbon monoxide,[21] carbon dioxide, sulphur dioxide,[22] alkyl halides,[23-26] and many other "electrophilic" organic compounds.[27-39]

Sodium naphthalene can undergo two types of reaction: 1) an electron transfer reaction as illustrated (eq. 3) for the formation of the anthracene radical anion (the position of the equilibrium depending on the relative electron affinities of hydrocarbons A and B.)



(3)

2) a "nucleophilic" reaction, as in the reaction of sodium naphthalene acting as a base towards water to form dihydronaphthalene.[18,19] (eq. 4)



(4)

This duality of reactivity of sodium naphthalene has been the subject of recent studies by Bank and co-workers. [19,20] These investigators have attempted to correlate the competition between electron transfer and proton abstraction with the states of ion-pairing in a variety of solvents or combination of solvents. The importance of solvation and ion-pairing in radical anion chemistry is well documented.[40,41]

Kinetic studies have shown that for electron transfer from sodium naphthalene, the reactivity order is "free" > "loose" > "contact-ion" pairs, whereas for proton transfer to sodium naphthalene by water, the order is exactly the reverse, "contact" ions > "loose" > "free" ions.[19]

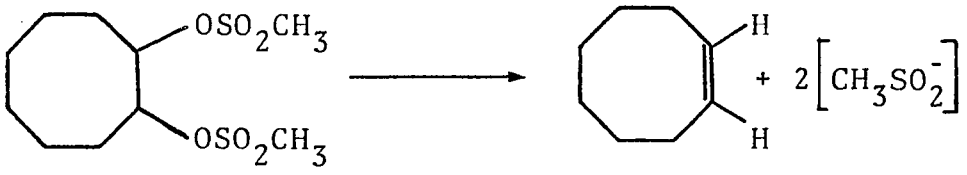
In the reaction of sodium naphthalene with an organic substrate which offers both the possibility of electron transfer and proton abstraction, such as phenylacetonitrile, the conclusion reached was that electron transfer can be varied from a minor process to a major process by solvent variations.[20] For example, a solvent such as tetrahydrofuran which favours the formation of tight ion-pairs favours the "nucleophilic" pathway, whereas a solvent such as dimethoxyethane which tends to loosen ion-pairs, favours the electron-transfer pathway.[19,20]

The versatility of aromatic radical anions as

electron transfer reagents is evident by the many transformations which they can accomplish. For example, sodium naphthalene and sodium biphenyl cleave sulphonamides to the corresponding amines at room temperature[27,28] (eq. 5), sulphonates to alcohols [29,30] (eq. 6), and vicinal dimesylates undergo reductive elimination to the alkenes [31] (eq. 7).

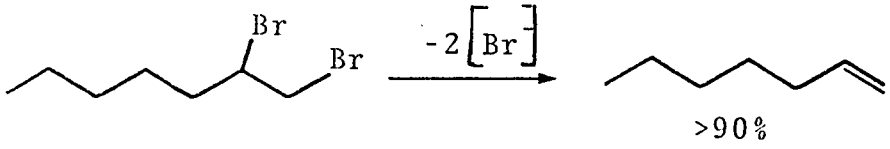
(5)

(6)



(7)

Organic halides are also easily reduced (alkyl,[23-26] vinyl,[32] and phenyl[23,33-35]); vicinal dibromides undergo elimination to the alkene [36,37] (eq. 8), and geminal dihalides give rise to carbenes.[38] Trifluoroethyl ethers



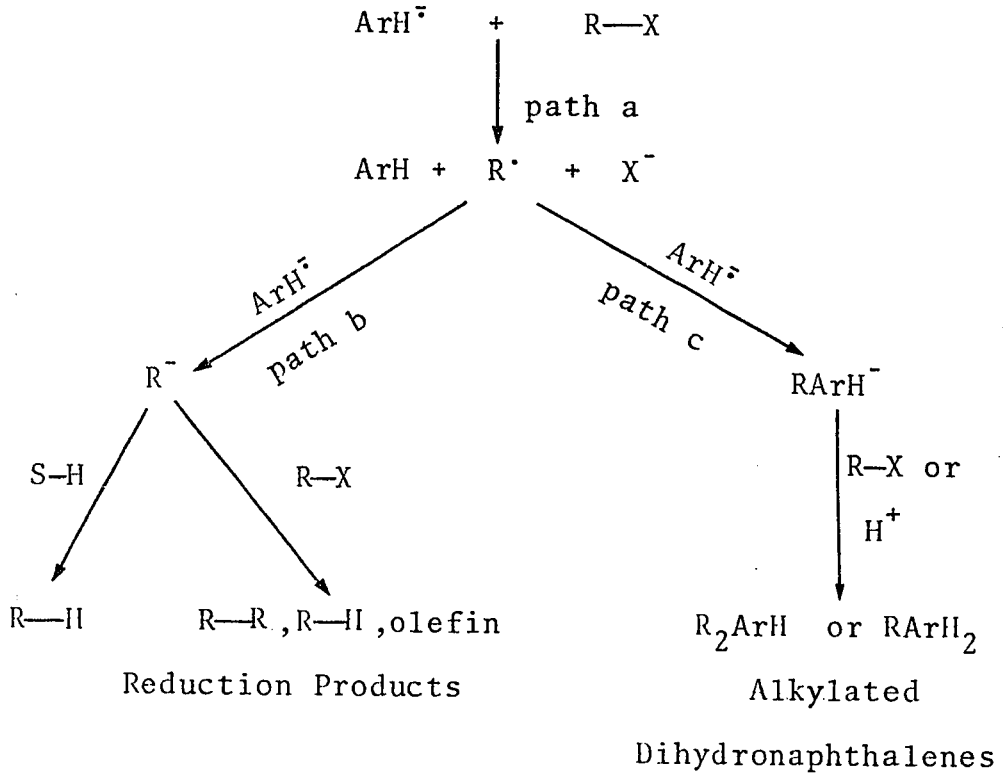
(8)

are converted to the corresponding alcohols.[39] (eq. 9)

$$RO{-}CH_2{-}CF_3 \xrightarrow{-[F^-]} RO{-}H + [CH_2{=}CF_2] \quad (9)$$

Even hydrogen [42,43] and nitrogen [44] are reduced by sodium naphthalene to hydride and ammonia respectively.

The reaction of alkyl halides with sodium naphthalene has been studied intensively,[24-26] and is believed to occur according to the following general mechanism, where $ArH^{\cdot-}$ refers to the aromatic radical anion (the cation is omitted for convenience throughout).



The most important feature of this mechanism is the partitioning of the reaction into paths b and c after the first electron transfer and the loss of the halogen has taken place. When the intermediate radical has a greater electronegativity than simple alkyl radical, as in the reduction of vinyl[32] or phenyl[33-35] halides, or has an electronegative substituent on the β-carbon (as is the case in the reduction of vicinal dihalides[36,37] or dimesylates,[31] and trifluoroethyl ethers[39]), the reaction is channelled almost completely through path b.

Finally, the easy preparation of alkali metal-aromatic hydrocarbon complexes as solutions in tetrahydrofuran or dimethoxyethane,[17] their high stability for long periods of time at room temperature under an inert atmosphere,[29] and most important, their high reactivity as reducing solutions, make them attractive reagents in organic synthesis.

In the following pages, two aspects of the chemistry of aromatic radical anions has been investigated: a) their reaction as reducing agents to induce the reductive dehalogenation of α-halo ketones as a possible route to the corresponding ketones (Chapter I), and b) to initiate carbon-carbon bond formation in a reductive cyclization of unsaturated ketones (Chapter II).

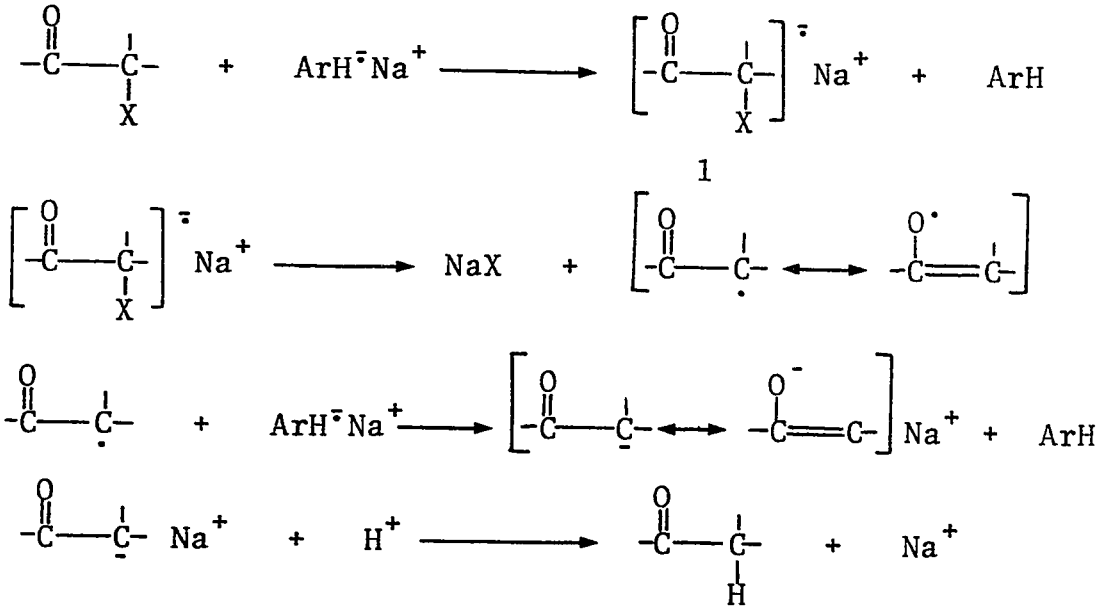
CHAPTER I

THE REDUCTIVE DEHALOGENATION OF α-HALOKETONES AND THEIR CORRESPONDING ETHYLENE KETALS

INTRODUCTION

The observation that α-halo carbonyl compounds are normally reduced at potentials significantly less negative than the potential required for either the corresponding ketone or the halide [45-47] led to the expectation that electron transfer from an aromatic radical anion to an α-haloketone would be a relatively facile process. (Scheme I)

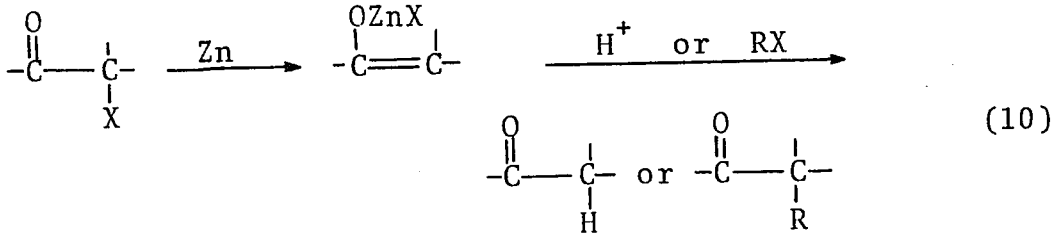
Scheme I



Loss of halide from a transient haloketo radical anion (1), followed by subsequent transfer of a second electron was expected to be a favourable pathway since it would lead to a resonance stabilized carbanion.

In fact, reduction of α-haloketones to their corresponding dehalogenated ketones by electron transfer from a metal has long been known.[48]

The most commonly used method for the reduction of an α-haloketone to the corresponding dehalogenated ketone is the action of zinc metal in acetic acid.[49,50] The reaction presumably occurs via the formation of a zinc enolate which may be "trapped" by alkylation, when the reaction is performed in a non-protic solvent.[51]

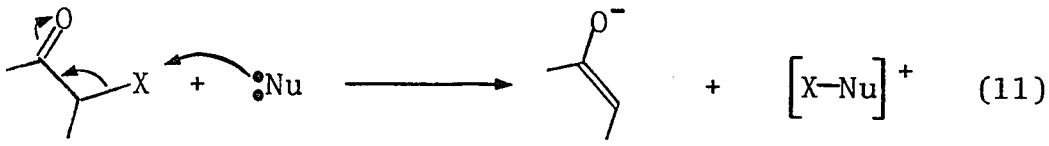


(10)

The use of magnesium as a reductive agent, on the other hand, affords a mixture of products due to subsequent reaction of the magnesium enolate with starting α-haloketone.[48a] This method is thus of little synthetic utility.

Removal of the α-halogen can also be accomplished by the action of highly polarizable nucleophiles. In that process, it has been suggested that the halogen

is lost as a "positive" species.[52] (eq. 11) Treatment



(11)

of an α-haloketone with triphenylphosphine or a trialkylphosphite in a protic solvent has been shown by Borowitz and coworkers to yield the dehalogenated ketone.[48b]

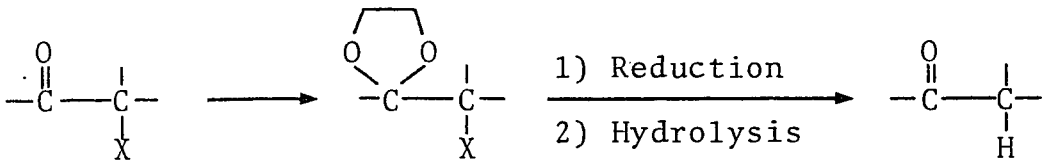
A more recent method developed by Townsend and Spencer effects the dehalogenation by the use of lithium iodide and boron trifluoride etherate in essentially quantitative yields.[53] The reaction is thought to take place via the intermediacy of an enol fluoroborate.

Amines are also good polarizable nucleophiles. The formation of the dehalogenated ketone in the dehydrohalogenation of α-haloketones with substituted pyridines (such as picoline, collidine or lutidine) is always considered an undesired side-reaction.[54] Hydrazines, on the other hand, react with α-haloketones to give deoxydehalogenation to the alkene and/or dehydrohalogenation products.[48c]

Thiolate anion also reduces α-haloketones to the parent carbonyl compounds, but in variable yields.[55]

In contrast to these methods, removal of the α-halogen by such powerful electrophiles as $AgSbF_6$ has been achieved. The process is thought to take place via the formation of an α-oxocarbonium ion intermediate.[56]

During the course of this study of the reductive dehalogenation of α-haloketones by aromatic radical anions, an alternate approach via the α-haloketals, as illustrated in equation 12, was also briefly investigated.

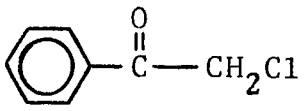


(12)

RESULTS AND DISCUSSION

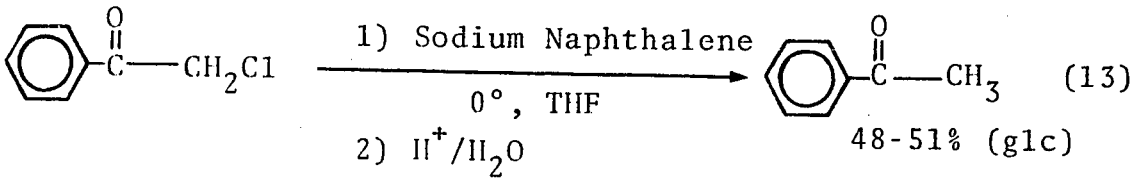
Dehalogenation of α-Haloketones

Phenacyl chloride (2) was chosen as a simple model compound to study the reductive dehalogenation since both the reactant and expected product (acetophenone) are commercially available materials.



2

Preliminary experiments using solutions of sodium naphthalene in tetrahydrofuran at 0°C, to which a solution of 2 in tetrahydrofuran was added during periods ranging from 2 to 30 minutes, showed that at least two molar equivalents of the radical anion was necessary for complete utilization of the α-haloketone. After quenching with dilute acid, complex mixtures were obtained of which the major component (other than naphthalene) was acetophenone. (eq. 13) However, when a large excess of



(13)

sodium naphthalene (6 equiv.) was used, a low yield of acetophenone was obtained (ca. 10%) along with unreacted substrate.

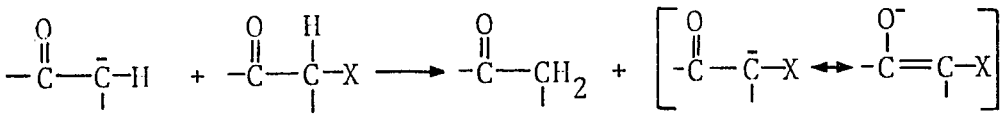
An investigation of the reaction conditions

necessary for optimum yields of ketone was undertaken. Inverse addition, that is, addition of sodium naphthalene to a solution of phenacyl chloride at 0°C, resulted in the utilization of less than two equivalents of sodium naphthalene. No α-haloketone was detected after hydrolysis by dilute acid.

Conditions approximating high dilution, that is, slow, dropwise addition of the α-haloketone to a dilute solution of sodium naphthalene (ca. 0.05M), gave complete utilization of phenacyl chloride, but with no improvement in the formation of acetophenone (Table I, entries 1-3). Table I reports the results achieved in this manner using a variety of α-haloketones. In all cases, except for the alicyclic chloroketones, complete utilization of the substrate was observed.

The fact that some α-haloketone was not dehalogenated by sodium naphthalene in spite of the long reaction times reported in table I and of the large excess of reducing agent used with phenacyl chloride, indicates that the substrate had been "inactivated" in some way.

From the original scheme, if an enolate is formed as a direct consequence of dehalogenation, then it is conceivable that some α-halo enolate is formed by abstraction of the α-hydrogen, as follows:



(14)

TABLE I

Dehalogenation of α-Haloketones with Sodium Naphthalene in Tetrahydrofuran

	Substrate	Scale (mmole)	Molar Ratio[a]	Time[b] (hr)	Temp (°C)	Product	Yield[c] (%)
1.	Phenacyl chloride	2.5	1:3.5	2.5	0	Acetophenone	30
2.	"	2.5	1:3.5	4.0	0	"	44
3.	"	2.5	1:3.5	4.0	-78	"	38
4.	Phenacyl bromide	2.5	1:3.5	4.0	0	"	30
5.	α-Bromopropiophenone	5.0	1:4.0	8.0	0	Propiophenone	77
6.	2-Chlorocyclohexanone	5.0	1:4.0	8.0	0	Cyclohexanone	39[d]
7.	"	5.0	1:4.0	6.0	0	"	57[d]
8.	2-Chlorocyclopentanone	5.0	1:4.0	7.5	0	Cyclopentanone	17[d]

(a) Substrate (α-haloketone):Sodium naphthalene

(b) Time of addition of substrate plus an additional stirring period of 0.5 hr

(c) Yields estimated by glc analysis

(d) Unreacted substrate detected by glc after hydrolysis

The α-hydrogen of an α-haloketone is relatively more acidic than that of the corresponding non-halogenated ketone by at least 2 to 3 pKa units [57,58] and is also more acidic than the α'-hydrogen.[59] The resulting α-halo enolate would be expected to be less reactive towards further reduction by electron transfer, since it is already a negatively charged species.

The α-halo enolate could also result from the "basic" character of sodium naphthalene. Protic compounds such as water[18,19] and even amines (p-toluidine at room temperature [28]) are known to rapidly protonate sodium naphthalene (eq. 2). Considering the gross difference in acidity between water and p-toluidine (10 pKa units[57]) it is fair to say that reaction between sodium naphthalene acting as a base and the α-haloketone acting as a proton source might be responsible for some of the deactivation of α-haloketones towards reduction.

An attempt to decrease the basic character of the reducing agent was then undertaken. First, dimethoxyethane was substituted for tetrahydrofuran as the reaction medium. Closson and coworkers [27,28] had observed at this time that dimethoxyethane appeared to be somewhat advantageous due to the greater ease of formation of the radical anion in this solvent, and, in the sulphonamide cleavage process (eq. 5), afforded yields which were generally somewhat higher than in tetrahydrofuran.

The reaction was carried out in a manner analogous to the initial exploratory experiments (eq. 13), since long addition periods and dilution appeared to be of no practical advantage. Therefore, fast addition (2-5 min) of phenacyl chloride to three equivalents of sodium naphthalene in dimethoxyethane, afforded, after an additional 5-10 minute stirring period, a 53% yield of acetophenone.

Closson and coworkers had also observed that proton abstraction from the arenesulphonamide of primary amines was suppressed at lower temperatures, and that electron transfer was considerably faster than acid-base reactions in changing the electron transfer reagent from sodium anthracene, to sodium naphthalene to sodium biphenyl.[28] Since α-haloketones are presumably weaker acids than primary sulphonamides,[57] the use of lower reaction temperature and the action of sodium biphenyl and sodium anthracene were briefly investigated. These results are reported in Table II.

Although, as previously discussed, it has been reported that dimethoxyethane affords a solvated sodium naphthalene ion-pair system which favours the electron transfer pathway to a greater extent than tetrahydrofuran,[19,20] only a slight advantage is gained by the use of that solvent in the reduction of α-haloketones. Moreover the reaction appeared to be highly sensitive to the stoichiometry of the reactants.

TABLE II

Dehalogenation of α-Haloketones with Aromatic Radical Anions in Dimethoxyethane

	Substrate (A)	Reagent[a] (B)	Molar Ratio A : B	Temp (°C)	Product	Yield[b] (%)	% Unreacted Substrate[b]
1.	Phenacyl chloride	$NaC_{10}H_8$	1:3.0	0	Acetophenone	53[c]	0
2.	Phenacyl bromide	$NaC_{10}H_8$	1:3.0	0	"	19[d]	0
3.	"	$NaC_{10}H_8$	1:2.1	-35	"	26[d]	0
4.	"	$NaC_{10}H_8$	1:2.2	-70	"	19	0
5.	"	$NaC_{12}H_{10}$	1:2.2	0	"	21-25	0
6.	"	$NaC_{12}H_{10}$	1:2.2	-35	"	28	0
7.	"	$NaC_{14}H_{10}$	1:2.0	0	"	<10	-
8.	α-Bromopropiophenone	$NaC_{10}H_8$	1:3.0	0	Propiophenone	64	0
9.	α-Bromoisobutyrophenone	$NaC_{10}H_8$	1:3.0	0	Isobutyrophenone	66	0
10.	"	$NaC_{10}H_8$	1:2.0-2.2	0	"	100[e]	0
11.	Adamantyl bromomethyl ketone	$NaC_{10}H_8$	1:3.0	0	Adamantyl methyl ketone	76	0
12.	2-Chlorocyclohexanone	$NaC_{10}H_8$	1:3.0	0	Cyclohexanone	41	18
13.	"	$NaC_{10}H_8$	1:2.3	0	"	48-54	30
14.[f]	"	$NaC_{10}H_8$	1:4.0	0	"	37[f]	29[f]
15.	2-Chlorocyclopentanone	$NaC_{10}H_8$	1:3.0	0	Cyclopentanone	6	41
16.	"	$NaC_{10}H_8$	1:2.3	0	"	24	19
17.	"	$NaC_{10}H_8$	1:2.3	0	"	8	38
18.	"	$NaC_{10}H_8$	1:2.1	-70	"	17	28
19.	"	$NaC_{12}H_{10}$	1:2.1	0	"	10-14	30
20.	"	$NaC_{12}H_{10}$	1:2.1	-70	"	17	28

(a) $NaC_{10}H_8$ = Sodium naphthalene; $NaC_{12}H_{10}$ = Sodium biphenyl; $NaC_{14}H_{10}$ = Sodium anthracene

(b) Yields estimated by glc analysis

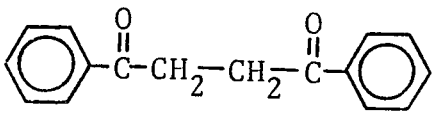
(c) 1,4-Diphenyl-1,4-butadione was formed in 4% yield (glc)

(d) 1,4-Diphenyl-1,4-butadione was formed in 2.5% yield (glc)

(e) Isolated in 79% yield

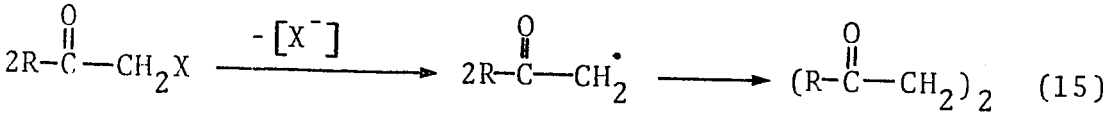
(f) Tetrahydrofuran was used as solvent

In an attempt to shed further light on the fate of the substrate, the mixtures obtained from the experiments in which low ketone formation was observed were examined more closely. They were usually found to be highly complex and efforts at identifying the many components proved fruitless. By chromatographic techniques only naphthalene, reduced naphthalenes, and the dehalogenated ketone could be readily separated. In the case of the reduction of α-chloro- and α-bromoacetophenone, a dimer (3) was isolated and found to be formed to an



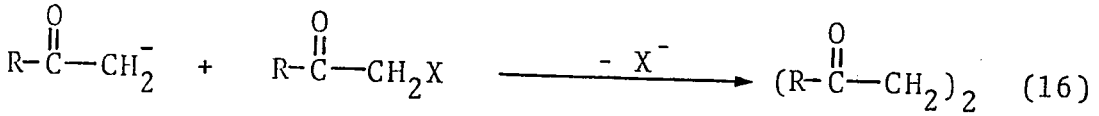
3

extent of 4% for the chloro compound and 2.5% for the bromo ketone. This compound could probably have arisen, either by radical coupling (eq. 15), or by alkylation of



(15)

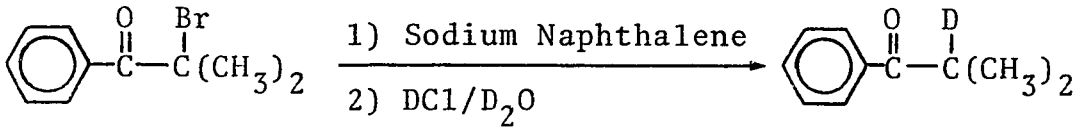
an enolate by the substrate (eq. 16).



(16)

To gain some insight into the mechanism of the dehalogenation, the mixture obtained from the addition of α-bromoisobutyrophenone (4) to 2.0-2.1 equivalents of sodium naphthalene was quenched with deuterochloric acid

in deuterium oxide (DCl/D_2O), expecting to introduce deuterium at the α-position as indicated in equation 17.



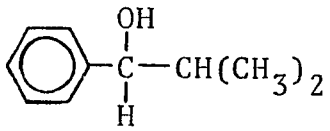
4 (17)

Surprisingly, nuclear magnetic resonance (nmr) and mass spectral analysis showed at the most 2.3% deuterium incorporation in the isolated ketone. Careful blank experiments were run to ensure that no deuterium could be lost or introduced during the isolation procedure.

Therefore, it is clear that the hydrogen is introduced in the molecule, at least for that particular substrate, *before* quenching with an external proton source. Furthermore, addition of isobutyrophenone to an excess of sodium naphthalene in dimethoxyethane at 0°C showed that the ketone was partially consumed. This could therefore account for the decreased yield of isobutyrophenone when an excess (one equiv.) of sodium naphthalene is present (Table II), since, if the ketone is formed in situ, it is destroyed (at least partially) by this excess.

When the isobutyrophenone-sodium naphthalene reaction is quenched with DCl/D_2O, the recovered ketone contained variable amounts of deuterium (26-48% by mass spectral analysis). Furthermore, a product of this reaction is the reduced compound, the alcohol 5, which has incorporated

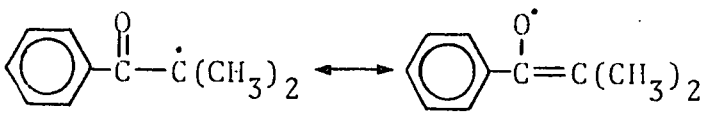
up to 90% deuterium (by nmr) on the carbon bearing the oxygen. This alcohol probably results via the interme-



5

diacy of a ketyl. (Electron transfer by the naphthalene radical anion to an aromatic ketone is known to be a favourable process according to polarographic data.[47])

The initial hypothesis, that a carbanion (as enolate) is formed as the immediate product of dehalogenation (Scheme 1) probably does not hold in the case of the reduction of α-bromoisobutyrophenone. At present, we can only speculate as to the source of hydrogen. A likely source in the reaction mixture before the hydrolysis step is the solvent. Abstraction of a proton by an enolate from dimethoxyethane (at low temperatures) is rather improbable since this solvent is generally used as reaction medium for the formation of enolates from ketones by strong bases.[60] On the other hand, the introduction of the α-hydrogen could occur by hydrogen atom abstraction by the α-keto radical (or its resonance structure, the vinyloxy radical) (6). Ethers are usually considered to be



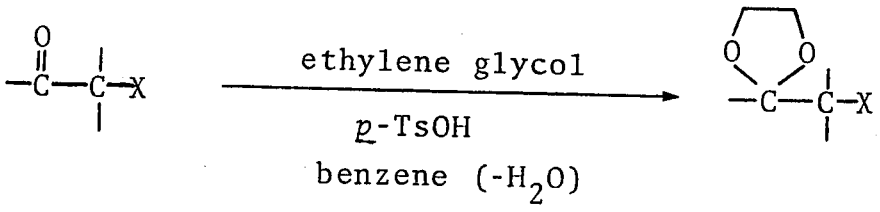
6

poor hydrogen atom donors, at least according to the classification by Bridger and Russell,[61] unless the radical generated in this manner, (in this case 6) is a particularly "hot" radical.

Dehalogenation of α-Haloketals

As an alternative approach to the reduction of α-haloketones by aromatic radical anions, the reduction of α-haloketals was briefly investigated.

The ethylene ketal of 2-chlorocyclohexanone, 2-chlorocyclopentanone, and phenacyl bromide were prepared by acid-catalyzed ketalization and azeotropic removal of water (eq. 18).

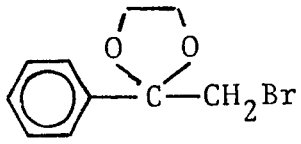


(18)

Addition of the ethylene ketal of 2-chlorocyclohexanone to 2 equivalents of sodium naphthalene in dimethoxyethane at 0°C, followed by acid hydrolysis, resulted in the formation of cyclohexanone in 97% yield. Similarly, the ethylene ketal of 2-chlorocyclopentanone afforded 72% cyclopentanone. The reduction could also be performed directly on the crude reaction product from the ketalization experiment affording an overall yield of 70% for cyclopentanone.

When the same process was repeated with the ketal

of phenacyl bromide and 2.2 equivalents of sodium naphthalene, a 46% overall yield of acetophenone was obtained. The radical anion was completely consumed, and some unreacted substrate was present in the mixture after hydrolysis. Therefore, a closer analysis of the reaction was undertaken. On addition of the bromoketal 7 to sodium



7

naphthalene (5 equivalents) in dimethoxyethane, only traces of acetophenone appeared on glc analysis of the products. Furthermore, the presence of styrene was inferred by glc peak enhancement. On inverse addition of sodium naphthalene to 7, the mixture underwent a series of colour changes as indicated below:

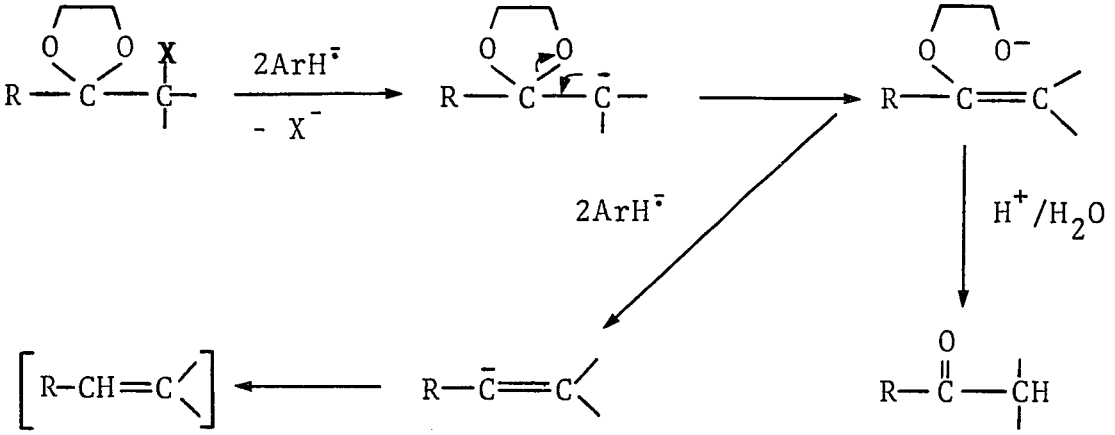
Sodium Naphthalene added (equiv.)	Colour	Acetophenone % (glc)	Unreacted 7 % (glc)
0 to 1	Yellow		
1.2	Green	63	31
1.9	Dark blue	83	<20
2.4	Mauve	96	0
2.7	Brown	74	0
4.4	Brown-green	16	0

The reaction was repeated, and to the crude product

from the ketalization reaction of phenacyl bromide, sodium naphthalene was added until a mauve colour appeared. Acetophenone was isolated in a 78% overall yield from phenacyl bromide.

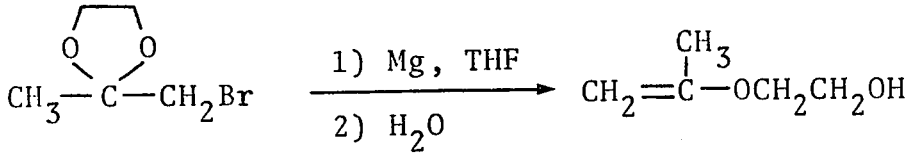
The following mechanism is proposed (Scheme II) for the reduction of an α-haloketal, involving cleavage of a carbon-oxygen bond of the ketal group via a β-elimination.

Scheme II



The same type of β-elimination has been suggested by S.D. Sargent [39] in the cleavage of trifluoroethyl ethers by sodium naphthalene and by Closson and coworkers in the conversion of vicinal dimesylates to alkenes[31]. Elimination also occurs in the reduction of organic halides in which a substituent (halogen, OH, OR, OCOR) is present at the β-position which can be lost as a stable anion.[62,63] Furthermore, Feugeas [63] has studied the reaction of magnesium with halodioxolanes and observed opening of the dioxolane ring, yielding enol ethers as illustrated in the

following example. (eq. 19)



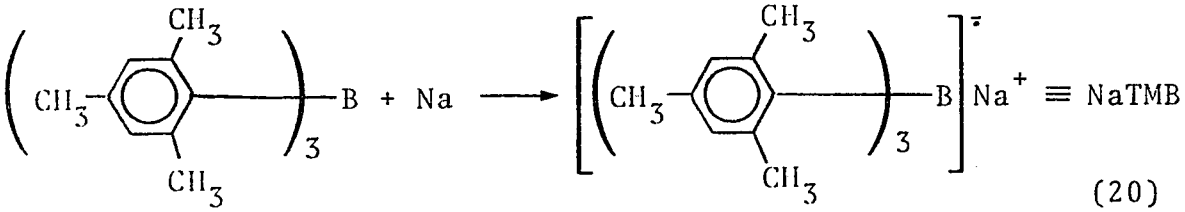
(19)

In scheme II, the intermediate vinyl ether is prone to further reductive cleavage, at a rate which is faster for R = phenyl than for R = alkyl. Benzyl ethers are known to undergo facile carbon-oxygen fission under conditions of dissolving metal reductions.[64-66]

Reduction of α-Haloketones with Sodium Trimesitylboron

In an attempt to circumvent the subsequent side-reactions after initial electron transfer to an α-haloketone, and to avoid the possibility of the radical anion acting as a base, a more selective electron transfer reagent was briefly investigated.

Trimesitylboron (TMB) reacts readily with sodium and other alkali metals in ether-type solvents, forming blue paramagnetic solutions which remain unchanged for extended periods of time.[67] (eq. 20) The bulky mesityl group of

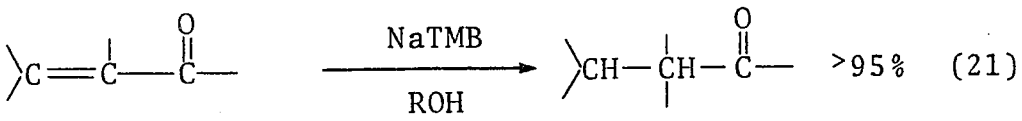


(20)

trimesitylboron serves to impede dimerization of the radical anion as well as inhibiting formation of

quaternary boron compounds [9,10] or rapid reaction with protic substances.[68]

Darling and coworkers [68] have realized the reduction of enones with this reagent in the presence of proton sources. (eq. 21) The ketone formed in the reaction



(21)

was found to be relatively unreactive towards further reduction by the trimesitylboron radical anion as shown by the high yield of ketone obtained.

2-Chlorocyclohexanone was converted quantitatively to cyclohexanone upon its slow addition (in dimethoxyethane solution) to 3 equivalents of sodium trimesitylboron in dimethoxyethane at 0 to -5°. In a similar way, 2-chlorocyclopentanone afforded cyclopentanone in a high yield (86%). Exploratory experiments showed that the excess reagent and low temperature were necessary for maximum conversion, especially for 2-chlorocyclopentanone.

In conclusion, the dehalogenation of an α-haloketone by radical anions to its corresponding ketone has been shown to be a facile process. Although radical anions from aromatic hydrocarbons proved to be species of very high reactivity for this transformation and gave rise to several by-products, by the use of a system of

attenuated reactivity (the sodium trimesitylboron radical ion system) the reduction has been accomplished successfully.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded using a Perkin-Elmer 337G, Perkin-Elmer 421G or Unicam SP 200 Infrared Spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 or HR-100 Spectrometer. Unless otherwise stated, carbon tetrachloride (CCl_4) was employed as the solvent with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ values relative to TMS = 0. The following abbreviations are used in the text: s = singlet, d = doublet, sep = septet, and m = multiplet.

Mass spectra were recorded on an AEI Model MS-2 or Model MS-9 spectrometer.

Gas liquid chromatography (glc) was performed using an Aerograph A-90-P3 and Varian Aerograph Series 1200 gas chromatographs. The following columns were used: Column A: 5'/1/8" 10% SE-52 on Chromosorb G-DMCS; Column B: 5'/1/8" 15% SE-30 on Chromosorb W; Column C: 5'/1/8" 10% Squalane on Chromosorb W; Column D: 10'/1/8" 10% Apiezon L on Firebrick; Column E: 5'/1/8" 10% Carbowax 20M on Chromosorb W; Column F: 10'/1/8" 10% NPGSE on Chromosorb W; Column G: 5'/1/8" 10% Carbowax 6000 on Chromosorb W.

All products were isolated and identified by comparison (physical properties and spectroscopic behaviour) with commercially available samples.

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Refractive indices were measured on a Bausch and Lomb Abbé-3L Refractometer.

All reactions were carried out using oxygen-free nitrogen.[69]

Preparation of Aromatic Radical Anion Solutions

Stock solutions of sodium naphthalene (0.1 - 0.4M) were prepared by stirring (with a glass-covered magnetic bar) sodium pellets (1/16" to 1/4") with 1.1 to 3.0 molar equivalents of naphthalene in dry tetrahydrofuran or dimethoxyethane, in a sealed system under an atmosphere of nitrogen at room temperature (25°-27°). Formation of the radical anion appeared to be sensitive to traces of oxygen or other impurities and the time required for complete reaction of the sodium under these conditions was quite variable. The active sodium content was determined by titration of 10 ml aliquots with 1.0N solution of absolute ethanol in benzene, to the disappearance of the green colour.[70]

Solutions of sodium biphenyl and sodium anthracene were prepared in a similar manner.

Preparation of α-Bromoisobutyrophenone.[71]

Addition of bromine to 15 g (0.1 mole) of isobutyrophenone in chloroform at 25° until the colour of bromine persisted, afforded upon distillation 19 g (86%) of α-bromoisobutyrophenone as a colourless liquid, bp 120-120.5°(7 mm) [lit.[72a] 120-130°(12 mm)].

Reaction between Phenacyl Chloride and Sodium Naphthalene in Tetrahydrofuran.

A solution of phenacyl chloride (1.7 g, 7.8 mmole) in 20 ml of tetrahydrofuran was added dropwise during 30 minutes to 3 molar equivalents of sodium naphthalene (0.1M) at 0°. After stirring for an additional 15 minutes, the dark green reaction mixture was poured over ice-cold dilute hydrochloric acid, saturated with sodium chloride, and extracted with *n*-pentane. The organic phase was washed with saturated sodium bicarbonate solution, then with brine, and dried (Na_2SO_4). After partial removal of the solvent, glc analysis (Column A, 110°) of the concentrate indicated a 51% yield of acetophenone.

The reaction was repeated. An addition period of phenacyl chloride of 2 to 5 minutes, followed by stirring for another 5 minutes, afforded acetophenone in a 48% yield by glc (Column A, 110°).

In the same way, addition during 5 minutes to 6 molar equivalents of sodium naphthalene, followed, after

a 5 minute stirring period, by work-up as described previously (ice-cold dilute hydrochloric acid, and ether extraction) gave acetophenone in a 11% yield (glc; Column A, 110°). The presence of unreacted phenacyl chloride was detected by glc.

Inverse addition: A solution of phenacyl chloride (0.39 g, 2.5 mmole) in 50 ml of tetrahydrofuran was cooled to 0° . A solution of sodium naphthalene (0.23M) was added dropwise. After the addition of 15 ml (1.4 equiv.) the green colour persisted. The mixture was stirred for 5 minutes during which time the temperature was allowed to rise to 25°. The colour changed to dark brown; 4 ml of sodium naphthalene solution was added and after 20 minutes, the reaction was stopped by pouring into an equal volume of ice-cold dilute hydrochloric acid. The resulting mixture was extracted as described previously. The yield of acetophenone was estimated by glc as 21% (Column A, 110°).

General Procedure for the Reaction between α-Haloketones and Sodium Naphthalene under dilute Conditions (refer to Table I for Substrates)

A tetrahydrofuran solution of α-haloketone (0.01 - 0.03M) was added dropwise to a 0.04 - 0.06M solution of sodium naphthalene (3 to 4 equiv.) at 0°. After complete addition of the substrate (time indicated in Table I),

the dark green solution was stirred for an additional 30 minutes, then poured into ice-cold dilute hydrochloric acid. After a work-up analogous to that previously described (ether extraction), the concentrate was analysed by glc. Isolation was performed by chromatography over silica gel using Skelly B and subsequently chloroform as eluants. The products were identified by comparison with commercially available samples. The yields of ketones reported in Table I were estimated by glc (Acetophenone: Column A, 110°; propiophenone: Column A, 145°; cyclohexanone: Column A, 75°; cyclopentanone: Column C, 65°). Unreacted 2-chlorocyclohexanone (Table I, entries 6 and 7) was detected by glc (Column A, 130°). Unreacted 2-chlorocyclopentanone (Table I, entry 8) was detected by glc (Column A, 120°).

General Procedure for Reaction of α-Haloketones with Aromatic Radical Anion in Dimethoxyethane (Table II). Reaction between Phenacyl Chloride and Sodium Naphthalene.

A solution of phenacyl chloride (3.1 g, 200 mmole) in 50 ml of dimethoxyethane was added dropwise (ca. 5-10 minutes) to a 0.1M solution of sodium naphthalene (3 molar equivalents) at 0°. After stirring for an additional 10 minutes, the reaction mixture was poured into ice-cold dilute hydrochloric acid. After saturation with sodium chloride, the mixture was extracted with diethyl ether.

The organic extract was washed with saturated sodium bicarbonate solution, followed by brine solution, and dried (Na_2SO_4). Upon concentration (rotary evaporator) the residue which was obtained was shown to contain a 54% yield of acetophenone by glc (Column A, 110°). The residue was chromatographed over neutral (Woelm) alumina, Activity III, using Skelly B, then Skelly B-ether, then ether as eluants. In order of elution, naphthalene and dihydronaphthalene, acetophenone (0.45 g, 19%) and a white solid (0.13 g, 2.7%) were obtained. The solid was recrystallized from 95% ethanol and yielded colourless needles, mp 142-142.5° (lit.[72b] 144°) and was identified as 1,4-diphenyl-1,4-butadione. Ir ($CHCl_3$): 1680 (C=O), 1600, 1580, 2000-1700 (monosubstituted phenyl), 1450 cm^{-1} (active methylene); nmr: $\underline{\delta}$ 3.46 (s, 4) $C\underline{H}_2C{=}O$, 7.30-7.70 (m, 6) and 7.95-8.15 (m, 4) $C_6\underline{H}_5$; mass spectrum m/e: M^+ 238.

The products listed in Table II were obtained in a similar manner and identified by comparison with commercially available samples. The following conditions were used for the estimation of yields by glc: propriophenone, Column A, 145°; isobutyrophenone, Columns D+E, 240°; adamantyl methyl ketone, Column B, 200°; cyclohexanone, Column A, 75°; 2-chlorocyclohexanone, Column A, 130°; cyclopentanone, Column C, 65°; 2-cyclopentanone, Column A, 120°.

Reaction between α-Bromoisobutyrophenone and Sodium Naphthalene followed by Deuteration.

A solution of α-bromisobutyrophenone (0.57 g, 2.5 mmole) in 10 ml of dry dimethoxyethane was added to a 0.1M sodium naphthalene solution (2.0 molar equivalents) at 0°. After stirring for 10 minutes, the reaction mixture was poured into 100 ml of ice-cold 2N DCl in D_2O [prepared from 37% DCl (Carl Roth OHG) and deuterium oxide, (99%)]. Quick extraction with anhydrous diethyl ether (3 x 50 ml) was followed by washing the organic extract with 5 ml of brine (made by saturating deuterium oxide with sodium chloride). After drying (Na_2SO_4), the solution was concentrated (rotary evaporator). The residue [containing 92% isobutyrophenone by glc (Column D+E, 240°)] was chromatographed over neutral (Woelm) alumina, Activity I, using freshly distilled (from lithium aluminium hydride) Skelly B, then Skelly B:anhydrous diethyl ether (1:2 by volume) as eluants. A fraction of isobutyrophenone (0.15 g, 44%) displayed the following: nmr: $\underline{\delta}$ 1.10 (d, J = 8 cps) $(C\underline{H}_3)_2CH$, 3.42 (sep, J = 8 cps) $C\underline{H}(CH_3)_2$, 7.3-7.9 (m) $C_6\underline{H}_5$. The integration indicated a ratio of 6.0:1.0:5.0±5% for $(C\underline{H}_3)_2:C\underline{H}:C_6\underline{H}_5$ respectively. Mass spectrum m/e: 148 (M^+), 149 ($M^+ + 1$, 10.6% of M^+), calculated for $C_{10}H_{12}O$ ($M^+ + 1$. 10.8%). No deuterium incorporation.

Alternatively, a solution of $\underline{\alpha}$-bromoisobutyrophenone (2.5 mmole) in 10 ml of dimethoxyethane was added, as

described before, to a solution of 2.1 equivalents of sodium naphthalene at 0°. The reaction was hydrolysed quickly by adding 4 ml of 2N DCl in D_2O. Work-up as before afforded 99% isobutyrophenone as estimated by glc analysis (Column D+E, 240°). Chromatography as before yielded 0.36 g (97%) of the isobutyrophenone "fraction". Analysis by nmr, as described above, showed no detectable deuterium incorporation. The mass spectrum of the crude sample, and of a sample purified by preparative glc (20% SE-30, 210°) showed m/e at 148 (M^+), 149 (M^++ 1, 13.4% of M^+) for 2.3% deuterium incorporation.

A sample of isobutyrophenone (0.5 ml) treated in a manner analogous to the work-up and isolation procedure (with 2N DCl in D_2O) showed no detectable deuterium incorporation by nmr and mass spectral analysis. A sample (0.3 ml) of isobutyrophenone which was chromatographed on a column of neutral alumina (Woelm) Activity III (deactivited with D_2O) showed no detectable deuterium incorporation by nmr and mass spectral analysis.

Reaction between Isobutyrophenone and Sodium Naphthalene.

A solution of freshly distilled isobutyrophenone (0.37 g, 2.5 mmole) in 10 ml of dimethoxyethane was added dropwise to 2.1 equivalents of a 0.1M solution of sodium naphthalene at 0°. The mixture was quenched after a 5 minute stirring period by addition of 4 ml of 2N DCl in

D_2O. Glc analysis (Column D+E, 240°) showed an estimated 45% yield of unreacted ketone. Isolation by chromatography on neutral alumina Activity I afforded a sample of ketone which contained up to 15±5% deuterium incorporated at $C\underline{H}(CH_3)_2$. Mass spectrum m/e: 148 (M^+), 149 (M^++ 1, 102% of M^+) for 47.2% deuterium incorporation.

The reaction was repeated. Quenching after 2 to 3 minutes yielded 60% isobutyrophenone by glc (Column F, 220°). Preparative thin layer chromatography [Precoated silica gel F_{254} plates, 20x20x0.2 cm (E. Merck, Darmstadt)] using Skelly B, then Skelly B:diethyl ether (6.5:1.5 by volume) as eluants afforded 0.16 g (42%) isobutyrophenone. Mass spectrum m/e: 148 (M^+), 149 (M^++ 1, 47% of M^+) for 26% deuterium incorporation. A less mobile component was isolated (0.97 g; 26%) which was identified as isopropylphenylcarbinol. A sample purified by preparative glc (15% FFAP, 205°) displayed the following: ir (liquid film): 3450 (bonded OH), 3040 3060 2000-1700 700 (mono-substituted phenyl), 1025 cm^{-1} (C–O–H); nmr: $\underline{\delta}$ 0.72 0.88 (d of d, J = 7 cps, 6) $(C\underline{H}_3)_2CH$, 1.6-2.1 (m, 1) $C\underline{H}(CH_3)_2$, 4.20 (d, J = 7 cps, 0.1) $C\underline{H}CH(CH_3)_2$ (10%) and $C\underline{D}CH(CH_3)_2$ (90%), 7.20 (s, 5) $C_6\underline{H}_5$), 2.20 (s, 1) ($O\underline{H}$, exch by D_2O); mass spectrum m/e: 150 (M^+), 151 (M^++ 1, 770% of M^+) for 89% deuterium incorporation. Spectroscopic data were similar to a sample of isopropylphenylcarbinol obtained from a similar experiment but using a

protic acid quench.

Preparation of the Ethylene Ketal of 2-Chlorocyclohexanone.[73]

A mixture of 2-chlorocyclohexanone (20 g, 0.15 mole), ethylene glycol (10 g), and 0.10 mg of *p*-toluenesulphonic acid in 50 ml of benzene was refluxed for 18 hours with azeotropic removal of water. After shaking with KOH pellets, fractional distillation afforded 17 g (63%) of the ethylene ketal of 2-chlorocyclohexanone, bp 90° (13 mm); n_D^{25} 1.4845; ir (liquid film): 1200-1000 (C–O–C), 750 cm^{-1} (C–Cl); nmr: δ 1.2-2.4 (br m, 8) $-(CH_2)_4$, 3.75-4.15 (AA' BB' m superimposed on m, 5) $(CH_2O)_2$ and CH–Cl; mass spectrum m/e: 176 $[M^+(Cl_{35})]$, 178 $[M^+(Cl_{37})]$.

Preparation of the Ethylene Ketal of 2-Chlorocyclopentanone.[74]

In the same manner, 8.1 g (68 mmole) of 2-chlorocyclopentanone was treated with 4.5 g of ethylene glycol and afforded 8.2 g (74%) of the ethylene ketal of 2-chlorocyclopentanone, bp 64° (4 mm) [lit.[74] 87-89° (15 mm)]; n_D^{25} 1.4758; ir (liquid film): 1200-1000 (C–O–C), 850 cm^{-1} (C–Cl); nmr: δ 3.80-4.05 (m, 5) $(CH_2O)_2$, CH–Cl, 1.50-2.30 (m, 6) $-(CH_2)_3$; mass spectrum m/e: 162 $[M^+(Cl_{35})]$, 164 $[M^+(Cl_{37})]$.

Preparation of the Ethylene Ketal of Phenacyl Bromide.[75]

In a similar manner, 7.9 g (4 mmole) of phenacyl bromide was treated with 2.5 g of ethylene glycol in benzene. Removal of the solvent yielded a crude residue which was washed with water. After drying in air, recrystallization from ether-*n*-pentane provided the ethylene ketal of phenacyl bromide (7.4 g; 76%) as cream-coloured crystals, mp 59.5-60° (lit.[75] 59.5-61.5°); ir (CS_2): 3100-3000 2000-1600 700 (monosubstituted phenyl), 1410 (CH_2), 1200-1000 cm^{-1} (C–O–C); nmr: δ 3.55 (s, 2) $C\underline{H}_2Br$, 3.65-4.63 (AA'BB' m, 4) $(C\underline{H}_2–O)_2$, 7.17-7.68 (m, 5) $C_6\underline{H}_5$; mass spectrum m/e: 164 [$M^+(Br_{79})$-phenyl], 166 [$M^+(Br_{81}$-phenyl].

Reaction between the Ethylene Ketal of 2-Chlorocyclohexanone and Sodium Naphthalene.

A solution of the ethylene ketal of 2-chlorocyclohexanone (0.90 g, 5.0 mmole) in 15 ml of dimethoxyethane was added dropwise during 15 minutes to a solution of 0.1M sodium naphthalene (2.1 equivalents) at 0°C. After stirring for an additional 15 minutes, the reaction mixture was poured into dilute hydrochloric acid and stirred for 18 hours at room temperature. Extraction with ether, followed by washing of the organic extract with saturated sodium bicarbonate solution, then with brine solution, and drying (Na_2SO_4) afforded, on glc analysis (Column A,

100°) of the concentrate obtained after removal of the solvent, 97% cyclohexanone.

Reaction between the Ethylene Ketal of 2-Chlorocyclopentanone and Sodium Naphthalene.

In a similar way, a solution of 0.41 g (2.5 mmole) of the ethylene ketal of 2-chlorocyclopentanone in 15 ml of dimethoxyethane was treated with 2.1 equivalents of sodium naphthalene. The yield of cyclopentanone was estimated as 72% by glc (Column C, 60°).

Dehalogenation of 2-Chlorocyclopentanone via Formation of the Ethylene Ketal by Sodium Naphthalene.

2-Chlorocyclopentanone (1.19 g, 10 mmole) was treated with 0.64 g of ethylene glycol and 5 mg of *p*-toluenesulphonic acid in 25 ml of benzene. After refluxing for 5 hours with azeotropic removal of water, the solution was washed with sodium bicarbonate solution and dried (Na_2SO_4). The solvent was removed (rotary evaporator). The residue was dissolved in 20 ml of dimethoxyethane and added during 4 minutes to a sodium naphthalene solution (225 ml of 0.10M) as before. The yield of cyclopentanone in this reaction was estimated as 70% by glc (Column G, 75°).

Reaction between the Ethylene Ketal of Phenacyl Bromide

and Sodium Naphthalene.

A solution of the ethylene ketal of phenacyl bromide (0.25 g, 1.0 mmole) in 10 ml of dimethoxyethane was added dropwise to 2.7 equivalents of sodium naphthalene solution (0.10M) at 0°. Before complete addition of the bromoketal, the green colour of the radical anion disappeared. The addition was stopped. An additional 2.6 equivalents of sodium naphthalene solution were added to the reaction mixture. The dropwise addition of the bromoketal solution was resumed. The resulting brown mixture was stirred for 2 minutes and quenched with dilute hydrochloric acid. Analysis by glc (Column B, 180°) showed only traces of acetophenone. A more volatile component appeared which had a retention time equal to that for styrene.

Alternatively, the sodium naphthalene solution (0.19M) was added dropwise to 0.62 g (2.5 mmole) of bromoketal in 10 ml of dimethoxyethane at 0°. As the radical anion solution was added, it was immediately consumed and the reaction mixture became yellow. After 1.2 equivalents of radical anion solution had been added, the mixture turned green and analysis by glc (Column B, 180°) indicated 63% acetophenone and approximately 31% bromoketal. The addition of sodium naphthalene was continued and the reaction mixture gradually changed to a dark blue colour (1.9 equivalents), Glc analysis as

before showed 83% acetophenone and less than 20% bromoketal. As the addition was continued, the mixture turned to a light mauve (2.4 equivalents of sodium naphthalene; 96% acetophenone, 0% bromoketal), then to a dark brown colour (2.7 equivalents of sodium naphthalene; 74% acetophenone). A total of 4.4 equivalents was added before the green colour of the radical anion could be noticed. Analysis of the final mixture after acid hydrolysis afforded a 16% yield of acetophenone by glc (Column B, 180°).

Dehalogenation of Phenacyl Bromide via Formation of the Ethylene Ketal by Sodium Naphthalene.

Phenacyl bromide (9.9 g, 50 mmole) was ketalysed as described previously. The crude product was dissolved in 100 ml of dimethoxyethane and cooled to 0°. To this solution was added, dropwise, a solution of sodium naphthalene (440 ml of 0.25M) until the reaction mixture turned and remained mauve. The mixture was poured into dilute hydrochloric acid and stirred for 36 hours at room temperature. The usual work-up (ether extraction) yielded a crude residue after removal of the solvent (rotary evaporator). The residue was chromatographed on alumina (BDH) using Skelly B, then ether as eluants. Distillation of the yellow oil obtained afforded 4.7 g (78%) acetophenone, bp 77-79°(12 mm), n_D^{20} 1.5350 [lit.[76] bp 79° (10 mm), n_D^{20} 1.5372].

Preparation of Sodium Trimesitylboron Solution.

Thin sodium shavings (0.38 g, 1.6 mg. atoms) were added to 0.55 g (1.5 mmole) of trimesitylboron in 25 ml of dry dimethoxyethane. The blue colour formed immediately on addition of the metal. The mixture was stirred at room temperature (with a glass-covered magnetic bar) for 3.5 hours.

Reaction between 2-Chlorocyclohexanone and Sodium Trimesitylboron.

A solution of 2-chlorocyclohexanone (0.066 g, 0.5 mmole) in 3 ml of dimethoxyethane was added dropwise during 5 minutes to the chilled sodium trimesitylboron solution prepared above (3 equivalents, 0 to -5°). The dark blue reaction mixture was stirred for an additional 10 minutes and quenched by the addition of 2 ml of saturated ammonium chloride solution. The blue colour was destroyed by passing a stream of air through the mixture. The layers were separated and the aqueous phase was extracted with ether. The combined organic phase was washed with brine solution and dried (Na_2SO_4). Analysis by glc (Column E, 130°) showed 100% cyclohexanone. Upon concentration (rotary evaporator), the residue displayed ir (CCl_4): 1720 cm^{-1} (C=O).

Reaction between 2-Chlorocyclopentanone and Sodium Trimesitylboron.

In the same way, a solution of 2-chlorocyclopentanone((0.5 mmole) in dimethoxyethane was added to a solution of sodium trimesitylboron (3 equivalents, -5°). The yield of cyclopentanone was estimated as 86% by glc (Column C, 110°), and no starting chloroketone was detectable by glc. The reaction was repeated on a larger scale (1.5 mmole). Upon concentration of the organic extract at atmospheric pressure, a white solid precipitated on cooling the concentrate (10 ml). Two drops of water were added and the solid was filtered and washed with ice-cold methanol. The filtrate was dried (Na_2SO_4) and the solvent removed by distillation at atmospheric pressure. A sample of cyclopentanone was isolated from the crude oily residue by preparative glc (Column E, 120°) which was identical to the commercially available material.

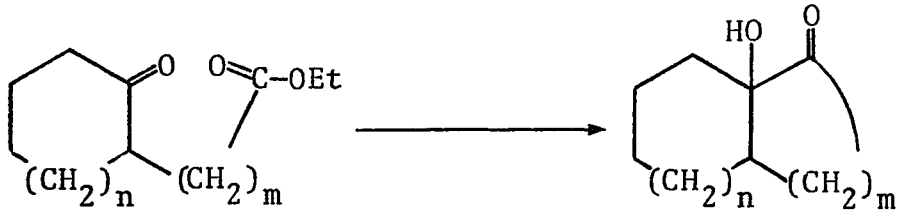
CHAPTER II

THE REDUCTIVE CYCLIZATION OF UNSATURATED KETONES

INTRODUCTION

Relatively few reactions of aromatic hydrocarbon radical anions have been investigated for inducing intramolecular cyclizations.[23,77-79] The conversion of α,ω-diesters by the action of sodium metal into cyclic acyloins is a typical example of an intramolecular reductive cyclization, believed to occur by an electron transfer process.[80] However, the use of radical anions, such as sodium naphthalene, has been found to fail as an acyloin-condensing agent.[23,77]

Gutsche and coworkers [78] have studied the cyclization of ω-ketoesters by reaction with aromatic hydrocarbon radical anions. (eq. 22) The use of sodium and



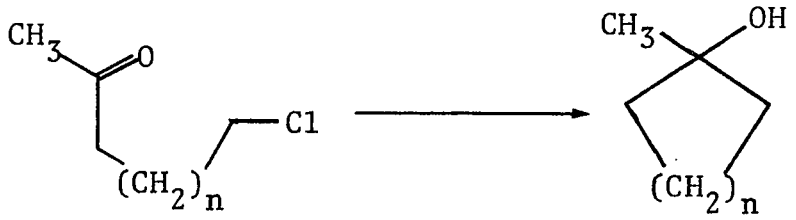
(22)

8 9

potassium naphthalene as well as sodium phenanthrene, gave the cyclic hydroxy ketone 9 in yields of 30 to 50%

only for the cases (in 8) where n = 1 or 2, m = 2. Sodium biphenyl was somewhat less effective than sodium naphthalene. Lithium naphthalene and sodium anthracene failed to yield any cyclized product. These workers postulated that the coupling step proceeds via a nucleophilic addition of the ketone dianion (originating from a two electron transfer to the keto carbonyl group) to the carbonyl group of the ester.

Sodium naphthalene and sodium phenanthrene have also been used by House and coworkers [79] in an attempt to obtain intramolecular alkylation of a ketyl radical anion in the reduction of ω-chloroketones. (eq. 23)



(23)

10 (n = 1 or 2) 11

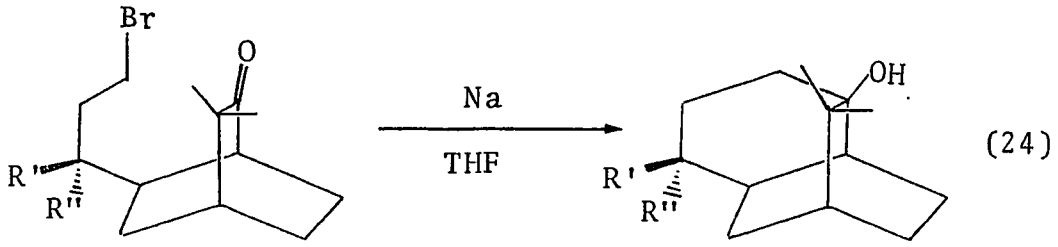
Although some success was achieved in obtaining some five- and six-membered ring alcohols in this way, the majority of the product was the dehalogenated alicyclic ketone. However, in an analogous type of reaction, Corey and Kuwajima [81] treated the corresponding iodoketones of structure 10 with the dianion of nickel tetraphenylporphine and obtained the cyclic alcohols 11

in yields of 61 (n = 1) and 88% (n = 2).

Comparison of half-wave potentials (measured under comparable conditions, versus the normal calomel electrode) of the respective carbon-halogen and carbonyl bonds indicate that the nickel tetraphenylporphine dianion (the half-wave potentials for nickel tetraphenylporphine are -1.18 and -1.75V)[82] is expected to reduce the carbon-iodine bond (-1.67V) [47] rather than the keto carbonyl group (-2.2 to-2.5V)[47].

The two types of substrates cited previously (the ketoesters 8 and the chloroketones 10) have also yielded some cyclized products by the action of sodium in liquid ammonia.[78,79]

Danishefsky and Dieman [83] have reported the formation of a cyclic alcohol, by treatment of the bromoketone 12 with sodium in tetrahydrofuran. (eq. 24)



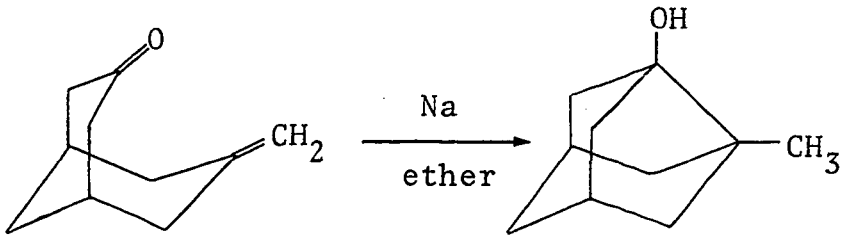
(24)

12 R'= H, R''= Me or R'= Me, R''= H

ca. 25% 13

The formation of cyclic alcohols from bifunctional substrates (in which one of the functions is a carbonyl group) appears to be a favourable reaction when the

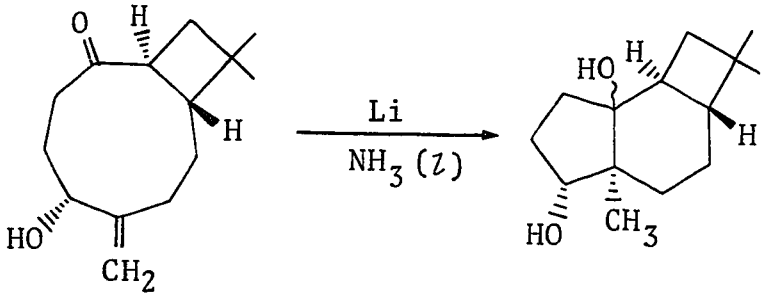
geometry of the molecule places the functions in close proximity. The bicylic ofefin 14 yields 15 as the sole product on reduction with sodium in moist ether.[84] (eq. 25)



(25)

14 15

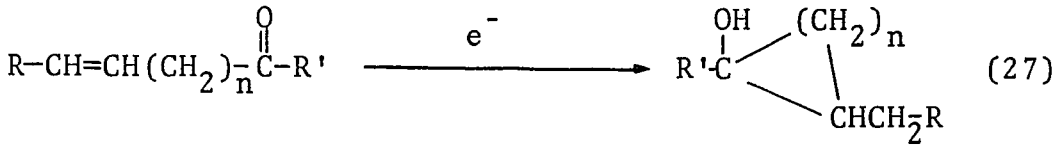
Similarly, the keto-olefin 16 affords the alcohol 17 in 30% yield on treatment with lithium in liquid ammonia.[85] (eq. 26)



(26)

16 17

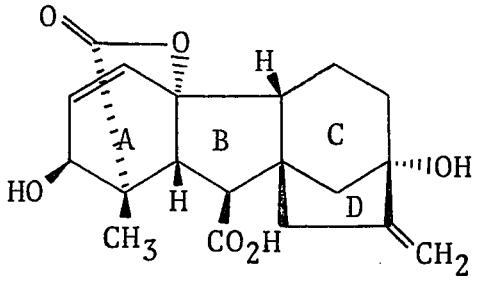
Shono and Mitani [86] have recently shown that intramolecular cyclization of simple alicyclic olefinic ketones could be achieved by electro-reduction in dioxane-methanol (using tetraethylammonium *p*-toluenesulphonate as the supporting electrolyte). (eq. 27) In this way, five-



18 19 (n = 3,4) (27)

and six-membered cyclic tertiary alcohols (19) were obtained in moderately good yields (35-66%).

The existence in some natural products, such as gibberellic acid (20) of a bicyclo[3.2.1]-octane system

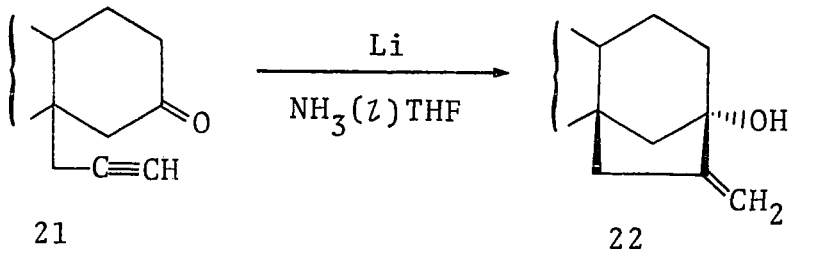


20

with the synthetically challenging features of an exocyclic methylene group adjacent to a bridgehead tertiary hydroxyl has stimulated the development of various synthetic approaches to the construction of the C/D ring system. These usually involve reductive cyclization of a molecule with bifunctionality arranged in a 1-5 manner.

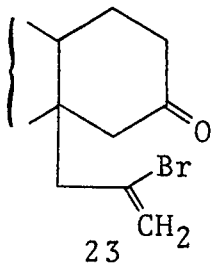
The most direct approach was utilised by Stork and coworkers who achieved the synthesis of the C/D ring system by the chemical reduction of a keto-acetylene (partial

structure 21) with lithium in liquid ammonia-tetrahydrofuran solution.[87,88] (eq. 28) The formation of the



21 22 (28)

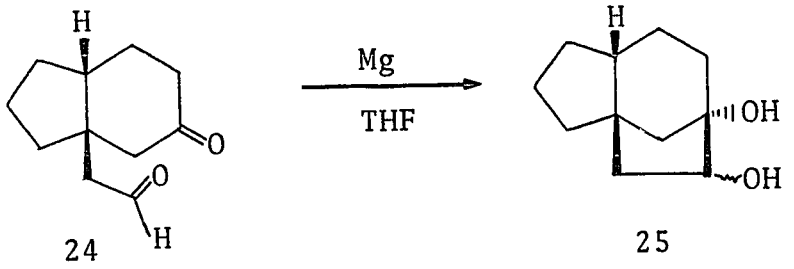
cyclic alcohol 22 was found to be highly dependent on the geometrical orientation of the propargyl group. Cyclization was more favourable when the propargyl group was in a 1,3-axial position to the carbonyl group. Also, the same type of cyclic alcohol was obtained by Corey and coworkers [89] on treatment of a bromovinyl ketone (partial structure 23) with di-*n*-butylcopperlithium.



23

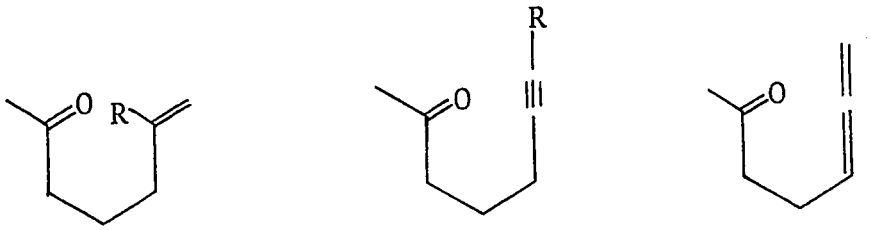
The success of the reaction was critically dependent on proper selection of conditions of temperature and solvent.[81]

Several other indirect approaches to the construction of this system have been accomplished.[90-95] Worthy of note is the pinacol cyclization of the keto-aldehyde 24 to the diol 25 using magnesium in tetrahydrofuran.[93] (eq. 29)



24 25 (29)

The purpose of the present investigation was to study the possibility of effecting cyclization of unsaturated ketones by electron transfer from an aromatic radical anion. Simple unsaturated model systems were elected for study, such as olefinic, acetylenic and allenic ketones (26 - 30).



26 R = H 28 R = H 30

27 R = CH_3 29 R = CH_3

It was hoped that by probing the possible generality of this reductive cyclization for a variety of simple unsaturated systems, this approach could yield some understanding of the use of electron transfer reagents in the cyclization of more complex molecules.

RESULTS AND DISCUSSION

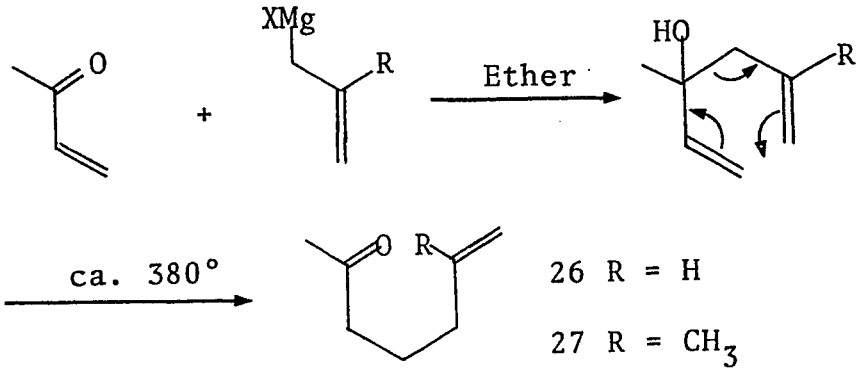
The observation that non-conjugated olefins are not readily reduced by electrolytic methods [47,96] as opposed to a ketonic carbonyl group [47] suggested that the cyclization of unsaturated ketones such as 18 (in equation 27) was probably initiated by electron transfer to the carbonyl moiety of the molecule. Cyclization of substrates 14 and 16 (eqs. 25 and26) probably arises also by initial electron transfer to the carbonyl moiety. However, under certain conditions of dissolving metal solutions (such as lithium-ammonia-alcohol and lithium-ethylamine-alcohol combinations), terminal olefins have been observed to undergo reduction to the corresponding alkanes.[97] On the other hand, terminal olefins have also been found to be stable under conditions such as sodium in liquid ammonia (in the presence of ammonium sulphate).[98] Consequently, the search for an aromatic radical anion which would effectively and selectively transfer an electron to an aliphatic carbonyl group was undertaken.

Comparison of reported half-wave potentials, measured under relatively comparable conditions, was used as a guide for exploratory experiments. The values for several substrates considered are:[47] naphthalene, -2.50V; biphenyl, -2.65V; phenanthrene, -2.70V; aliphatic ketone,

-2.2 to -2.5V, versus the normal calomel electrode. (The electron affinity increases as the negative value tends to 0.00V.)

Biphenyl was initially chosen as the hydrocarbon component of the electron transfer reducing agent. It was felt that electron transfer from sodium biphenyl would occur selectively to the carbonyl group since terminal olefins had been observed to be stable to this reagent.[36] (eq. 8).

The reductive cyclization of 6-hepten-2-one (26) and 6-methyl-6-hepten-2-one (27) was studied. These substrates were prepared by the Cope rearrangement of the corresponding allyl methyl vinyl carbinols. The latter were obtained from the addition of the respective allyl or methallyl Grignard reagents to methyl vinyl ketone, as shown below.[99] (eq. 30)



(30)

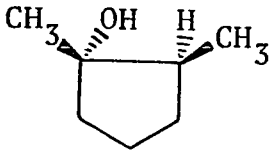
26 R = H

27 R = CH_3

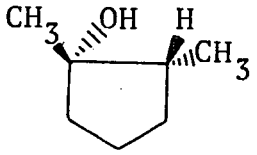
An attempt at preparing 26 by the 1,4-addition of allylcopper (prepared from equivalent amounts of allylmagnesium bromide and cuprous iodide)[100] to methyl vinyl

ketone failed to give any appreciable amount of the desired product (26).

When three equivalents of sodium biphenyl were added to a tetrahydrofuran solution of 26 (-70°, then ca. 25° for 3 hours) a 38% yield of the cyclic alcohol, 1,2-dimethylcyclopentanol was obtained as a mixture of cis (31a) and trans (31b) isomers (in a ratio of 76 to 24 respectively). However, unreacted substrate was also

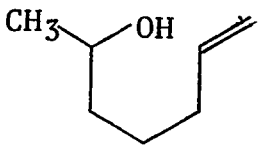


31a



31b

present in a 35% yield. At higher temperatures for the addition of reagent (-35 to -40°) and longer reaction times (18 hours at 25°) after addition was complete, there resulted a slow but incomplete utilization of the substrate (22% unreacted) with no appreciable increase in the yield of 31 (43%). A trace amount of the olefinic alcohol 32 was also formed.



32

In a preliminary experiment using dimethoxyethane as solvent, an amount of sodium biphenyl reagent (less than 2 equiv.) had accidently been used. The radical

anion was completely consumed and the resulting mixture showed (glc) only traces of cyclic alcohol 31. Additional sodium (in pieces) was added and the mixture was stirred (-45°) until the blue colour of the biphenyl radical anion appeared. This early experiment was followed (glc) by periodically sampling aliquots, and revealed only a slight increase in the yield of 31. Therefore, to study the effect of a proton source, some *t*-butyl alcohol was added. The blue colour disappeared, and then reappeared (after 3 to 5 hours), at which point glc analysis showed that all the ketone had reacted. The yield of cyclic alcohol 31 was estimated as 60%.

To confirm these results, a mixture of 6-hepten-2-one, biphenyl (6 equiv.), sodium metal (20 equiv.) and *t*-butyl alcohol (10 equiv.) were reacted (-45°) in dimethoxyethane until the colour of the radical anion persisted. At this point, the substrate had been completely consumed, and the only products were a mixture of the isomeric alcohols 31a and 31b in a ratio of 89:11 (63% yield).

Many factors had been changed in this reaction (solvent, stoichiometry of the reagents, and the presence of a proton source). To probe which of these factors were favourable for cyclization the following experiment was performed. To a tetrahydrofuran solution of the enone (-35°), only sodium was added. After 30 minutes,

the only detectable product was a trace of the trans alcohol 31b. Addition of *t*-butyl alcohol (1 equiv.) resulted in the formation of the olefinic alcohol 32 in ca. 45% yield. Addition of biphenyl to this mixture resulted in the appearance of the cis alcohol 31a, and the yield of acyclic alcohol 32 was unaffected.

The following conclusions could be drawn from these observations. Firstly, although the sodium biphenyl radical anion could induce the cyclization, it did not necessarily have to be preformed (i.e., it could be generated *in situ*.) Secondly, the presence of a proton source was required for complete utilization of the starting material, the olefinic ketone 26.

As a result, optimization of the yield of cyclic alcohols was attempted by varying some reaction parameters, such as solvent, proton source,and temperature. The results are presented in Table III.

From these results, it should be noted that the reaction of 6-hepten-2-one (26) with sodium biphenyl appeared to approach 50% conversion in the absence of a proton source (Entries 1, 2, and 5). In the presence of a proton source, and when tetrahydrofuran was used as solvent, there was no major effect on the formation of the cyclized alcohol. (Entries 1 and 2 versus entries 3 and 4) It would seem that reaction of the biphenyl

TABLE III

Reductive Cyclization of 6-Hepten-2-one by Sodium Biphenyl

Reagent	Proton Source	Solvent	Molar Ratio Reagent:Ketone: Proton Source	Time of Addition (hr)	Time of Reaction (hr)	Temp (°C)	Yield of Products[a] 26[b]	31a	31b	32	Ratio 26 : 31
1. [NaBiphenyl][c]	none	THF	3.2 :1 : 0	1.0	-	-70	-	-	-	-	- -
					3.0	25	35	29	8.9	-	48 : 52
2. [NaBiphenyl][c]	none	THF	6.0 :1 : 0	1.0	1.0	-35to-40	-	-	-	-	45 : 55
					18	25	22	36	7.0	<5	34 : 67
3. Na, Biphenyl	t-BuOH	THF	(3:3):1 : 1	0[d]	2.3	-35t -40	-	-	-	-	40 : 60
					10	25	-	-	-	-	32 : 68
- -	t-BuOH	-	0 :0 : 1	-	0.5	25	---not measured---				34 : 66
4. Na, Biphenyl	H_2O	THF	(6:3):1 :33	0[d]	2.0[e]	-35to-40	-	-	-	-	
					5.0	"	10	42	14	<5	18 : 81
5. Na, Biphenyl	none	DME	(6:3):1 : 0	0[d]	1.0[e]	"	-	-	-	-	56 : 44
					3.0	"	-	-	-	-	44 : 56
					7.0	"	-	-	-	-	38 : 70
- -	t-BuOH	-	0 :0 : 1	-	0.75	"	0	63	12	0	0 :100
6. Na, Biphenyl	t-BuOH	DME	(20:10):1: 6	0[d]	6.0[e]	-45	0	56	7.4	0	0 :100
7. Na, Biphenyl	H_2O	DME	(6:3):1 :1.2	1.0	1.5[e]	-35to-40	0	72	20	0	0 :100

(a) Yields were determined by glc. (b) Unreacted 6-hepten-2-one

(c) A solution of preformed sodium biphenyl was added to the unsaturated ketone. (In all other cases, the sodium biphenyl was formed in situ.)

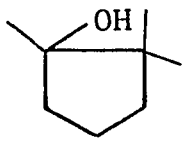
(d) The reagent (sodium and biphenyl, not preformed), the ketone, and the proton source were mixed together at -35to-40°.

(e) Time at which the blue colour of the radical anion appeared and persisted.

radical anion with the proton source is highly competitive with electron transfer to the olefinic ketone in tetrahydrofuran. However, dimethoxyethane allows the formation of the radical anion and its reaction as an electron transfer reagent in the presence of a proton source. These observations are in accord with the conclusions reached by S.Bank and coworkers,[19,20] on the related sodium naphthalene system as previously noted in the general introduction to Part I. That is, solvents such as dimethoxyethane which favour the formation of loose ion-pairs also favour the electron transfer pathway.

Thus, optimum yields for this reaction were obtained (Entry 7) when the olefinic ketone was slowly added simultaneously with a small excess of water (1.2 equiv.) to a mixture of sodium and biphenyl at ca. -35 in dimethoxyethane and the mixture stirred until the colour of the radical anion appeared and persisted.

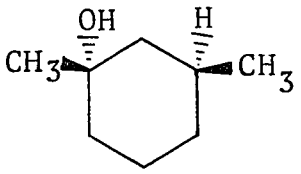
Yet, when this procedure was applied to 6-methyl-6-hepten-2-one (27), the expected cyclic alcohol, 33, was



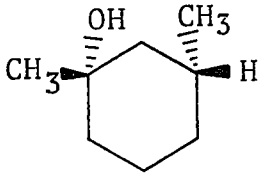
33

not formed. After stirring for 5 hours (subsequent to the persistence of the blue colour) 50% of 27 had been

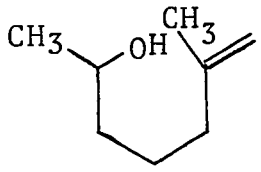
consumed. After 18 hours at room temperature, only traces of starting material were present along with small amounts of three components (<5%). They were assigned structures 34 (a and b) and 35 on the basis of glc retention time, by comparison with authentic samples.



34a



34b



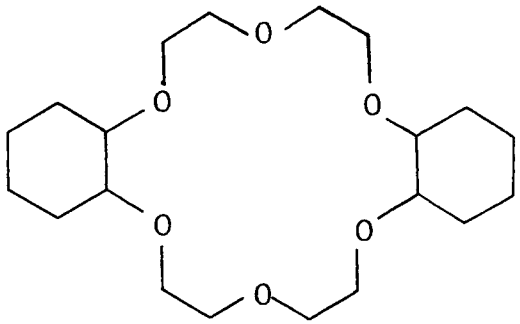
35

Reaction of 27 with preformed sodium biphenyl and either water (at -35 to -40°) or *t*-butyl alcohol (at 0°) as proton sources, did not effect the formation of the desired cyclic alcohol.

The reluctance of 27 to cyclize was not an entirely unexpected result. Shono and Mitani,[86] in their electrolytic process (eq. 27), had obtained the olefinic alcohol 35 as the only product in a low yield (12%) upon electrolytic reduction of 6-methyl-6-hepten-2-one (27).

Examination of molecular models indicated that steric crowding between the olefinic methyl group and the methyl carbonyl group on approach for the formation of a five-membered ring might be an important factor for the failure of the ring closure. Attempts at minimizing the effective bulkiness surrounding the presumed intermediate, the ketyl functionality, was investigated.

Crown ethers such as dicyclohexyl-18-crown-6, (36), are known to be effective selective complexing agents for cations such as sodium and potassium.[101] The use of



36

36 with sodium biphenyl, it was hoped, would separate the sodium cation from the vicinity of the ketyl oxygen by complexation, thus rendering a less crowded transition state for ring closure. When the olefinic ketone 27 was treated with the sodium biphenyl-crown ether combination, there resulted the formation of a new component in the product mixture (in a trace amount), which was assigned the structure of the desired alcohol, 33, on the basis of its glc retention time. However, the sodium biphenyl-crown ether reagent was also observed to be less stable (in dimethoxyethane) at room temperature than the uncomplexed reagent. Thus, the result obtained in the reaction with 27 might also have been due to a change in the reactivity of the radical anion, brought about by the cation-complexing ether.

Therefore, the reduction with other radical anions

was investigated. Darling and coworkers [68] have used alkali metal-trimesitylboron complexes as reducing agents for enones. These reagents have the additional advantage of being unreactive towards protic solvents.

As was reported earlier (Chapter I), sodium trimesitylboron proved to be a successful reducing agent for the dehalogenation of α-chlorocyclanones. However, its reaction with non-activated ketones, such as dialkyl ketones, has also been reported to be negligible.[68] On the other hand, it was hoped that its use with a crown ether might result in the formation of a sodium-trimesityl boron complex with increased reactivity for electron transfer to a carbonyl group.

The reaction of 6-methyl-6-hepten-2-one (27) with a sodium trimesitylboron solution (in dimethoxyethane) containing *t*-butyl alcohol and crown ether 36 afforded, as the only product after a slow reaction (16 hrs, 25°), the uncyclized alcohol 35 in 71% yield based on converted ketone.

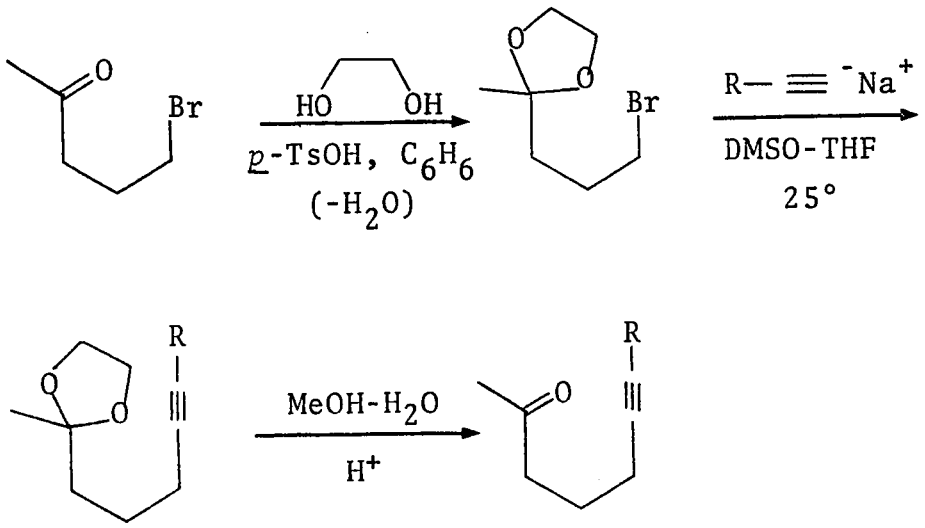
Successful ring closure was finally achieved, when 27 was treated with a dimethoxyethane solution of lithium trimesitylboron and *t*-butyl alcohol at 0°. The reaction was virtually complete after addition of the substrate. A mixture of 1,2,2-trimethylcyclopentanol (33) and the olefinic alcohol 35 (47 and 48% yield respectively) was

formed. In the absence of trimesitylboron, the reduction of 27 using lithium and *t*-butyl alcohol, under the same conditions, afforded a 97% yield of 35 and only traces of 33.

The reduction of the acetylenic ketones 28 and 29 with these reagents (sodium biphenyl, sodium and lithium trimesitylboron) was studied.

The acetylenic ketones were prepared as shown in scheme III. The ethylene ketal of 5-bromo-2-pentanone was alkylated with either sodium acetylide or sodium

Scheme III

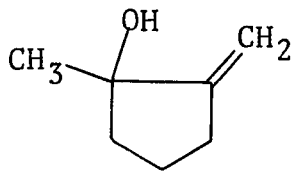


28 R = H (59%)

29 R = CH_3 (29%)

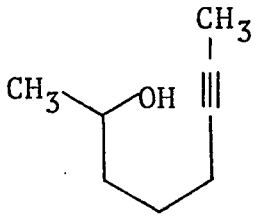
methylacetylide,[102] respectively, followed by mild hydrolysis according to the method of Stork and coworkers.[87]

6-Heptyn-2-one (28) was reduced under the same conditions as those for optimum cyclization of the corresponding olefinic ketone 26 (i.e., Table III, entry 7). (Two equivalents of water were used instead of the 1.2 equivalents cited.) The cyclic alcohol, 1-methyl-2-methylenecyclopentanol (37) was formed in 83% yield (glc) (isolated, 58%).



37

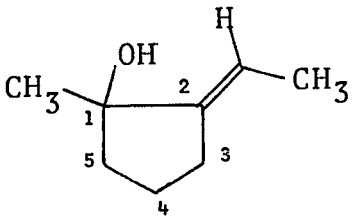
Treatment of 6-octyn-2-one (29) in the same manner resulted in a very slow reaction. After 5 hours, some unreacted ketone remained (6%). On glc analysis, two products were present, the desired cyclic alcohol, 2-ethylidene-1-methylcyclopentanol (15%) and the uncyclized alcohol 38. Addition of 29 (with *t*-butyl alcohol) to a



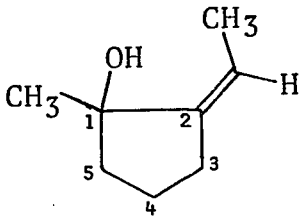
38

preformed sodium biphenyl solution gave only traces of these products after one hour at 0° along with 81% unreacted acetylenic ketone.

However, addition of 29 (in dimethoxyethane, with 2.2 equiv. of *t*-butyl alcohol) to a preformed solution of sodium trimesitylboron (3 equiv.) led to complete utilization of the acetylenic ketone after 5 hours (at 0 to -5°). Nmr analysis of the crude product indicated the presence of equal amounts of the cyclic alcohol and 38. The cyclic alcohol, 2-ethylidene-1-methylcyclopentanol was tentatively assigned the anti configuration, 39a,



39a



39b

on the basis of the chemical shifts of the protons of the olefinic methyl group. The yield of alcohol 39a was estimated as 30% (glc).

When 29 was added to a preformed solution of lithium trimesitylboron in dimethoxyethane containing *t*-butyl alcohol (-5 to -10°), this led to virtually complete utilization of the substrate immediately on addition. The mixture consisted of ca. 75% 39a (glc) as the major component and 38 as a minor component. The isolated mixture was shown to contain a third component (by nmr) which was assigned the structure 39b. The three components were present in the ratio of 5:14:81 (38:39b:39a).

These structural assignments (39a and 39b) were confirmed by nmr spectroscopy using the paramagnetic shift reagent, tris(heptafluoro-dimethyloctanedionato)-europium [$Eu(fod)_3$]. The observed chemical shifts of the protons on the ethylidene group and the protons of the C_1-methyl group with and without $Eu(fod)_3$ are given in Table IV. By making use of the fact that the isotropic shifts decrease with increasing distance of the respective nuclei from the bonding site,[104,105] (in this case, the Eu-OH complex), the assignment can be made by comparing the various changes in chemical shifts ($\Delta\delta$) in the major (39a) and minor (39b) components of the product mixture, on a qualitative basis.

The magnitude of these changes ($\Delta\delta$) in the resonances of the vinyl proton and of the protons of the C_1-methyl group in 39a indicate that both types of protons are approximately at the same distance from the paramagnetic europium-hydroxyl complex (4.50 vesus 4.32 in Table IV). The same argument applies for the changes ($\Delta\delta$) in 39b. The resonance of the protons on the C_1-methyl group is shifted by approximately the same amount as that of the vinyl proton. On the other hand, comparison of the differences in chemical shifts ($\Delta\delta$) of the protons in the ethylidene group ($C{=}C\underline{H}$ and $C{=}C{-}C\underline{H}_3$) reveals that a larger $\Delta\delta$ is observed for the vinyl proton in 39a as opposed to the methyl protons (4.32 versus 0.79). This order is

TABLE IV

Chemical Shifts[a] for 2-Ethylidene-1-methylcyclopentanol

	Anti (39a)			Syn (39b)		
	CH_3-C-OH	C=C-H	C=C-CH_3	CH_3-C-OH	C=C-H	C=C-CH_3
Normal	1.24	5.43	1.56	1.36	5.35	1.77
Eu(fod)$_3$[b]	5.74	9.75	2.35	4.08	7.05	3.86
$\Delta\delta$	4.50	4.32	0.79	2.76	1.70	2.09

(a) Given in δ units, measured at 100 MHz in CCl_4

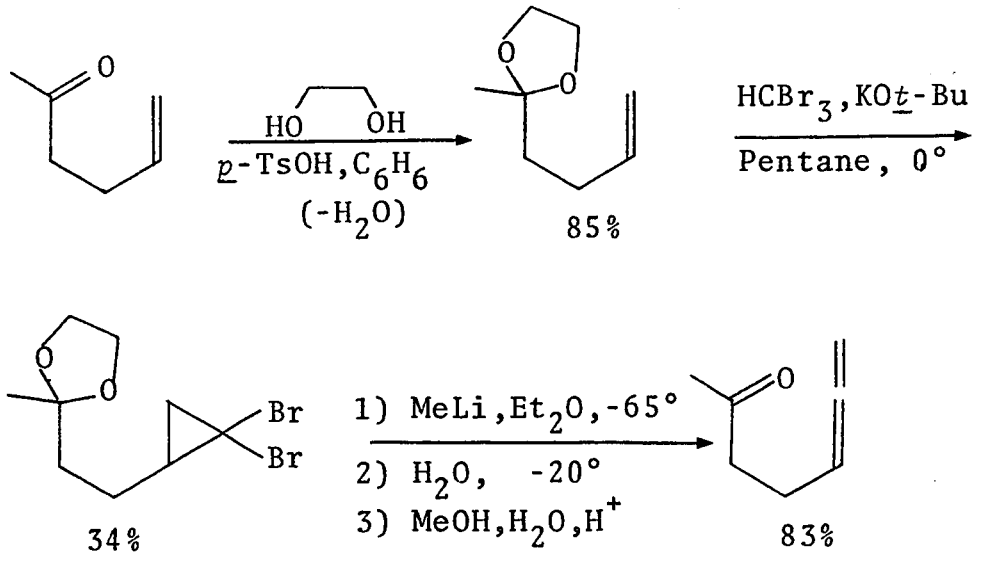
(b) Ca. one equivalent of shift reagent

reversed in 39b (1.70 versus 2.09).

Finally, the reductive cyclization of a simple allenic ketone was investigated.

5,6-Heptadien-2-one (30) was synthesised by a modification of the method of Crandall and Mayer[106] from the appropriate olefinic ketal. As represented in scheme IV, condensation with dibromocarbene gave the

Scheme IV



30

1,1-dibromocyclopropane adduct. The latter, on treatment with methyl lithium followed by mild hydrolysis gave the desired product.

The allenic ketone 30 was found to be more reactive towards the electron transfer reagents than any of the other substrates studied.

The allenic ketone was treated under the conditions

whereby 6-hepten-2-one and 6-heptyn-2-one gave maximum yields of cyclized product (i.e., entry 7, Table III). There was obtained the cyclic alcohol 37 in 15% yield.

Attempts at attenuating the conditions, by performing the reaction at -70°, by addition to 3 equivalents of preformed sodium biphenyl (in DME:THF, 4:1) led, after 15 minutes, to a 51% yield of cyclized product (37). On the other hand, a very slow reaction occurred when 30 was added to a preformed sodium trimesitylboron solution (ca. -35°) in dimethoxyethane. After 2 hours a ratio of 90:10 of 30 to 37 was reached. Warming above 0° resulted in a fast disappearance of the substrate and the formation of 37 in a 50% yield.

No appreciable increase in the yield of 37 was achieved by performing the reaction at 25° using *t*-butyl alcohol as proton source (54-59%).

However, when a large excess of *t*-butyl alcohol (10 equiv.) was added to the prechilled sodium trimesitylboron solution (0 to -5°) prior to the addition of the allenic ketone, the yield of cyclized product rose to 71-74%. It was later discovered that allylic alcohols such as 37 and 39 were very prone to decomposition (by dehydration) in the injector inlet of the gas chromatograph during analysis, indicating that the yields of 37 obtained in the preceding set of experiments were

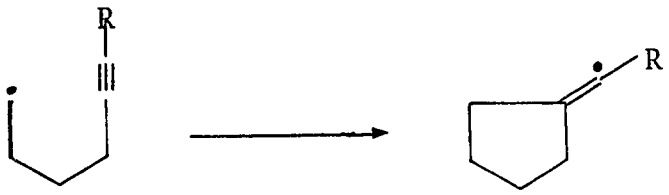
probably higher than the values reported. It was found for 39, that reducing the injector temperature from 200° to ca. 130-140° minimized this decomposition.

All the substrates studied in this investigation, compounds 26-30, cyclized with preferential ring closure to form the five-membered cycle. Examination of molecular models of these substrates indicate that overlap between the p-orbitals at C_2 and C_6, is a geometrically favourable process.

Although there is no experimental evidence in support of any particular mechanistic scheme, there are, however, reports of preferential ring closure to five-membered rings in somewhat related systems. 5-Hexenyl radicals, represented by structure 40, have been observed to give preferential closure to the five carbon cycle [107] (eq. 31). Similarly, the related 5-hexynyl

(31)

40



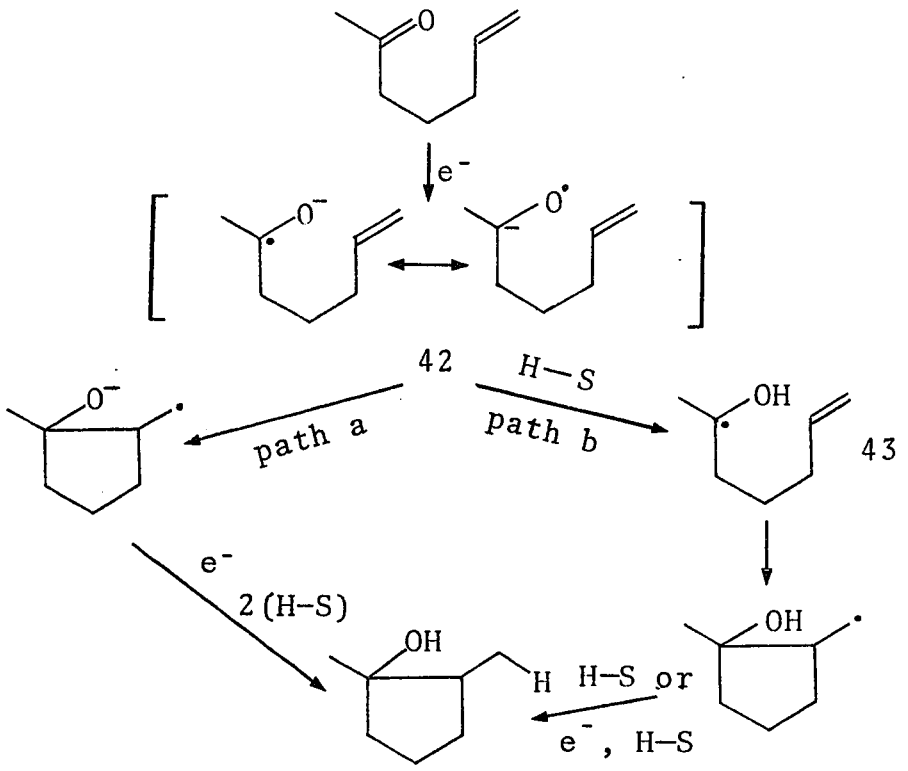
(32)

41 R = H or Me

radicals such as structure 41 have also been observed to close in the same way.[108] (eq. 32)

Despite the fact that no mechanistic studies were performed in the present investigation, an attractive and reasonable pathway for the reductive cyclizations can be postulated, by analogy with the above. This is illustrated in Scheme V for the cyclization of 6-hepten-2-one. Initial electron transfer to the

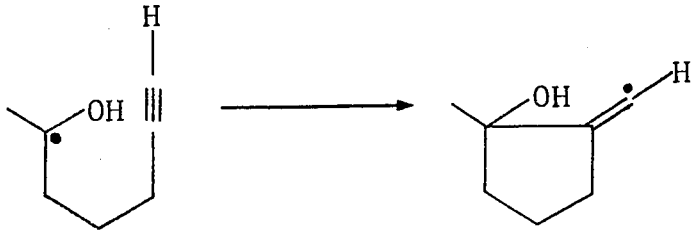
Scheme V



unsaturated ketone gives rise to a ketyl (42). Cyclization at that stage, (via path a) has been proposed by Greenwood, Qureshi, and Sutherland [85] for the formation of 17 from 16 (eq. 26). However, ring closure of an alkoxy radical (43), as obtained via path b, by proton

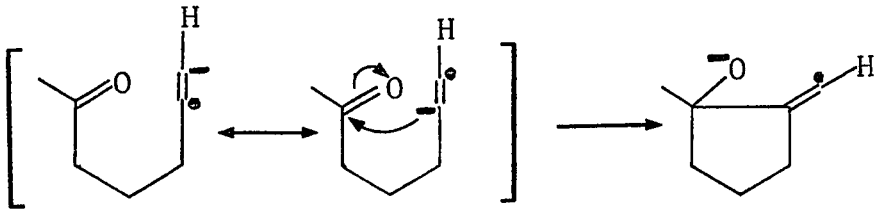
abstraction from some donor (water or *t*-butyl alcohol) with preferential ring closure to a five-membered ring, finds ample analogy in the 5-hexenyl radical system (eq. 31).

A similar pathway could be invoked for the cyclization of acetylenic ketones. (eq. 33). Stork and coworkers



(33)

have proposed an initial electron transfer to the triple bond of an acetylenic ketone (eq. 34) yielding an



(34)

acetylenic radical anion which undergoes ring closure by nucleophilic addition of a vinyl carbanion to the carbonyl function.[87] As yet, no firm experimental evidence has been obtained to either strongly support or reject either of these proposals.

Recently it has been observed that five-membered rings can also be formed by the cyclization of 5-hexenyl organometallic compounds [109] and *δ*-acetylenic Grignard reagents. [108,110] Whether these are "radical"

or anionic cyclizations, however, remains to be determined.

In summary, it appears from this brief investigation that the use of radical anions as electron transfer reagents is a feasible and useful synthetic tool to effect intramolecular cyclizations.

However, many factors contribute to the success or failure of this process, such as solvent, temperature, counter ion, and proton source. All are important parameters which must be considered in applying this method to polyfunctional molecules of higher complexity so as to achieve cyclization selectively over other possible side-reactions.

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded on a Unicam SP 1000 Infrared Spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were run on a Varian A-60 or HR-100 Spectrometer. Unless otherwise stated, carbon tetrachloride (CCl_4) was employed as the solvent with tetramethylsilane (TMS) as the internal reference standard. Chemical shifts are reported as δ values relative to TMS = 0. The following abbreviations were used in the text: s = singlet, d = doublet, t = triplet, q = quartet, sex = sextet, and m = multiplet.

Mass spectra were recorded on an AEI Model MS-2 or Model MS-9 Spectrometer. Spectra are reported in the following fashion: m/e = peak mass (relative intensity).

Quantitative gas liquid chromatographic (glc) analyses were performed on Varian Aerograph Series 1200 and 1400 instruments versus a reference solution of the authentic compounds, using the following columns: Column A: 10% β,β'-oxydipropionitrile on Chromosorb W, 5'/1/8"; Column B: 15% Carbowax 600 on Chromosorb T, 5'/1/8"; Column C: 15% Carbowax 20M on Chromosorb W-AW-DMCS, 5'/1/8". Preparative gc work was performed on a Varian Aerograph A-90-P3 instrument using Column D: 15% STAP on Chromosorb W, 10'/1/4".

Refractive indices were measured on a Bausch and Lomb Abbé - 3L Refractometer.

All operations were carried out under an atmosphere of oxygen-free nitrogen.[69]

Preparation of Radical Anion Solutions.

Biphenyl was purified according to conventional methods.[111] Trimesitylboron was purified by sublimation [180-185° (2 mm)]. Tetrahydrofuran and dimethoxyethane were freshly distilled prior to use from lithium aluminium hydride and the sodium benzophenone ketyl respectively. The amount of solvent used in the following procedure corresponds to that amount which would be required to give the stated molarity in the specific experiments.

Sodium Biphenyl. All solutions were prepared by stirring magnetically (glass-coated stirring bar) at ambient temperature (24 - 26°) one equivalent of freshly cut sodium shavings with two equivalents of purified biphenyl in the desired solvent for 3 to 5 hours.

Sodium Trimesitylboron. Equivalent amounts of sodium shavings and trimesitylboron were added to dimethoxyethane. Formation of the blue colour of the radical anion-metal complex was immediate on mixing. The mixture was stirred for at least 3 hours at ambient temperature before use (glass-coated stirring bar).

Lithium Trimesitylboron. Solutions of this complex were formed in a manner similar to that of sodium trimesitylboron using 10 - 20% excess lithium metal. Formation of the characteristic blue colour was not immediate. Vigorous stirring was necessary to release the complex from the surface of the metal, which was initially formed as a black coating. Reaction times of 6 to 15 hours were allowed from the time the blue complex appeared in solution.

General Work-up and Isolation Procedure.

In the reaction between a radical anion solution and an unsaturated ketone, the following procedure was followed. Unless otherwise stated, the reaction mixture was quenched by addition of a saturated ammonium chloride solution (1/20 to 1/10 of volume), carefully, when unreacted metal was present. The aqueous layer was extracted with ether (3 times, equal volumes). The combined organic phases were washed with brine solution, and dried (Na_2SO_4). Concentration to a standard volume usually followed for glc quantitative analysis.

For isolation purposes, separation of the reaction components from the bulk of the biphenyl or trimesitylboron was accomplished in the following way. The organic extract was concentrated under vacuum (rotary evaporator, bath temperature below 60°). On cooling the concentrate in ice,

a solid usually separated. Half the volume of aqueous methanol (1:1 by volume) was added. If no solid separated, the solution was poured onto an equal volume of ice-cold aqueous methanol (1:1). The solid was filtered and washed (2 or 3 times) with aqueous methanol (1:1). The filtrate was saturated with sodium chloride and extracted with an equal volume of ether (3 times). The solvent was removed under vacuum until the concentrate showed two layers. These were separated and the aqueous layer was again extracted with ether. The combined organic phases were dried (Na_2SO_4) and the solvent removed. The second extraction usually afforded a concentrate free of any methanol or water.

Attempted Synthesis of 6-Hepten-2-one by Reaction of Allylcopper[100] with Methyl Vinyl Ketone.

Allylmagnesium bromide was prepared according to Grummitt *et al.*[112] by the addition of 18.8 g (0.155 mole) of allyl bromide to 7.4 g (0.30 g.- atom) of magnesium turnings in 200 ml of dry ether at 0°. The allyl Grignard solution was decanted from the unreacted magnesium by filtration through a glass-wool plug, under N_2. The solid was washed with anhydrous ether, and the washes added to the filtrate. Purified cuprous iodide (29.5 g, 0.155 mole) was added to the cooled Grignard solution (-78°), and the mixture was warmed (to -30 and -40°) for

2 hours with constant mechanical stirring. The dark red mixture was cooled (-78°) and 5.29 g (0.077 mole) of freshly distilled methyl vinyl ketone in ether was added dropwise during 2 hours. The reaction mixture was allowed to warm to 0° and poured into ice-cold saturated ammonium chloride solution. After ether extraction, the combined organic extracts were washed with brine solution, dried (Na_2SO_4), and concentrated (rotary evaporator). Distillation of the residue afforded 5.9 g (70%) of a fraction wihich distilled at 40-42° (15 mm). The product consisted of two components. A sample, separated by preparative glc (Column D, 120°), was shown to contain approximately 70% of the 1,2-adduct, allyl methyl vinyl carbinol, ir (liquid film): 3400 br (bonded OH), 3070, 1840, 1640, 990, 915 cm^{-1} ($CH=CH_2$); nmr: $\underline{\delta}$ 1.21 (s, 3) $C\underline{H}_3$-C-OH, 1.70 (s, exchd by D_2O) O$\underline{H}$, 2.24 (d of tr, 2, J = 6.5 and 1.0 cps) =CH-$C\underline{H}_2$-COH, 4.8-6.2 (m, 6) $[C\underline{H}_2=C\underline{H}-]_2$. The 1,4-adduct, 6-hepten-2-one was shown in the same way, to be present in 30% yield, ir (liquid film): 1715 (C=O), 1365 (activated methyl), 3070, 1830, 1640, 990, 915 cm^{-1} (-CH=CH_2); nmr: $\underline{\delta}$ 2.03 (s, 3) $C\underline{H}_3C=O$, 2.34 (t, 2, J = 6.5 cps) $CH_2C\underline{H}_2C=O$, 1.4 - 2.1 (m, 4) $C\underline{H}_2C\underline{H}_2C=$, 4.7 - 6.0 (m, 3) -$C\underline{H}=C\underline{H}_2$. An attempt at separating the ketone from the alcohol by vigorously stirring the distilled product-mixture in ether (200 ml) with 500 ml of saturated sodium bisulphite solution

failed in precipitating the bisulphite addition product after 10 days at room temperature, and upon cooling the bisulphite layer in ice.

Preparation of 6-Hepten-2-one (26) by Rearrangement of Allyl Methyl Vinyl Carbinol.

To an ether solution of allylmagnesium bromide (prepared as described previously) [112] was added, dropwise, an ether solution of methyl vinyl ketone (10.6 g, 0.155 mole). After stirring for 30 minutes at 0°, the reaction mixture was poured into an equal volume of saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine solution, dried (Na_2SO_4), and concentrated. The residue was pyrolysed by injecting slowly 0.5 ml samples on a column (5'/1/4") of glass beads at 380-390° with a nitrogen gas flow of 2.5 ml per minute, connected to a collector immersed in a Dry Ice-acetone bath. A light orange oil was obtained which was chromatographed over silica gel (Kiesel Gel) using *n*-pentane-ether (3:1 by volume) as eluant. The ketone-containing fraction was distilled, bp 56-57° (20 mm) [lit.[113] 41-43° (10 mm)].

Preparation of Methallyl Methyl Vinyl Carbinol.

A solution of 45 g (0.5 mole) of methallyl chloride in 45 ml of ether was added dropwise to 23 g (1 g.-atom) of magnesium turnings in 200 ml of ether at 0°. After 2 hours, the solution was decanted and the magnesium was washed several times with dry ether. To the cooled methallylmagnesium chloride solution (0°), was added dropwise a solution of methyl vinyl ketone (28 g, 0.4 mole) in 30 ml of ether. The mixture was allowed to warm to room temperature and worked up in a manner analogous to that described for the reaction of the allyl Grignard reaction. Fractional distillation of the crude product afforded 26 g (52%) of methallyl methyl vinyl carbinol, bp 54.5-55.0° (19 mm) [lit.[114] 46-47° (10 mm)], ir (liquid film): 3450 br (bonded OH), 1640 (C=C), 990, 920 (-CH=CH_2), 890 (C=CH_2), 1460, 1375 cm^{-1} (methyl); nmr: δ 1.25 (s, 3) C$\underline{H}_3$-C-OH, 1.64 (s, exch by D_2O) O$\underline{H}$, 1.26 (s, 2) C$\underline{H}_2$-C-OH, 1.80 (br d, 3, J = 1 cps) C$\underline{H}_3$-C=CH, 4.6 - 6.3 (m, 5) C=C$\underline{H}_2$ and C$\underline{H}$=C$\underline{H}_2$.

Rearrangement of Methallyl Methyl Vinyl Carbinol.[99] Preparation of 6-Methyl-6-hepten-2-ne. (27)

Under a pressure of 15 mm, 17.3 g (0.14 mole) of methallyl methyl vinyl carbinol was slowly distilled through a column (30 cm x 2.5 cm) packed with glass

helices, which was kept at a temperature of 390°. The rearranged product was condensed in a flask connected at the outlet of the column and immersed in a Dry Ice-acetone bath. Fractional distillation of the condensate afforded 2.9 g (17%) of a ketone-containing fraction, bp 72-74° (22 mm) which was shown to contain traces of an alcohol by ir. The product was further purified by preparative glc (Column D, 130°) yielding 27 as a colourless liquid, ir (liquid film): 1715 (C=O), 1365 (activated methyl), 3080, 1645, 890 cm^{-1} ($C=CH_2$); nmr: δ 1.4 - 2.3 (m, 4) CH_2-CH_2-C=, 1.73 (br s, 3) CH_3-C-CH_2, 2.10 (s, 3) CH_3C=O, 2.38 (t, 2, J = 7 cps) CH_2CH_2C=O, 4.78 (br s, 2) C=CH_2.

Preparation of 1,2-Dimethylcyclopentanol.

A solution of 2-methylcyclopentanone (2.05 g, 20.9 mmole) in 5 ml of ether was added dropwise to an ether solution of methylmagnesium iodide [from 3.41 g (24 mmole) of methyl iodide and 0.884 g (37 mg.-atom) of magnesium in 15 ml of ether]. The reaction was quenched by adding saturated ammonium chloride solution. Extraction with ether, followed by washing the ether extracts with brine solution, and drying (Na_2SO_4) gave, after removal of the solvent and fractional distillation, 1.4 g (58%) of 1,2-dimethylcyclopentanol [bp 63-64° (20 mm)] as an isomeric mixture. Preparative glc (Column D, 140°) afforded pure

trans-1,2-dimethylcyclopentanol (31b), n_D^{25} 1.4466 (lit.[115] 1.4463), and pure cis-1,2-dimethylcyclopentanol (31a), n_D^{25} 1.4514 (lit.[115] 1.4523).

Reaction of 6-Hepten-2-one (26) with Sodium Biphenyl.

In tetrahydrofuran at -70° (Table III, entry 1.)

A preformed sodium biphenyl solution (35 ml of 0.25M solution) in tetrahydrofuran was added, dropwise, during 1 hour, to 0.30 g (2.7 mmole) of 26 as a solution in 10 ml of tetrahydrofuran, cooled by a Dry Ice-acetone bath. The blue-green solution was allowed to warm to 25° and then, was magnetically stirred for 3 hours. The reaction mixture was quenched by pouring into an equal volume of ice-cold saturated ammonium chloride solution. The aqueous layer was extracted (3 times) with ether. The organic extracts were washed with brine solution and dried (Na_2SO_4). After removal of the solvent, the concentrate was shown to contain three components (other than biphenyl and reduced biphenyls), by glc analysis (Column A, 60°). By comparison with authentic samples (prepared previously), the components were identified (in order of elution) as 6-hepten-2-one (26) (35%), trans-1,2-dimethylcyclopentanol (31b) (8.9%) and cis-1,2-dimethylcyclopentanol (31a) (29%).

In tetrahydrofuran at -35 to -40°(Table III, entry 2.) A preformed solution of sodium biphenyl (50 ml,of 0.12M solution) in tetrahydrofuran, cooled to ca. -35° was added, dropwise, during 1 hour to a solution of 26 (0.112 g, 1.0 mmole) in 10 ml of tetrahydrofuran at -35 to -40°. The blue-green reaction mixture was stirred for an additional 2 hours. At this point, an aliquot quenched with ammonium chloride showed on glc analysis (Column A, 60°) a ratio of 26 to cyclic alcohol 31 of 45:55. The mixture was allowed to warm to 25°. After 18 hours, it was worked up in a manner similar to that described previously. Analysis by glc, as before, showed unreacted ketone 26 (22%), trans alcohol 31b (7.0%) cis alcohol 31a (36%), and a fourth component in less than 5%, which had the same retention time as 6-hepten-2-ol (32) (obtained from lithium aluminium hydride reduction of 26).

Reaction between 26 and Sodium Biphenyl (formed in situ) in Dimethoxyethane (Table III, entry 6.)

A solution of 26 (0.112 b, 1.0 mmole) in 15 ml of dimethoxyethane containing 0.92 g (6.0 mmole) of biphenyl and 0.74 g (10.0 mmole) of *t*-butyl alcohol was cooled to -45°. Addition of thin sodium shavings (0.46 g, 20 mg.-atoms) resulted in the immediate formation of a blue

colour on the surface of the metal, which was used up as it was formed. The mixture was stirred magnetically for 6 hours, at which point it turned blue, and no substrate was left (by analysis of an aliquot of the reaction mixture as before). Work-up according to the procedure described previously afforded trans- (31b) and cis-(31a) 1,2-dimethylcyclopentanol in 7.4 and 56% yield respectively as estimated by glc (Column A, 60°).

Reaction between 6-Hepten-2-one (26) and Sodium Biphenyl (formed in situ) in Tetrahydrofuran in the Presence of *t*-Butyl Alcohol (Table III, entry 3.)

To a solution of biphenyl (0.46g, 3.0 mmole) in 10 ml of tetrahydrofuran (at -35 to -40°), was added 0.070 g (3.0 mg.-atoms) of sodium shavings, followed by a solution of 26 (0.112 g, 1.0 mmole) and *t*-butyl alcohol (0.082 g, 1.1 mmole) in 2 ml of tetrahydrofuran all at once. After 2 hours of stirring, glc analysis (Column A. 60°) of an aliquot of the reaction mixture quenched with ammonium chloride showed a ratio of unreacted ketone 26 to cyclic alcohol 31 of 40:60. No appreciable change was observed after 3 hours. The mixture was allowed to warm to 25° and stirred for an additional 10 hours, during which time it turned blue. Glc analysis, as before, showed a ratio of 26 to 31 of 32:68.

Addition of 0.074 g (1.0 mmole) of *t*-butyl alcohol to the reaction mixture produced no detectable changes in the ratio of 26 to 31 after 0.5 hour (ratio 34:66).

Reaction of 6-Hepten-2-one(26) and Sodium Biphenyl (formed in situ) in Tetrahydrofuran in the Presence of Water. (Table III, entry 4)

A solution of biphenyl (0.46 g, 3.0 mmole) in 10 ml of tetrahydrofuran was cooled to -35 to -40°. Sodium shavings (0.14 g, 6.0 mg.-atoms) were added, immediately followed by 26 (0.112 g, 1.0 mmole) and water (0.053 g, 3.0 mmole) as a solution in 2 ml of tetrahydrofuran. After 2 hours of stirring, the mixture became blue. It was stirred for an additional 5 hours and worked-up as described previously in the general work-up procedure. Analysis by glc (Column A, 60°) showed 10% of unreacted ketone 26, 14% of trans cyclic alcohol 31b and 42% of the cis alcohol 31a. Traces (less than 5%) of 6-hepten-2-ol were also present.

Reaction between 6-Hepten-2-one (26) and Sodium Biphenyl (formed in situ) in Dimethoxyethane. (Table III, entry 5)

To a solution of biphenyl (0.46 g, 3.0 mmole) in 10 ml of dimethoxyethane (at -35 to -40°), was added successively 0.14 g (6.0 mg.-atoms) of sodium shavings, and

0.112 g (1.0 mmole) of 26. After 1 hour, the mixture became blue in colour. Analysis of an aliquot (quenched with ammonium chloride solution) indicated a ratio of unreacted ketone 26 to cyclic alcohol 31 of 56:44 (by glc, Column A, 60°). After an additional 3 hours and 7 hours of stirring, the ratio was estimated as 44:56 and 30:70 respectively. Water (0.053 g, 3.0 mmole) was added and after a period of 0.75 hour the substrate was completely consumed (by glc analysis of an aliquot of the reaction mixture as before). Work-up of the reaction mixture as described previously, afforded a yield of isomeric 1,2-dimethylcyclopentanols of 12% and 63% for the trans-isomer (31b) and the cis-isomer (31c) respectively, as estimated by glc (Column A, 60°).

Reaction between 6-Hepten-2-one (26) and Sodium Biphenyl (formed in situ) in Dimethoxyethane in the Presence of Water. (Table III, entry 7)

Sodium shavings (0.35g,, 15 mg.-atoms) were added to a solution of biphenyl (1.16 g, 7.5 mmole) in 45 ml of dimethoxyethane, cooled at -35 to -40°. The blue colour of the radical anion appeared on the surface of the metal. Immediately thereafter a solution of 26 (0.280 g, 2.5 mmole) and water (0.055 g, 3.0 mmole) in dimethoxyethane was added, dropwise, during 1 hour. The mixture was stirred for an additional 1.5 hours at which time

the blue colour of the radical anion appeared and persisted. The mixture was worked up as described previously. Glc analysis (Column A, 60°) showed a yield of trans-1,2-dimethylcyclopentanol (31b) of 20% and a yield of the cis-isomer (31a) of 72%. The alcohols were separated by preparative glc (Column D, 125°). Trans-1,2-dimethylcyclopentanol (31b), ir (liquid film): 3450 (bonded OH), 915 cm^{-1} (cyclic tertiary alcohol); nmr: δ 0.89 (d, 3, J = 7 cps) $C\underline{H}_3CH$, 1.19 (s, 3) $C\underline{H}_3C$-OH, 1.3 - 2.2 (m, 7) -$(C\underline{H}_2)_3C$ -; mass spectrum m/e: 114 M^+. Cis-1,2-dimethylcyclopentanol (31a), ir (liquid film): 3450 (bonded OH), 915 cm^{-1} (cyclic tertiary alcohol); nmr: δ 0.87 (d, 3, J = 7 cps) $C\underline{H}_3CH$, 1.10 (s, 3) $C\underline{H}_3C$-OH, 1.3 -2.2 (m, 7) -$(C\underline{H}_2)_3C\underline{H}$-, 2.46 (exch. by D_2O) O$\underline{H}$; mass spectrum m/e: 114 M^+; n_D^{25} 1.4510 (lit.[115] 1.4523).

Reaction between 6-Methyl-6-hepten-2-one (27) and Sodium Biphenyl (formed in situ) in the Presence of Water.

A solution of 0.32 g (2.5 mmole) of 27 and 0.055 g (3.0 mmole) of water in dimethoxyethane was added to 1.16 g (7.5 mmole) of biphenyl and 0.35 g (15 mg.-atoms) of sodium shavings in 50 ml of dimethoxyethane as described in the preceding experiment. The reaction mixture turned blue after 1 hour. After 5 hours of additional stirring, analysis of an aliquot of the reaction mixture

(quenched with ammonium chloride solution) indicated ca. 50% unreacted substrate (by glc, Column C, 105°). The mixture was allowed to warm to 25° and then worked up after 18 hours as described previously. Analysis by glc, as before, showed four components (in order of elution): unreacted ketone 27 (<5%), isomeric 1,3-dimethylcyclohexanol (34 a and b)(<1%), and 6-methyl-6-hepten-2-ol (35) (<5%). the structure assignments were based on glc peak enhancement of the respective component with authentic isomeric 1,3-dimethylcyclohexanol (prepared by the reaction of methylmagnesium iodide with 3-methylcyclohexanone) and authentic 35 (prepared by reduction of 27 with lithium aluminium hydride.)

Reaction of 6-Methyl-6-hepten-2-one (27) with Preformed Sodium Biphenyl.

A. Water as proton source. A solution of 27 (0.1 (0.126 g, 1.1 mmole) and water (0.053 gm 3.0 mmole) in 5 ml of dimethoxyethane was added dropwise to a solution of sodium biphenyl (10 ml of a 0.3M solution) in dimethoxyethane cooled to -35 to -40°. After stirring for an additional 1 hour, the mixture was worked up as described previously. Analysis by glc (Column C, 105° and 140°) showed an estimated yield of unreacted ketone 27 of 40% and a trace amount (<5%) of 6-methyl-6-hepten-2-ol (35).

B. *t*-Butyl alcohol as proton source. A solution of 27 (0.126 g, 1.1 mmole) and *t*-butyl alcohol (0.22 g, 3.0 mmole) in 5 ml of dimethoxyethane was added dropwise to a preformed solution of sodium biphenyl in dimethoxyethane at 0 to-5° (10 ml of a 0.3M solution). After 5 hours of additional stirring, the mixture afforded an estimated glc yield of unreacted ketone 27 of 49% and a trace amount (<5%) of 6-methyl-6-hepten-2-ol (35).

Reaction between 6-Methyl-6-hepten-2-one (27) and Sodium Biphenyl-Dicyclohexyl-18-crown-6.

Sodium (0.038 g (1.6 mg.-atoms), biphenyl (0.46 g, 3.0 mmole), and purified [101] dicyclohexyl-18-crown-6 (0.614 g, 1.6 mmole) were mixed in 15 ml of dimethoxyethane and stirred for 3 hours below 10°. Addition of 27 (0.126 g, 1.1 mmole) and *t*-butyl alcohol (0.22 g, 3.0 mmole) to the cold sodium biphenyl solution (0 to -5°), as described in the previous experiment gave, after 1.5 hours, a colourless mixture which contained on glc analysis (Column C, 105° and 140°) a trace amount (<1%) of a new component with retention time in the sample expected for 1,2,2-trimethylcyclopentanol (33), 36% of unreacted ketone 27, and less than 5% of 6-methyl-6-hepten-2-ol (35).

Reaction between 6-Methyl-6-hepten-2-one (27) and Sodium Trimesitylboron-Dicyclohexyl-18-crown-6.

Sodium shavings (0.038g, 1.6 mg.-atoms), trimesitylboron (0.55 g, 1.5 mmole), and purified [101] dicyclohexyl-18-crown-6 (0.614 g, 1.6 mmole) were mixed in 15 ml of dimethoxyethane and stirred for 3 hours below 20°. The dark blue solution was cooled to 0 to-5°, and a solution of 27 (0.126 g, 1.1 mmole) and *t*-butyl alcohol (0.22g,, 3.0 mmole) in dimethoxyethane was added. After stirring for 2.5 hours, no appreciable amount of starting ketone 27 had been consumed. The reaction mixture was warmed to 25° and stirred for an additional 16 hours. Analysis by glc , after work-up as before, showed an estimated yield of unreacted ketone 27 of 28% (Column C, 105°) and of 6-methyl-6-hepten-2-ol (35) of 52% (Column C, 140°).

Reaction between 6-methyl-6-hepten-2-one (27) and Lithium Trimesitylboron.

A solution of 27 (0.63 g, 5.0 mmole) in 20 ml of dimethoxyethane was added dropwise, during 25 minutes, to a 0.1M solution of lithium trimesitylboron (150 ml) cooled at 0 to -5°, to which had been added 1.11 g (15 mmole) of *t*-butyl alcohol. After stirring for an additional 30 minutes, the mixture was quenched by the

addition of saturated ammonium chloride solution. A gas was slowly evolved as the blue colour disappeared. The work-up was continued as in the previously described general procedure. Trimesitylboron was recovered quantitatively (5.53 g), mp 195-197° (lit.[9] 190.5-191.5°). A pale yellow oil was obtained which contained two components which were separated by preparative glc (Column D, 140°). The first component, 1,2,2-trimethyl-cyclopentanol (33) was obtained as a low melting solid, mp 23-27°, ir (liquid film): 3450 (bonded OH), 1470, 1460 (gem-dimethyl), 915 cm^{-1} (cyclic tertiary alcohol); nmr: δ 0.87 (s, 3), 0.97 (s, 3) $(CH_3)_2C$, 1.15 (s, 3) CH_3C-OH, 1.27 (exch. by D_2O) OH, 1.3 - 2.0 (m, 6) $-(CH_2)_3$; mass spectrum m/e: 128 M^+. The second component, 6-methyl-6-hepten-2-ol (35) was obtained as a colourless liquid, ir (liquid film): 3360 (bonded OH), 3080, 1650, 890 cm^{-1} ($C=CH_2$); nmr: δ 1.12 (d, 3, J = 6.5 cps) CH_3CH, 1.2 -1.7 (m, 4) $-(CH_2)_2-$, 1.72 (s, 3) $CH_3C=$, 2.9 (exch. by D_2O) OH, 3.7 (br sex, 1, J = 6-7 cps) -CH-OH, 4.5 (br s, 2) $C=CH_2$; mass spectrum m/e: 128 M^+. The yields of 33 and 35 were estimated by glc (Column C, 105° and 140°) as 47 and 48 % respectively.

Reaction of 6-Methyl-6-hepten-2-one (27) with Lithium Metal and *t*-Butyl Alcohol.

A mixture of lithium metal (0.043 g, 6.5 mg.-atoms) and *t*-butyl alcohol (0.15 g, 2.0 mmole) in 10 ml of dimethoxyethane was cooled to 0 to -5°. To this was added 0.063 g (0.5 mmole) of 27 in 4 ml of dimethoxyethane. After stirring for 2 hours, the unreacted lithium metal was carefully destroyed by slowly adding a saturated ammonium chloride solution. The layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine solution, and dried (Na_2SO_4). Removal of the solvent (rotary evaporator) afforded 0.07 g of a pale yellow oil. Analysis by glc (Column C, 105 and 140°) showed a trace amount of unreacted ketone 27 (<1%), a trace amount of 1,2,2-trimethylcyclopentanol (33) (<1%), and 97% of 6-methyl-6-hepten-2-ol (35). A sample of 35 isolated by preparative glc (Column D, 140°) was spectroscopically identical to the material isolated in the preceding experiment.

Preparation of the Ethylene ketal of 5-Bromo-2-pentanone.

α-Acetobutyrolactone (105 g, 0.8 mole) (prepared by the method of Zuidema, van Tamelen, and van Zyl[116] from ethylacetoacetate and ethylene oxide) was dissolved in 230 ml of acetic acid and heated to 70-75°. Hydrogen bromide was slowly passed through the hot solution during 7 hours (according to the method of W.R. Boon[117]).

The dark red solution was cooled, poured into water, and extracted with *n*-pentane. The organic extracts were washed successively with saturated sodium bicarbonate solution, and brine solution, then dried (Na_2SO_4). After removal of the solvent (rotary evaporator), the crude residue was dissolved in benzene (150 ml). Ethylene glycol (39 g) and 0.1 g of *p*-toluenesulphonic acid were added. The mixture was heated under azeotropic removal of water for 18 hours. The benzene solvent was partially distilled. The concentrate was shaken with solid sodium carbonate, and fractionally distilled. In that manner, 54 g (31%) of bromo ketal were obtained as a pale yellow liquid, bp 87-90° (7 mm), ir (liquid film): 1000 to 1300 cm^{-1} (C-O-C); nmr: δ 1.27 (s, 3) CH_3C-O, 1.4 - 1.8 (m, 4) CH_2CH_2C-O, 3.40 (t, 2, J = 7 cps) CH_2Br, 3.97 (s, 4) $(CH_2\text{-}O)_2$.

Preparation of 6-Heptyn-2-one (28).[102,118]

Freshly distilled dimethylsulfoxide (50 ml) was heated with 0.10 mole of sodium hydride (52% oil dispersion) at 70 to 78° until hydrogen evolution was complete. To the resulting mixture, 50 ml of dry tetrahydrofuran was added along with 0.5 g of triphenylmethane. Acetylene gas was passed through the mixture until the red colour of the trityl carbanion disappeared. A white

suspension was obtained. A solution of the ethylene ketal of 5-bromo-2-pentanone, prepared previously, (21 g, 0.10 mole) in 20 ml of tetrahydrofuran was added dropwise at 25° during 1 hour with stirring. After 18 hours at 25°, water was added, and the mixture was extracted with *n*-pentane. The organic extracts were washed with brine solution, dried (Na_2SO_4) and concentrated (rotary evaporator). The residue (16.5 g) [ir (liquid film): 3300, 2120 cm^{-1} (C≡C-H)] was hydrolysed in 50 ml of aqueous methanol (1:1 by volume) containing one drop of hydrochloric acid, according to the method of Stork and coworkers.[87] After heating below reflux for 1.5 hours, the solution was cooled and extracted with *n*-pentane. The organic extracts were washed with brine, dried (Na_2SO_4), and distilled. 6-Heptyn-2-one (28) (6.5 g, 59%) was obtained as a colourless liquid, bp 83-84° (43 mm) [lit.[87] 82-85° (41 mm)], n_D^{20} 1.4380; ir (liquid film): 1715 (C=O), 3300, 2120 cm^{-1} (C≡C-H); nmr: δ 2.12 (s, 3) $CH_3C=O$, 1.84 (t, 1, J = 2.5 cps) $CH_2C\equiv CH$, 2.53 (t, 2, J = 6.5 cps) $CH_2C=O$, 1.5 - 2.4 (m, 4) CH_2CH_2C ; mass spectrum m/e: 110 M^+

Preparation of 6-Octyn-2-one (29).[102,118]

A solution containing 0.033 mole of dimsyl sodium in 50 ml of dimethylsulfoxide and 50 ml of tetrahydrofuran was prepared in the same manner as described above

from 0.033 mole of sodium hydride. The mixture was cooled to 25° and 0.1 g of triphenylmethane was added as indicator. Propyne was passed through the mixture until the red colour disappeared. To the grayish-white slurry was then added a solution of 6.30 g (0.030 mole) of the ethylene ketal of 5-bromo-2-pentanone, dropwise, during 30 minutes. After stirring for 5 hours at 25°, the mixture was worked up as described previously for 6-heptyn-2-one. The reaction afforded 1.07 g (29%) of 29 as a colourless liquid, bp 69.5° (6.5 mm) [lit.[118] 75° (4.5 mm)], n_D^{20} 1.4486; ir (liquid film): 1715 cm^{-1} (C=O); nmr: δ 2.13 (s, 3) $CH_3C{=}O$, 1.73 (t, 3, J = 2.5 cps) $CH_3C{\equiv}CCH_2$, 2.48 (t, 2, J = 6.5 cps) $CH_2CH_2C{=}O$, 1.4 - 2.4 (m, 4) $CH_2CH_2C{\equiv}$; mass spectrum m/e: 124 M^+

Reaction between 6-Heptyn-2-one (28) and Sodium Biphenyl (formed in situ). Preparation of 1-Methyl-2-methylenecyclopentanol (37).

A solution of 28 (2.20 g, 20 mmole) and water (0.72 g, 43 mmole) in 10 ml of dimethoxyethane was added during 25 minutes to a mixture of sodium shavings (2.76 g, 120 mg.-atoms) and biphenyl (9.24 g, 60 mmole) in 150 ml of dimethoxyethane cooled at -35 to -40°. The blue colour of the radical anion, which formed at the surface of the metal was immediately consumed as it went into

solution. After stirring for 4.5 hours, the mixture turned blue. After 15 minutes of additional stirring, the reaction mixture was worked up in the manner described in the general work-up procedure. Analysis by glc (Column B, 105°) showed an estimated 83% yield of product 37. Isolation procedure afforded 4.66 g of a cloudy oil which upon fractional distillation gave 1.2 g (58%) 1-methyl-2-methylenecyclopentanol (37) as a colourless liquid, bp 49.5-50.0° (10.5 mm), n_D^{20} 1.4677; ir (liquid film): 3390 (bonded OH), 3080, 1660, 900 ($C=CH_2$), 920 cm^{-1} (cyclic tertiary alcohol); nmr: δ 1.32 (s, 3) CH_3C-OH, 1.4 - 2.0 (m, 4) $-(CH_2)_2$, 2.2 - 2.6 (m, 2) $-CH_2C=$, 2.68 (exch. by D_2O) OH; mass spectrum m/e(relative intensity): 112(3) M^+, 97(23) 94(37) 91(19) 79(100) 77(44) 43(23) 41(21) 39(37). Anal. Calcd. for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.66; H, 10.73.

Reaction between 6-Octyn-2-one (29) and Sodium Biphenyl (formed in situ).

A solution of 29 (0.124 g, 1.0 mmole) and water (0.042 g, 2.2 mmole) in dimethoxyethane was added to a mixture of sodium shavings (0.14 g, 6.0 mg.-atoms) and biphenyl (0.46 g, 3.0 mmole) in 15 ml of dimethoxyethane with stirring at -35 to -40°. After 5 hours, glc analysis (Column C, 130°; injector temperature, 135°) of an aliquot (quenched with ammonium chloride solution) showed

the presence of three components other than biphenyl and reduction products of biphenyl. Work-up, as described before, yielded a product mixture which contained (by glc, as before) approximately 15% of 2-ethylidene-1-methylcyclopentanol (39a), 6% of unreacted ketone 29, and a third component which was tentatively assigned the structure 6-octyn-2-ol (38) on the basis of its glc behaviour.

Reaction of 6-Octyn-2-one (29) with Sodium Biphenyl (preformed).

A solution of 29 (0.124 g, 1.0 mmole) and *t*-butyl alcohol (0.16 g, 212 mmole) in 5 ml of dimethoxyethane was added (during 15 min.) to a solution (0.25M) of sodium biphenyl (15 ml) in dimethoxyethane at 0 to -5°. After a stirring period of 1 hour, the reaction mixture contained by glc (Column C, 130°; injector temperature, 135°) analysis of an aliquot (quenched with ammonium chloride solution) only a trace amount of cyclized product 39, along with 81% unreacted substrate.

Reaction between 6-Octyn-2-one (29) and Sodium Trimesityl-boron.

A solution of 29 (0.124 g, 1.0 mmole) and *t*-butyl alcohol (0.16 g, 2.2 mmole) in 5 ml of dimethoxyethane was added , dropwise, during 15 minutes to a 0.1M solution

(30 ml) of sodium trimesitylboron in dimethoxyethane at 0 to -5°. After 5 hours, the starting ketone 29 was completely consumed. Analysis by glc (Column C, 130°; injector temperature, 135°), after work-up as described previously, showed two main components: 2-ethylidene-1-methylcyclopentanol (39a) in a yield of 30%, and 6-octyn-2-ol (38). Treatment according to the general isolation procedure described previously yielded 0.25 g of a cloudy yellow oil, which consisted by nmr of two major products in approximately equal amounts 39a and 38. Nmr (of the crude reaction product): δ 1.25 (s, 3) $C\underline{H}_3C$-OH, 1.57 (d of t, J = 7 cps, and 1.5 cps) $C\underline{H}_3CH$= 5.43 (q of t, J = 7 cps and 1.5 cps) $CH_3C\underline{H}=CCH_2$, 1.08 (d, 3, J = 6.5 cps) $C\underline{H}_3CH$-OH, 1.71 (t, 3, J = 2.5 cps) $C\underline{H}_3C\equiv C$-$CH_2$, 3.3 -3.8 (m, 1) $CH_3C\underline{H}$-OH.

Reaction between 6-Octyn-2-one (29) and Lithium Trimesitylboron.

A solution of 29 (0.30 g, 2.4 mmole) in 10 ml of dimethoxyethane, was added, dropwise, during 30 minutes, to a 0.1M solution (75 ml) of lithium trimesitylboron in dimethoxyethane cooled to -5 to -10°, to which had been added 0.53 g (7.2 mmole) of *t*-butyl alcohol. After complete addition, the acetylenic ketone 29 was almost completely consumed. The dark blue solution was stirred for an additional 20 minutes and then worked up in the

manner described previously. Analysis by glc (Column C, 130°; injector temperature, 135°) showed three components: the first (immediately following the solvent) was due to decomposition of the product(s); the second, estimated, as 78%, was the anti-isomer 39a of 2-ethylidene-1-methyl-cyclopentanol, and the third component was 6-octyn-2-ol (38) (long retention time). Upon isolation, 2.7 g of trimesitylboron (quantitative recovery) and 0.45 g of a yellowish residue were obtained. Molecular distillation of 0.36 g of the oil at 50-53° (bath) (9 mm), gave 0.14 g (58%) of product as a colourless liquid, ir (liquid film): 3380 (bonded OH), 3050, 1675, 840 (C=CH), 915 cm^{-1} (cyclic tertiary alcohol); Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.28. Found: C, 75.69; H, 11.44. Nmr analysis: δ 1.13 (d, J = 6.0 cps; irradiation at 3.69 caused collapse of the doublet into a singlet) $C\underline{H}_3C$-OH; 1.56 and 1.77 (d of t, J = 7 cps and 1.5 cps; irradiation at 5.41 caused the collapse of the doublet of triplet into two "sharp" multiplets) $C\underline{H}_3CH=C$ (syn and anti); 1.71 (t, J = 2.5 cps) $C\underline{H}_3C$ C-CH_2; 5.2 - 6.1 (two partly overlapping q of t; irradiation at 1.58 caused the collapse into a singlet at 5.43) $CH_3C\underline{H}$=C-CH_2 (syn and anti). Integration of the methyl groups at 1.13, 1.24, and 1.36 indicated a relative ratio of 5:81:14. On addition of one equivalent of $Eu(fod)_3$[103], the assignment was as follows: δ 2.35 (d, irradiation at

9.75 gave a singlet), 9.75 (broad quartet, irradiation at 2.35 gave a broad singlet), 3.86 (d, irradiation at 7.05 gave a singlet). The relative assignments are reported in Table IV. The major components was assigned the anti-configuration of 2-ethylidene-1-methylcyclopentanol (39a); the minor components were the syn-isomer 39b, and the reduced alicyclic product, 6-octyn-2-ol (38). Mass spectrum of crude product (glc inlet, Colum C, 70 to 170°, injector temperature 200°) m/e(relative intensity): major component (39a) 126(1) M^+, 108(38) 93(100) 91(37) 79(31) 77(38) 65(12) 51(11) 53(14) 41(16) 39(30); minor component (38) 126(<1) M^+, 93(50) 85(50) 67(52) 66(73) 45(100) 43(63) 41(50) 39(50).

Preparation of 5,6-Heptadien-2-one (30).

The allenic ketone 30 was prepared by a modification of the method of Crandall and Mayer.[106] The ethylene ketal of 5-hexen-2-one was prepared by treating 97 g (1.0 mole) of 5-hexen-2-one with 62 g of ethylene glycol, and 0.1 g of *p*-toluenesulphonic acid in 200 ml of benzene for 5 hours with azeotropic removal of water. The solution was shaken with solid potassium carbonate, and the solvent was removed at atmospheric pressure. Fractional distillation of the concentrate afforded 118 g (83%) of the ethylene ketal, bp 93-94° (75 mm) [lit.[106] 80-82° (43 mm)].

Bromoform (126 g, 0.5 mole) was added dropwise to a slurry of potassium *t*-butoxide (MSA Research corp.) (77 g, 0.7 mole) and a solution of the above ethylene ketal (71 g, 0.5 mole) in 200 ml of *n*-pentane at 0° during 1.5 hours. The mixture was allowed to stir at 25° for 18 hours. Water was added and the mixture extracted with ether. The organic extracts were washed with brine solution and dried (Na_2SO_4). Removal of the solvent and distillation afforded 53 g (34%) of dibromocarbene adduct, bp 102.5-103.5° (0.09 mm) [lit.[106] 101-105° (0.25 mm)].

To an ether solution of the dibromocarbene adduct (31.4 g, 0.1 mole) in 100 ml of solvent was added, dropwise, 140 ml of 1.0M methyllithium solution at -65° over 1.5 hours.[119] The mixture was allowed to warm to ca -30° and water was added cautiously to destroy any excess methyllithium. The layers were separated and the aqueous layer was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated (rotary evaporator). The crude allene ketal (19.3 g) was hydrolysed in 100 ml of aqueous methanol (1:1 by volume) containing one drop of hydrochloric acid, according to the method of Stork and coworkers.[87] After heating near reflux for 1.5 hours, the solution was extracted with *n*-pentane. After drying (Na_2SO_4), and removal of the solvent, the crude product thus obtained, was distilled. 5,6-Heptadien-2-one (30)

was obtained as a colourless liquid (9.15 g, 83%), bp 56-59° (11 mm) [lit.[106] 64-67° (15 mm)], n_D^{20} 1.4611; ir (liquid film): 1715 (C=O), 1950, 850 cm^{-1} ($CH=C=CH_2$); nmr: $\underline{\delta}$ 2.10 (s, 3) $C\underline{H}_3C=O$, 1.6 - 2.7 (m, 4) $C\underline{H}_2C\underline{H}_2C=$, 4.4 - 5.4 (m, 3) $-C\underline{H}=C=C\underline{H}_2$; mass spectrum m/e: 110 M^+. The keto-allene was shown to be 100% pure by glc (Column B, 105°).

Reaction of 5,6-Heptadien-2-one (30) with Sodium Biphenyl (formed in situ).

A solution of 30 (0.11 g, 1.0 mmole) and water (0.076 g, 2.0 mmole) in 5 ml of dimethoxyethane was added, dropwise, during 45 minutes to a mixture of sodium shavings (0.14 g, 6.0 mg.-atoms) and biphenyl (0.46 g, 3.0 mmole) in 10 ml of dimethoxyethane at -35 to -40°. During the addition, the mixture became yellow. The reaction mixture was stirred for an additional 1 hour at which time it turned blue, and all the substrate was consumed. Work up, as before, and glc analysis of the reaction product (Column B, 105°) showed 15% 1-methyl-2-methylenecyclopentanol (37) as the only product.

Reaction between 5,6-Heptadien-2-one (30) and Preformed Sodium Biphenyl.

A solution of 30 (0.11 g, 1.0 mmole) and water (0.076 g, 2.0 mmole) in dimethoxyethane was added to

a solution of sodium biphenyl (prepared from 0.462 g (3.0 mmole) of biphenyl and 0.138 g (6.0 mg.-atoms) of sodium shavings in dimethoxyethane:tetrahydrofuran (8 ml:2 ml) for 6 hours at 25°) at -70°. After the addition was complete (5 min.) all the keto-allene 30 was consumed. Work-up as before and glc analysis (Column B, 105°) showed a 51% yield of 1-methyl-2-methylenecyclopentanol (37).

Reaction between 5,6-Heptadien-2-one (30) and Sodium Trimesitylboron.

With water at -35 to -40°. A solution of 30 (0.11 g, 1.0 mmole) and water (0.076 g, 2.0 mmole) in dimethoxyethane was added to 25 ml of 0.1M solution of sodium trimesitylboron in dimethoxyethane at -35 to -40°. After 2 hours, glc analysis (Column B, 105°) of an aliquot quenched with ammonium chloride solution showed a ratio of keto-allene 30 to cyclized product 37 of 90:10. The solution was warmed slowly to ca. 10°. After 25 minutes, analysis by glc as before showed unreacted keto-allene 30 in less than 5% and cyclized product 37 in 50%.

With water at 0°. The above reaction was repeated at 0 to -5°. After stirring for 1.5 hours, analysis by glc, as before, showed unreacted keto-allene 30 (16%) and cyclized product 37 (52%).

With *t*-butyl alcohol at 25°. The above reaction was

repeated using *t*-butyl alcohol (0.148 g, 2.0 mmole) instead of water, and doing the addition at 25°. After 30 minutes, analysis of the reaction mixture by glc (Column B, 105°) as before revealed no starting material and a 59% yield of cyclized product, 1-methyl-2-methylenecyclopentanol (37). In the same manner, when 0.74 g (10 mmole) of *t*-butyl alcohol was used in that reaction, a 54% yield of 37 was obtained.

Reaction between 5,6-Heptadien-2-one (30) and Sodium Trimesitylboron at -5°.

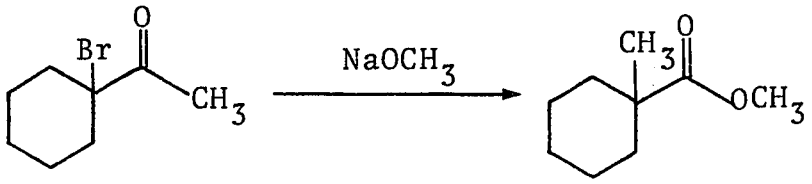
A solution of 30 (1.1 g, 10 mmole) in 20 ml of dimethoxyethane was added, dropwise, during 20 minutes to a solution of sodium trimesitylboron in dimethoxyethane (240 ml of 0.1M solution) cooled at -5° and containing 7.4 g (0.1 mole) of *t*-butyl alcohol. After 6 hours, the reaction was complete. Analysis by glc (Column B, 105°) showed 1-methyl-2-methylenecyclopentanol (37) as the only product (74%). Isolation as described in the general procedure afforded 8.6 g of trimesitylboron (quantitative recovery) and an oily cloudy residue (2.7 g). A sample purified by preparative glc (Column D, 110°) afforded pure cyclic alcohol 37 identical spectroscopically to the material obtained previously from the cyclization of 6-heptyn-2-one (28). Preparative glc at 150° yielded partially decomposed material.

PART II

THE SYNTHESIS OF α-HALOKETONES

INTRODUCTION

α-Haloketones undergo a variety of transformations which make them valuable precursors in many synthetic processes. They are used in the preparation of carboxylic acids (in the Favorsky rearrangement)[120] and in the stereoselective synthesis of olefins (Cornforth)[121] as illustrated in the following examples. (eqs. 35 and 36)



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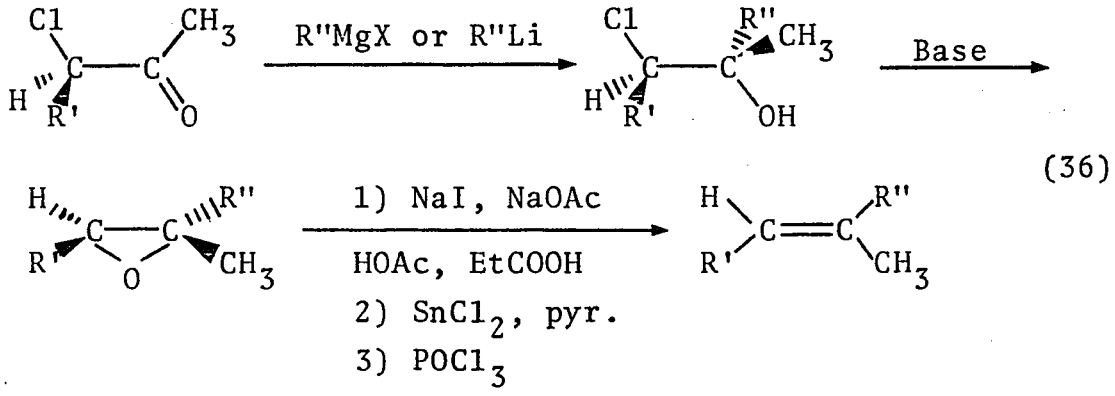
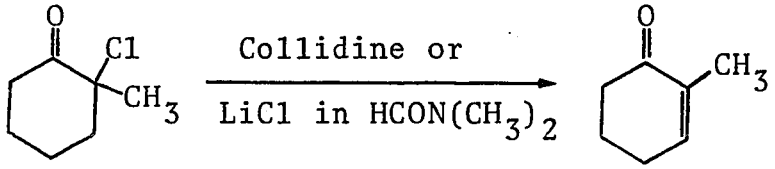


(36)

Because of their bifunctionality, they are useful as intermediates in the preparation of simple heterocycles (furans, and pyrroles).[122]

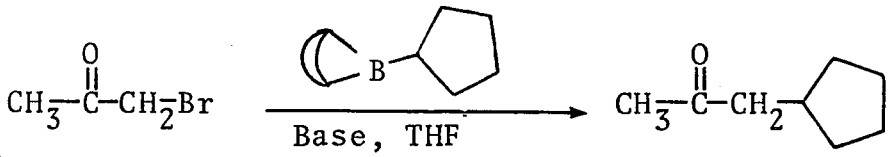
One of their more general applications has been in the preparation of α,β-unsaturated ketones (eq. 37)[123]

via halogenation of a ketone, followed by dehydrohalogenation.

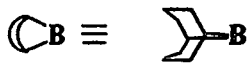


(37)

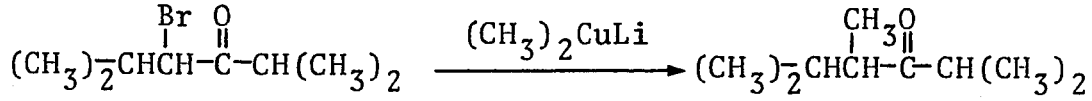
More recent uses of α-haloketones have been demonstrated by H.C. Brown and coworkers in their reaction with organoboranes to yield alkylated ketones, where the halogen has been substituted by an alkyl group (eq. 38),[124] and by



(38)

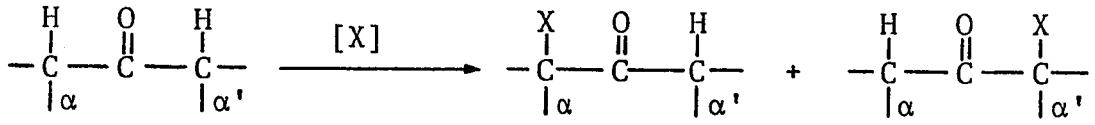
where 

Dubois and coworkers in their reaction with lithium cuprates (eq. 39) in a synthesis of hindered ketones.[125]



(39)

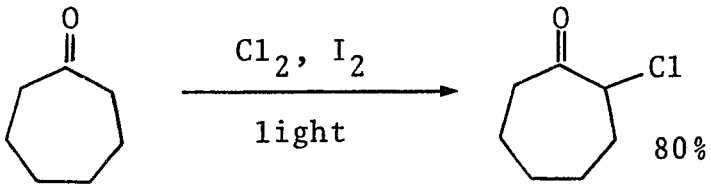
The most direct approach to the preparation of α-haloketones involves the halogenation of the corresponding ketone with a suitable halogenating agent.[126,127] The halogen enters one of the positions alpha to the carbonyl. (eq. 40)



(40)

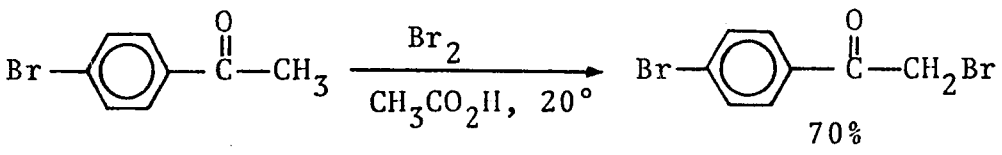
Chlorination can be brought about with elemental chlorine,[126,127] sulphuryl chloride,[128] and also (but less effectively) with N,N-dichloro-5,5-dimethylhydantoin,[129] selenium oxychloride,[130] and a combination of lead tetra-acetate and acetyl chloride.[131] Similarly, elemental bromine,[127] N-bromosuccinimide (NBS),[127] N,N-dibromo-5,5-dimethylhydantoin,[127,132] and bromine complexes (such as dioxane [133] and pyridine [134] dibromides) effect bromination.

Halogenation can be accomplished under free-radical conditions (using light, peroxides and other free-radical initiators)[127] (eq. 41)[135] as well as ionic conditions.



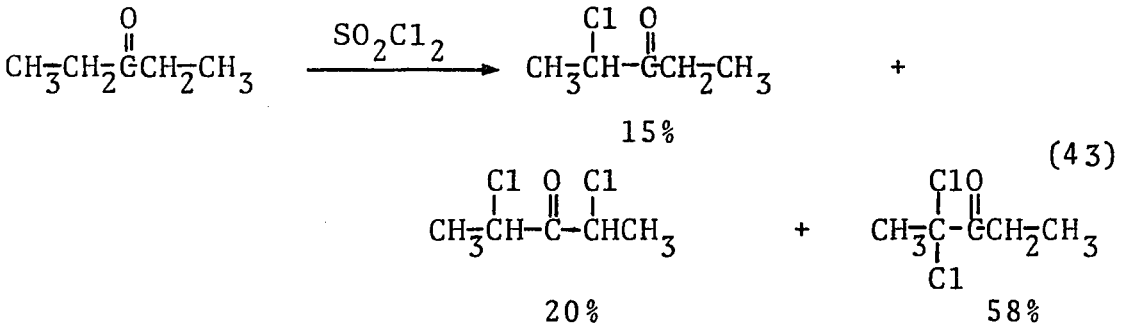
(41)

For the latter, the reaction is usually catalysed by acids (by the use of an acid as solvent, usually acetic acid) (eq. 42).[136] It may also be self-catalysed, since, when a neutral solvent is used (such as carbon tetrachloride or chloroform), after an initial induction period, some hydrogen halide is generated in the reaction mixture.



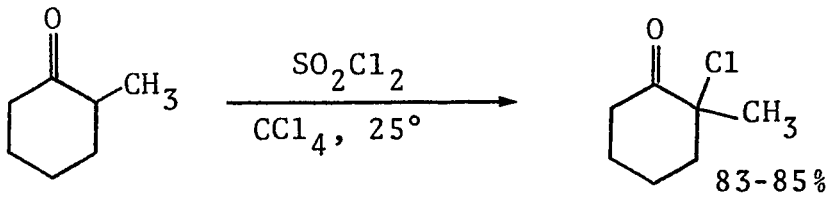
(42)

When the substrate has only one available alpha position (eq. 42), or is a symmetrical ketone (eq. 41), good yields of the monohalogenated ketone can be obtained. However, polyhalogenation often results, especially in the chlorination of acyclic ketones (eq. 43), which limits the application of this method.[137,128]



(43)

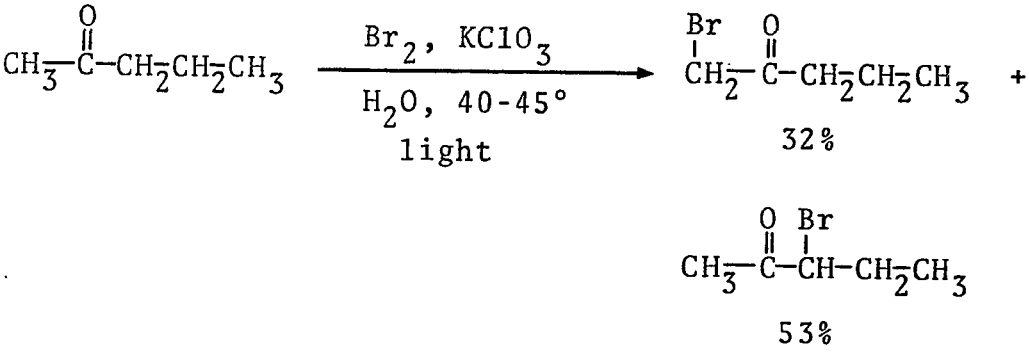
In the halogenation of unsymmetrical ketones, the position taken by the entering halogen is determined by various factors (acidity of α-hydrogen, rate of enolization in acid catalysed reaction,[138] steric requirement of the transition state leading to the halogenated product in substituted α-position,[128] etc.).[126] The order usually observed is tertiary > secondary > primary (eq. 44).[123]



(44)

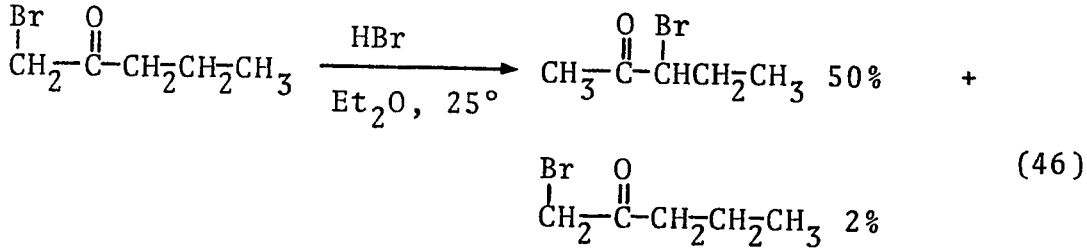
In some cases, the presence of an unsaturated substituent, such as a carbonyl group or an aromatic system, at the alpha position enhances the halogenation at that position.[127,128]

However, usually a mixture of positional isomers is obtained[137,139] (eq.45) which requires careful fractional separation, as illustrated in the bromination of 2-pentanone. (The potassium chlorate in the example acts to



(45)

remove the hydrogen bromide which may catalyse aldol condensation of the ketone. The same role is played by succinimide, a by-product of halogenation with N-halosuccinimide.) Furthermore, complications often arise by the ready acid-catalysed isomerization of the initially formed haloketone.[126,140-143] (eq. 46)[143]

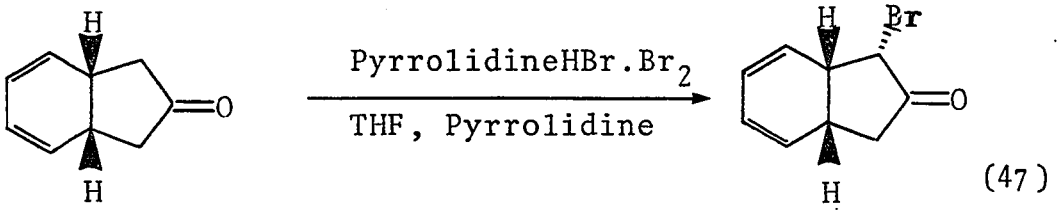


(46)

Various modifications have been applied in an attempt to obtain selectivity. Marquet and Gaudry have demonstrated that bromination of methyl ketones in the presence of methanol favours the formation of

bromomethyl ketones.[144] The same selectivity has been obtained in the bromination of dimethyl ketals and ethylene ketals, [145] as demonstrated by the same authors.

Halogenation with copper(II) halides,[146,147] in solvents such as dimethyl formamide, has been found to show specificity inasmuch as halogenation of double bonds does not occur. Some advantages have been gained by the use of perbromide salts (pyridine,[148] and pyrrolidine [149] hydrobromide perbromide, and phenyltrimethylammonium tribromide[150]) in small scale experimentation (easily weighed solids of high molecular weight) for their selectivity in the order ketone >> olefin >> enol acetate.[149-152] (eq. 47)[151]



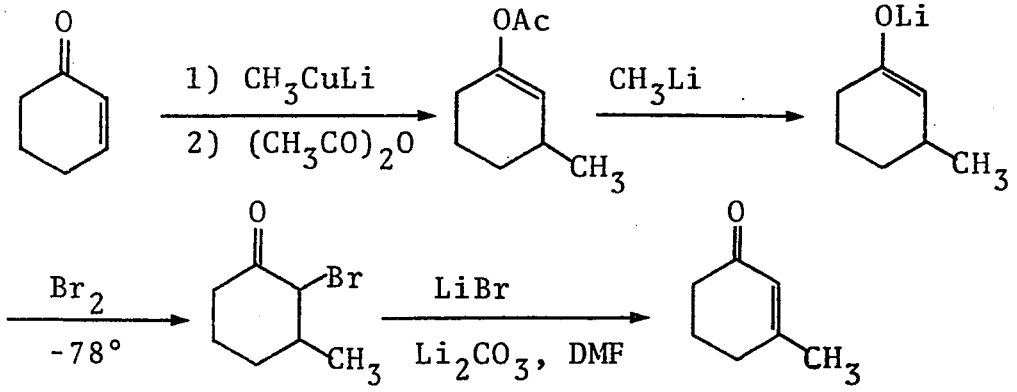
(47)

These perbromide salts will also brominate alpha to a ketal [149,150] at the less highly substituted position preferably,[152] yielding an alternate route to the α-haloketone.

Halogenation can also be catalysed by base. This reaction, which is believed to involve an enolate,[153] usually leads to polyhalogenation due to the increased acidity of the α-hydrogen by the newly introduced α-halogen

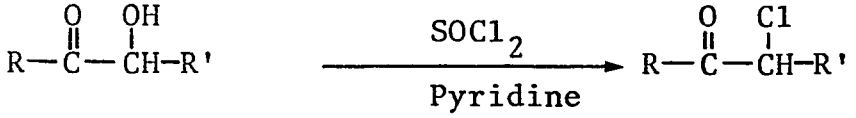
substituent. Base catalysis is usually used for the conversion of methyl ketones into acids via trihalomethyl ketones which are cleaved in the basic medium (the Haloform reaction).[154]

However, a recent report claims to convert specifically generated lithium enolates into α-bromoketones, uncontaminated with the α'-isomer, by low-temperature bromination.[155] An illustration is the transformation of cyclohexenone into 3-methylcyclohexenone (75% overall yield). (eq. 48)



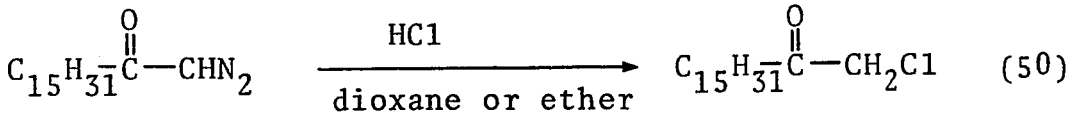
(48)

An alternate approach for the generation of position specific halogenated ketones is the transformation of a substrate which already contains an α-keto substituent. Examples are α-hydroxy ketones (acyloins) and α-diazoketones as illustrated in equations 49 to 51.[156-158]



(49)

(50-80%; R, R'= Alkyl)



(50)

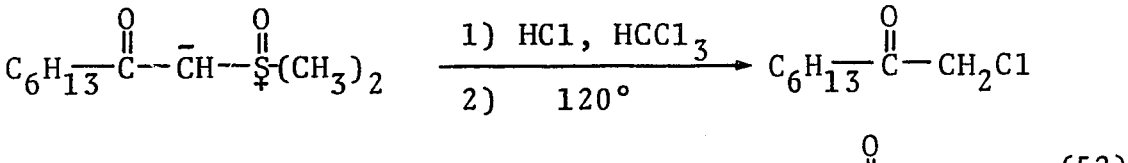
95%

(51)

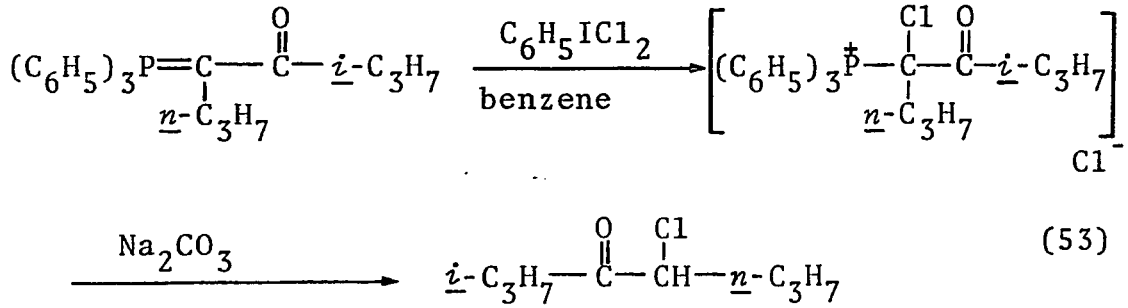
(50-80%; R=Alkyl)

Although both these methods afford a high yield of pure haloketone, they suffer from the unavailability of the starting materials. (The acyloin route is restricted to symmetrical types, [159] and the use of diazoketones is useful only for diazomethyl ketones. [160])

The halogenation of acyl ylids have successfully yielded position specific haloketones, as in the chlorination of acyloxosulphonium ylids [161] (eq. 52)and alkylidene phosphoranes [162] (eq. 53).



(52)

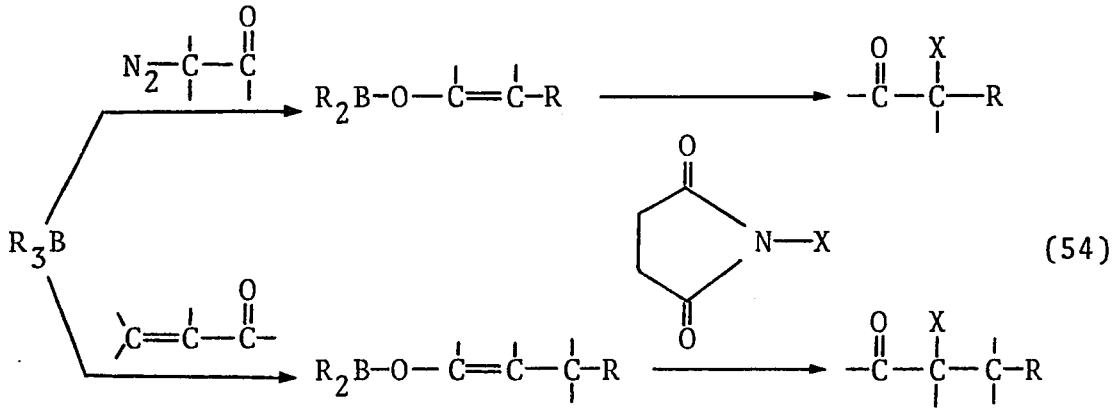


(53)

This latter method offers the advantage of leaving a degree of freedom in the construction of the carbon skeleton of the alkylidene phosphorane, although halogenation is restricted to chlorination.

Although enol acetates can be readily transformed into α-bromoketones [163] and represent a preferred route to α-iodoketones,[164] this approach depends on the site-specific formation of the necessary enol acetates. Usually they are obtained from the parent ketone as a mixture of isomers.

However, a regiospecific synthesis of enol borinates has recently been achieved, and these intermediates have been demonstrated by J. Bridson to undergo facile halogenation.[165] Thus they offer a route to α-haloketones whose carbon skeletons (dictated in part by the structure of the organoborane) can be constructed in a stepwise manner. (eq. 54)

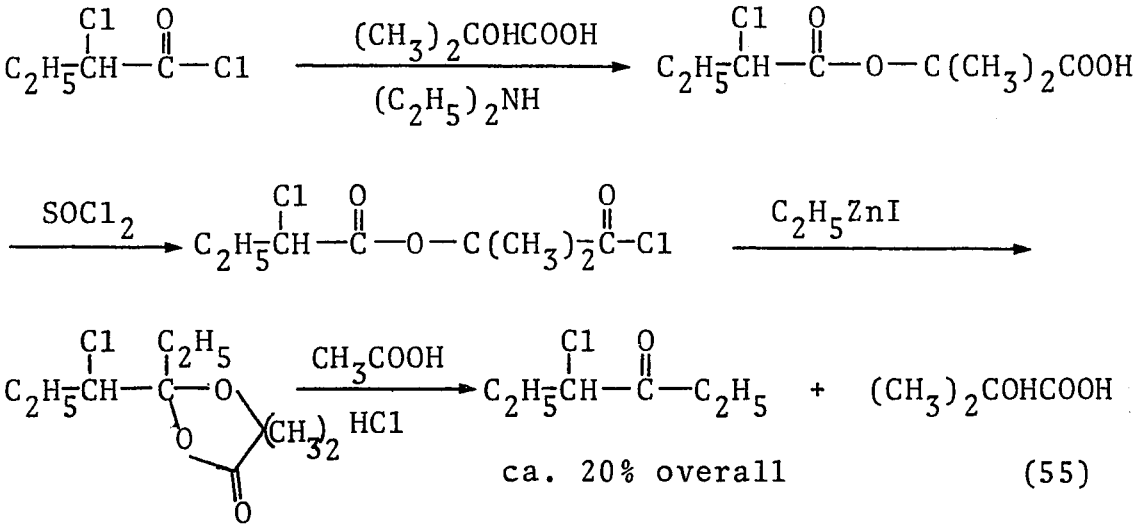


(54)

A third approach employed for the synthesis of α-haloketones has been modelled along the lines of

available general ketone synthesis. This involves either the reaction between an organometallic compound (organozinc, cadmium or magnesium)[166] and an acid chloride, or the acylation of an active methylene compound.[167]

The first literature example of such an approach stems from the work of Blaise on organozinc compounds. An α-chloroacid chloride was treated with an organozinc halide via a cyclic oxoketal which, as opposed to an α-haloketone, is unreactive towards the organometallic reagent (eq. 55).[168]

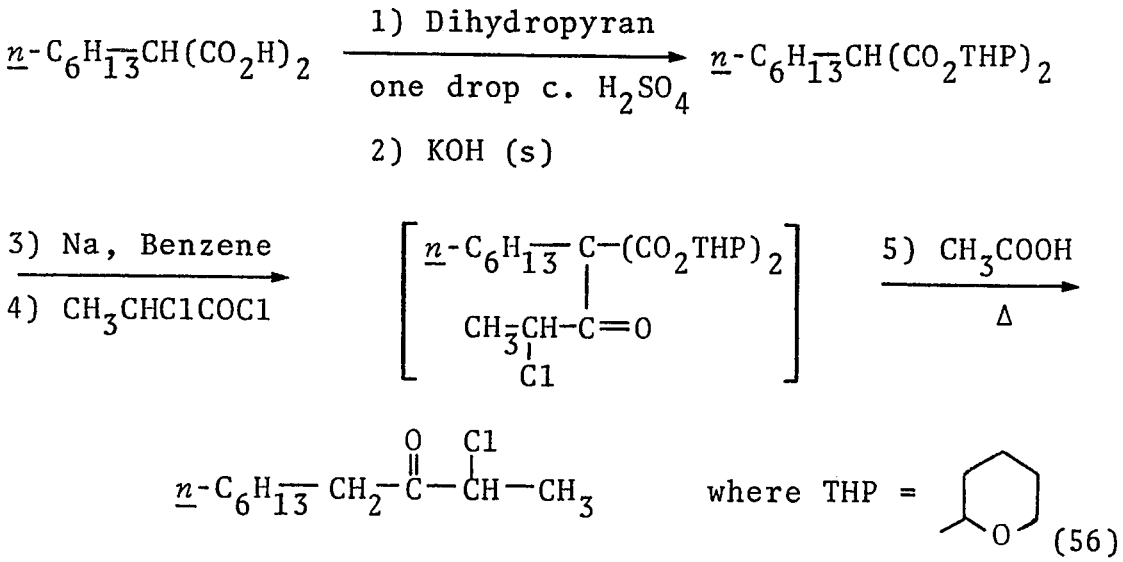


ca. 20% overall (55)

Chlorinated acid chlorides have also been reported to yield α-haloketones on treatment with organocadmium compounds,[169] but in low yields. The reaction of an α-haloacid chloride with a Grignard reagent has been restricted rather severely because of the tendency of Grignard reagents to undergo addition to the carbonyl group to form tertiary alcohols. Grignard reagents have found some utility in the

preparation of some α-fluoro ketones by the addition of alkylmagnesium compounds (RMgX and R_2Mg) at low temperature to α-fluoroesters.[170]

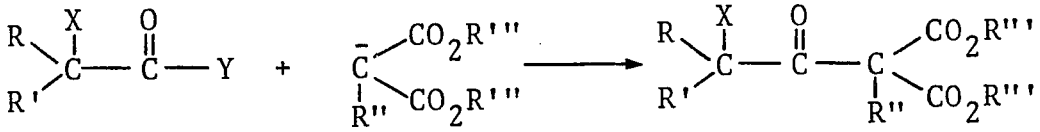
Although a variety of methods have been devised to avoid strong hydrolytic conditions in the cleavage of β-ketoesters and β-ketodiesters (by the use of benzyl,[171] tetrahydropyranyl[172] and *t*-butyl ester[173] protecting groups), the approach involving the acylation of an active methylene compound has not been generally applied to the preparation of α-haloketones. Only one example has been reported. Bowman and Fordham utilised tetrahydropyranyl esters as a replacement for benzyl esters in the preparation of easily reducible ketones (benzyl esters are cleaved by hydrogenolysis), and in their study, 2-chloro-3-decanone was prepared from 2-chloropropanoyl chloride in a 92% yield.[172] (eq. 56)



(56)

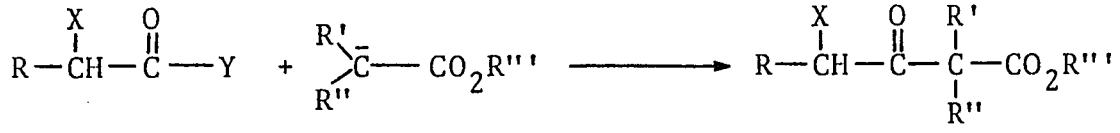
Because α-haloacid halides are readily prepared (by halogenation of the corresponding acid via the Hell-Volhard Zelinsky reaction, or of the malonic acid),[174,175] and substituted malonic acids are easily available (alkylation of malonate esters, or carbonation of monocarboxylic acids),[176,177] the structure of the α-haloketone can be rigidly controlled.

Consequently, the purpose of the present work was to investigate the general applicability of the acylation of malonate esters for the preparation of α-haloketones of type A. (eq. 57)



$$\xrightarrow[+2[H^+]]{-2[CO_2R'''']} \quad \underset{\text{Type A}}{\text{R}\overset{\text{X}}{\underset{\text{R}'}{\text{C}}}\text{—}\overset{\text{O}}{\text{C}}\text{—CH}_2\text{—R}''} \qquad (57)$$

Also, a route to α-haloketones of type B was briefly investigated via the acylation of disubstituted monocarboxylic esters. (eq. 58)



$$\xrightarrow[+[H^+]]{-[CO_2R'''']} \quad \underset{\text{Type B}}{\text{R—CH}\overset{\text{X}}{\text{—}}\overset{\text{O}}{\text{C}}\text{—CH}\overset{\text{R}'}{\underset{\text{R}''}{}}} \qquad (58)$$

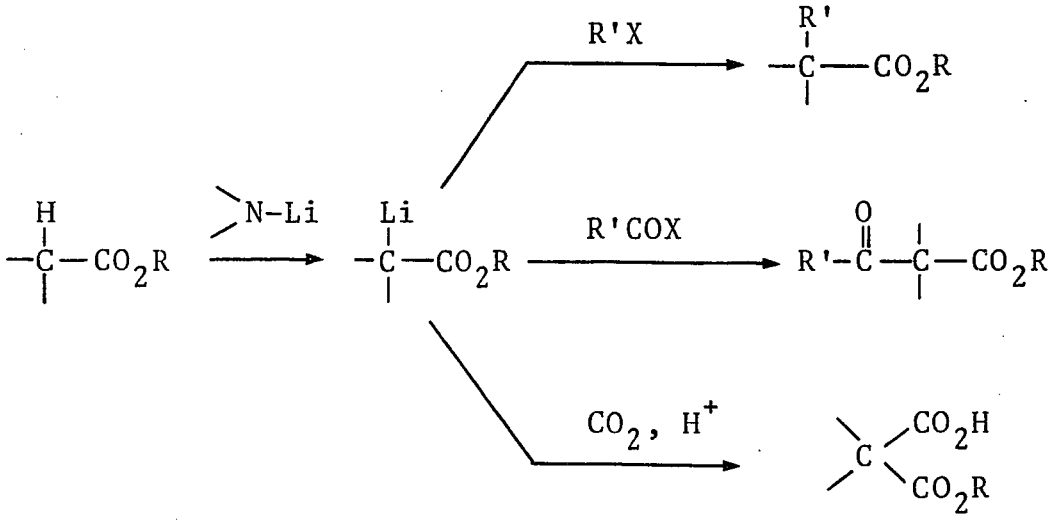
Enolates of monocarboxylic esters have been generated in a variety of ways. Hauser and coworkers have obtained enolates by either the action of lithium amide in liquid ammonia,[178] or the alkali salts of triphenylmethane,[179] on ethyl and *t*-butyl esters. Alkali salts of bis(trimethylsilyl)amine have also been employed to produce ester enolates, the lithium enolates being more stable than the sodium enolates.[180,181]

These bases are most successful with relatively unreactive esters such as ethyl isobutyrate or *t*-butyl esters. Even in these cases, however, the enolate solutions must be utilized soon after their formation to prevent appreciable condensation of the enolate with any unreacted ester.

Recently, Rathke and Lindert have shown that lithium N-isopropylcyclohexylamide (LiICA) reacts with a wide variety of esters at low temperature in tetrahydrofuran to produce solutions of the corresponding lithium enolates.[182] Self-condensation of the ester does not occur, even when such solutions are allowed to reach room temperature. The success of LiICA is attributed to its solubility in the solvent at low temperature and to its ability to effect rapid irreversible proton abstraction from the esters.

As shown in the following equation, (eq. 59) these enolate solutions have been successfully alkylated,[182]

acylated,[183] and carbonated;[177] affording α-substituted esters in high yields.



(59)

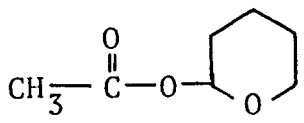
RESULTS AND DISCUSSION

PREPARATION OF α-HALOKETONES VIA THE ACYLATION OF ESTERS OF MALONIC ACIDS

The success obtained by Bowman and Fordham [172] in the synthesis of ketones via the acylation of bistetrahydropyranyl malonates and the high yield of 2-chloro-3-decanone formed by this route suggested that the investigation should be carried out, at first, along these lines.

The Bowman experiment was repeated (eq. 56). 2-Chloropropanoyl chloride was reacted with the sodium salt of bistetrahydropyranyl *n*-hexylmalonate followed by ketonic cleavage with acetic acid in refluxing benzene. Except for the use of a sodium hydride dispersion in lieu of sodium metal, the experiment was conducted using materials described previously in equation 56.

Several difficulties were encountered. Most important, the material obtained distilled over a wide range, and consisted mainly of a low boiling fraction which was identified as tetrahydropyranyl acetate 44. The higher



44

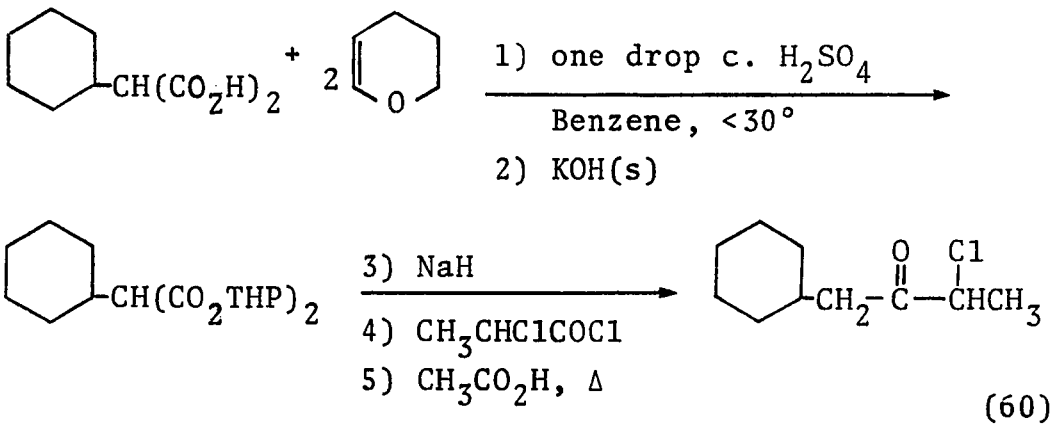
boiling fractions contained a mixture of 44, 2-chloro-3-decanone, and some acidic component which was not identified.

Obviously the simple water or base wash required in the work-up (as described in the Bowman procedure) was not sufficient to remove the large amount of acetate formed during the acetic acid cleavage.

Tetrahydropyranyl esters are readily cleaved by aqueous acids.[184] Thus, modification of the work up by including successively alternating dilute acid and base washes of the crude reaction product resulted in almost complete removal of 44. Infrared analysis of the reaction mixture before this work-up showed a broad absorption from 1720 to 1740 cm^{-1}. The 1720 cm^{-1} absorption was attributed to the ketone carbonyl and the 1740 cm^{-1} to the ester carbonyl. Thus, with each successive wash, it proved possible to follow the disappearance of the ester 44 from the product mixture.

Therefore, by including this modification, a 72% yield of 2-chloro-3-decanone was obtained.

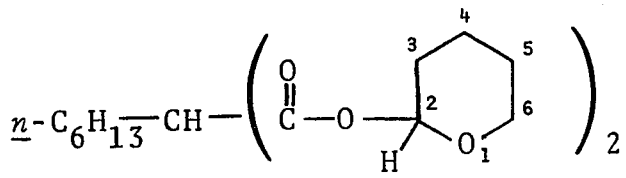
The reaction was repeated with cyclohexylmalonic acid (eq. 60). A 48% yield of 3-chloro-1-cyclohexyl-2-butanone was obtained. Although formation of the malonate



(60)

ester appeared complete under the conditions used for *n*-hexylmalonic acid (30 minutes below 30°), a large amount of solid was formed on shaking the solution with potassium hydroxide (to remove traces of unreacted acid).

As a consequence of this observation, it was decided to survey this multi-step approach in a way as to evaluate the efficiency of every step. Using *n*-hexylmalonic acid as the model compound, the formation of the diester was measured by proton magnetic resonance spectroscopy using the hydrogen at C_2 of the tetrahydropyranyl ring in 45 (δ 5.94) versus bromoform (H_{HCBr_3}, δ 6.99) as internal standard.



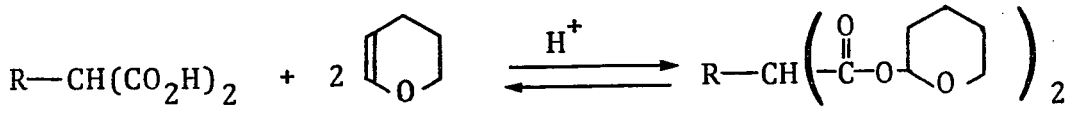
45

Thus, using a stoichiometry of 1.5 mole of dihydropyran per carboxylic acid group, addition of the acid (solid), portion by portion, to a benzene solution of dihydropyran containing a drop of sulphuric acid, resulted in a yield of ester of at least 90±5% after 30 minutes at room temperature. A ratio of one mole of dihydropyran per carboxylic acid group gave only a 71-79 % conversion under these conditions.

Since the reaction is carried out at room temperature, and since most simple malonic acids are insoluble (or only

slightly soluble) in benzene under these conditions, the extent of reaction can be followed qualitatively by observing the dissolution of the acid. On the other hand, the reaction is highly exothermic, and care must be taken to add the solid very gradually. To overcome this technical problem, the reaction under homogeneous conditions was investigated. Addition of 3 molar equivalents of dihydropyran to a solution of *n*-hexylmalonic acid in tetrahydrofuran afforded only 35±5% ester after 30 minutes at 25°. When the reaction was repeated at reflux temperature, a 69±5% yield was obtained after 30 minutes.

The reaction of dihydropyran with a hydroxyl group is considered to be a reversible process.[172] Fortunately, the equilibrium for ester formation (eq.61) appears to

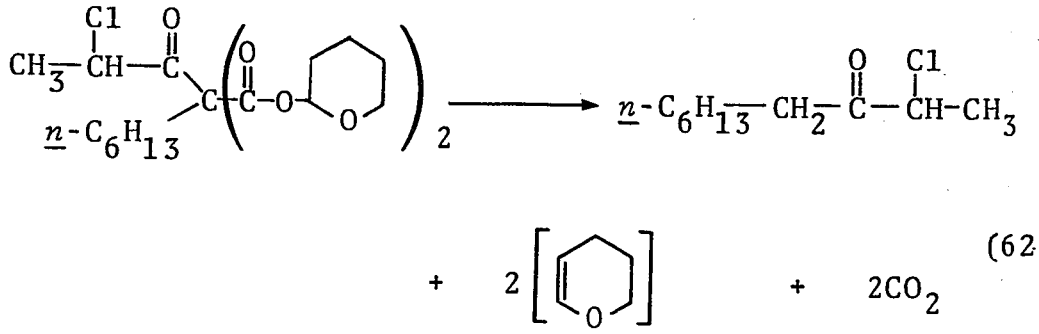


(61)

lie in favour of the ester in benzene as solvent. As long as excess dihydropyran is used, virtually complete esterification can be achieved in a reasonable time.

The reaction of the bistetrahydropyranyl ester 45 was found to be relatively fast with sodium hydride as a base. Similarly, the next stage of the synthesis was complete within 15 minutes at 20-25° using 2-chloropropanoyl chloride and the sodium salt of *n*-hexylmalonate diester.

The ketonic cleavage step (eq. 62) was investigated using several acid catalysts (acetic acid, *p*-toluene-sulphonic acid, and sulphuric acid) of varying stoichiometry (0.15 to 5 equivalent per ester group) by following the carbon dioxide evolution.



(62)

With no acid catalyst, that is, simply heating the reaction mixture to reflux, a slow evolution of carbon dioxide resulted after 2 hours. A 41% yield of chloro ketone was formed. Surprisingly, addition of acid (acetic or *p*-toluenesulphonic) in amounts of 0.15-0.20 mole per mole of ester groups, also resulted in a very slow rate of decomposition. The yield of product was only ca. 50% or less after 1.5 hours under reflux. Similarly, 1.0 mole of *p*-toluenesulphonic acid per mole of ester groups afforded incomplete carbon dioxide evolution and resulted in a 36% yield of chloroketone after 2.5 hours. Sulphuric acid, on the other hand, resulted in the formation of a tarry material and a 46% yield of chloro ketone after 1.8 hours.

However, an excess of acetic acid, ca. 5 moles per

mole of ester group, resulted in a very fast evolution of carbon dioxide as the reaction mixture was brought to reflux. 2-Chloro-3-decanone was formed in a 94% yield.

Using this second modification, 2-chloro-3-heptanone and 2-chloro-5-methyl-3-heptanone were prepared in a 69% and 62% yield, respectively, from *n*-propyl and 2-butyl malonic acid and 2-chloropropanoyl chloride.

To minimize handling losses in this multi-step transformation, the possibility was explored of conducting the entire sequence as a "one pot synthesis". On the assumptions that the esterification step was quantitative (or nearly quantitative) and that the excess of dihydropyran would not interfere in the subsequent steps of the reaction, the solution obtained from the esterification step was used without the prior treatment with potassium hydroxide and without concentration (to remove excess dihydropyran).

In the event, sodium hydride was used in a slight excess (0.01-0.02%) to neutralize the small amount of sulphuric acid used in the esterification step. This led to a quantitative yield of 2-chloro-3-decanone from the *n*-hexylmalonic acid-2-chloropropanoyl chloride combination. Too large an excess of sodium hydride (10% excess) proved to be detrimental since a decreased yield of product was observed (78% 2-chloro-3-decanone).

On the other hand, this modification led to

inconsistent results on repeating the reaction several times. The solutions obtained from the esterification step were often highly coloured, even when great care was taken to control the temperature in the highly exothermic esterification step (by a very slow addition of the acid). These coloured solutions reacted immediately at 25° on addition to a slurry of sodium hydride in benzene, affording quantitative evolution of hydrogen. However, yields of 2-chloro-3-decanone varying from 70 to 100% were obtained.

This inconsistency was attributed to the use of concentrated sulphuric acid as an acid catalyst, which brought about an undesired reaction (probably polymerization) of the dihydropyran. *p*-Toluenesulphonic acid as catalyst was found to give more consistent results. The reaction was finally conducted in the following simple way. Dihydropyran (3 moles) was added to a slurry of the malonic acid (1 mole) and ca. 0.5 mg of anhydrous *p*-toluesulphonic acid[185] in benzene. The esterification was complete within 30 minutes of dissolution of the acid.

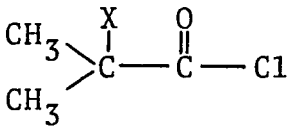
A quantitative yield of 2-chloro-3-decanone was obtained when the diester of *n*-hexylmalonic acid was formed in this way, and its crude solution was used in the subsequent steps (metalation, acylation and ketonic cleavage).

As a result of the various modifications which optimized the yield of 2-chloro-3-decanone and simplified the

handling of this multi-step procedure, the preparation of several α-haloketones from substituted malonic acid-α-haloacid chloride combinations (of structurally different types) was investigated. The results are listed in Table V.

Except for phenylmalonic acid, all the acid substrates reported in Table V gave a soluble sodium salt when their respective bistetrahydropyranyl esters were treated with sodium hydride.

The 2-halo-2-methylpropanoyl chlorides (46) required a higher temperature (65°) and a longer reaction time than the non-methylated analog for completion of the acylation step. The low yield of α-haloketone from 46 was



46

a) X = Cl

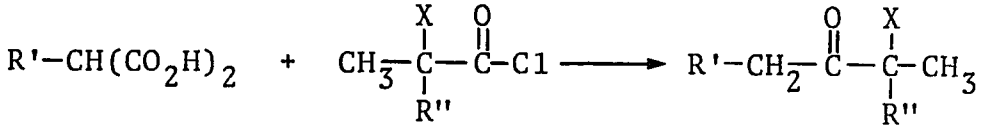
b) X = Br

attributed to incomplete ketonic cleavage at the temperature used. Heating to reflux for 1.5 hours showed only a 13% yield (glc) of 2-chloro-2-methyl-3-heptanone from the *n*-propylmalonic acid-46a combination. Isolation of the chloroketone by distillation of the crude reaction product obtained after work-up doubled the yield.

Consequently, the ketoester 47 was obtained by the acylation of the sodium salt of bistetrahydro *n*-propylmalonate with 46a. Heating the crude ester at ca. 165° under

TABLE V

Preparation of α-Halokekones (Procedure A)



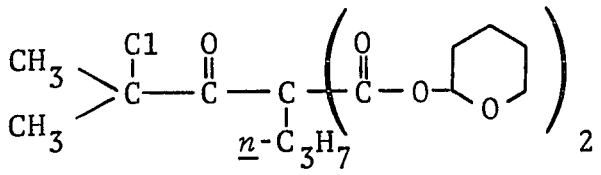
R'	R''	X	α-Haloketone	Yield, % (isolated)
n-C_6H_{13}	H	Cl	*n*-$C_6H_{13}CH_2COCHClCH_3$	100[a]
cyclo-C_6H_{11}	H	Cl	*cyclo*-$C_6H_{11}CH_2COCHClCH_3$	97
sec-C_4H_9	H	Cl	*sec*-$C_4H_9CH_2COCHClCH_3$	81
n-C_3H_7	H	Cl	*n*-$C_3H_7CH_2COCHClCH_3$	61
n-C_3H_7	H	Br	*n*-$C_3H_7CH_2COCHClCH_3$	81 (68[b])
n-C_3H_7	CH_3	Cl	*n*-$C_3H_7CH_2COCCl(CH_3)_2$	27[c]
n-C_3H_7	CH_3	Br	*n*-$C_3H_7CH_2COCBr(CH_3)_2$	9[d]
C_6H_5	H	Cl	$C_6H_5CH_2COCHClCH_3$	55
C_6H_5	H	Br	$C_6H_5CH_2COCHBrCH_3$	<2

(a) Yield estimated by glc.

(b) Acylation with 2-bromopropanoyl bromide

(c) Glc yield determined on the distillate

(d) Contaminated with dehydrobrominated product



47

vacuum with removal of the volatile products by distillation afforded a mixture of dihydropyran, 2-chloro-2 methyl-3-heptanone (67% yield) and an unidentified acidic component.

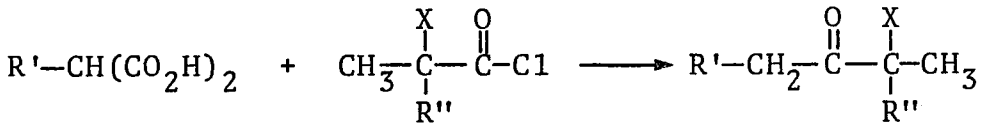
Table VI lists the results obtained with other malonic acid-acid chloride systems with the pyrolysis type of ketonic cleavage. Phenylmalonic acid failed to yield any condensation product with 46. This may have been due to a combination of factors (i.e., the heterogeneous nature of the reaction and a less reactive α-haloacid chloride.)

Based on analogy with the thermal decomposition of β-ketomalonic acids to ketones, the formation of α-haloketone most likely proceeds by the mechanism depicted in Scheme VI -- an internal proton abstraction from the tetrahydropyranyl group via a six-membered ring intermediate with elimination of dihydropyran followed by two successive eliminations of carbon dioxide as illustrated.

When the decomposition is carried out in the presence of acetic acid in refluxing benzene the dihydropyran is "removed" from the process as tetrahydropyranyl acetate (44) which has been shown to be stable under these

TABLE VI

Preparation of α-Haloketones (Procedure B)



R'	R''	X	α-Haloketone	Yield, % (isolated)
n-C_3H_7	CH_3	Cl	n-$C_3H_7CH_2COCCl(CH_3)_2$	74
n-C_3H_7	CH_3	Br	n-$C_3H_7CH_2COCBr(CH_3)_2$	56[a]
C_6H_5	H	Cl	$C_6H_5CH_2COCHClCH_3$	57
C_6H_5	H	Br	$C_6H_5CH_2COCHBrCH_3$	37[b]
C_6H_5	CH_3	Cl	$C_6H_5CH_2COCCl(CH_3)_2$	0[c]
C_6H_5	CH_3	Br	$C_6H_5CH_2COCBr(CH_3)_2$	0[d]

(a) Product was obtained as a mixture containing 21% 2-methyl-1-hepten-3-one

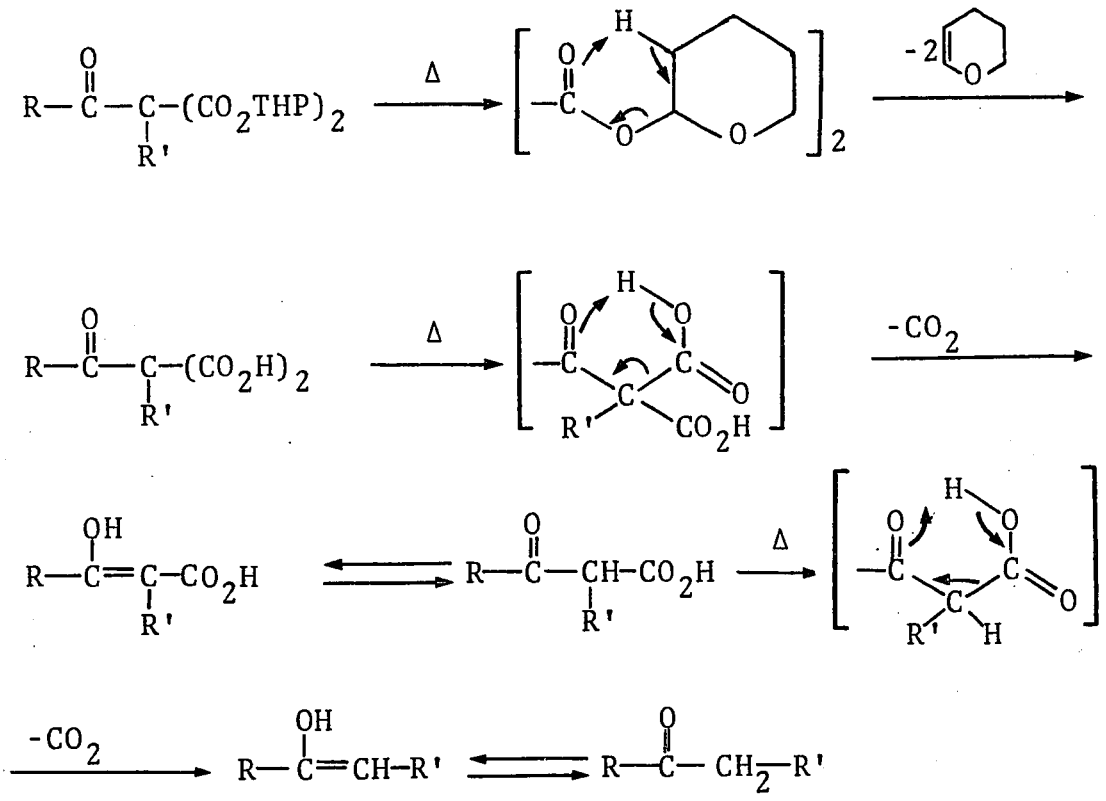
(b) 2-Bromopropanoic acid (54%) was also isolated.

(c) 2-Chloro-2-methylpropanoic acid (76%) was the only compound isolated.

(d) 2-Bromo-2-methylpropanoic acid (78%) was the only compound isolated.

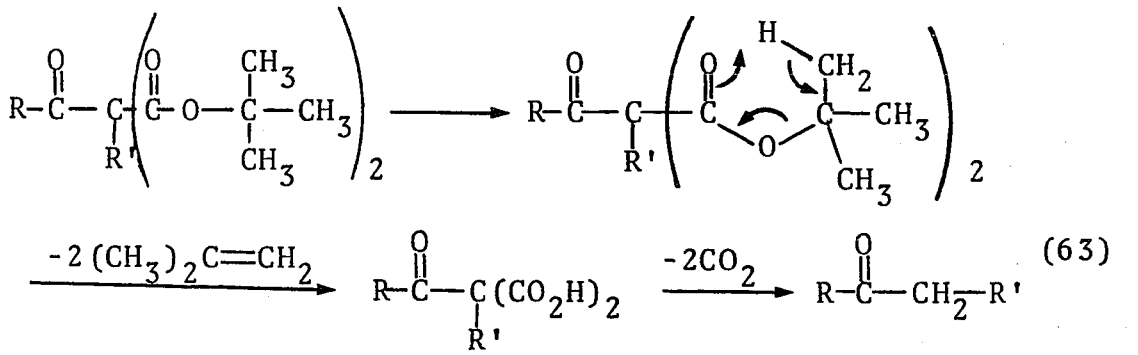
conditions.[172]

Scheme VI



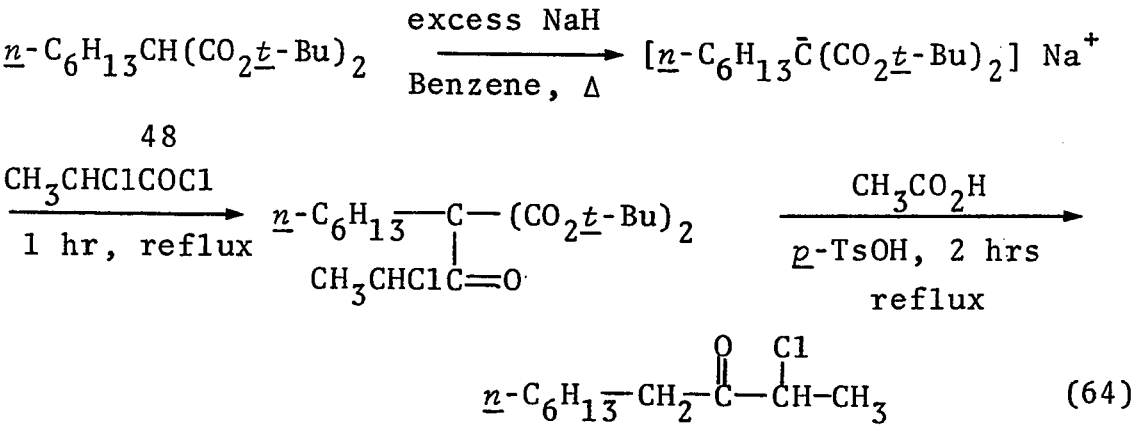
The preparation of α-haloketones via the acylation of di-*t*-butyl malonates was also briefly investigated.

At about the same time as Bowman devised the use of tetrahydropyranyl esters in the synthesis of ketones, Johnson and Fonken [173] found that di-*t*-butyl malonates could be used in an analogous way for the synthesis of simple ketones. The cleavage of *t*-butyl esters is presumably a cleaner reaction since the *t*-butyl group is lost as gaseous isobutylene. (eq. 63)



(63)

Reaction of di-*t*-butyl *n*-hexylmalonate and 2-chloropropanoyl chloride according to the Johnson procedure,[173] illustrated in equation 64, resulted in a low yield (27%) of 2-chloro-3-decanone.



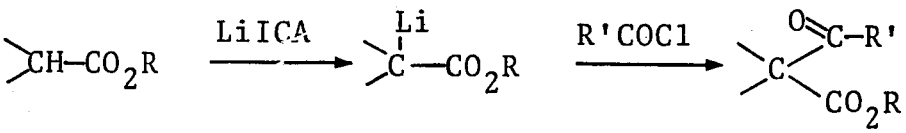
(64)

As opposed to the tetrahydropyranyl ester method, the reaction of sodium hydride with 48 was much slower. It required 4.5 hours of heating under reflux for complete hydrogen evolution.

As a result of the long reaction time required in this procedure and of the low yield of chloroketone obtained above, this approach was not further investigated.

PREPARATION OF α-HALOKETONES VIA THE ACYLATION OF ESTERS OF MONOCARBOXYLIC ACIDS

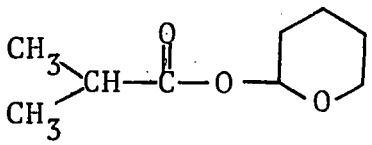
Rathke and coworkers[183] have reported that ester enolates, prepared by the reaction of lithium isopropylcyclohexyl amide (LiICA) with an ester of a monocarboxylic acid at -78°, could be successfully acylated at that temperature with an acid chloride. (eq. 65)



(65)

This suggested the possibility that α-haloketones could be prepared by this method if an α-haloacid chloride were to be used in the acylation step.

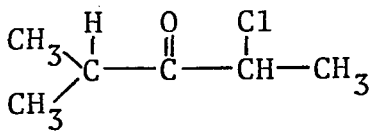
Thus, using the tetrahydropyranyl ester of 2-methylpropanoic acid (49) metalation was accomplished by addi-



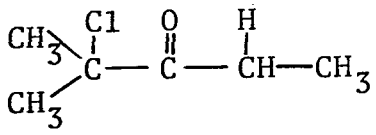
49

tion of the ester 49 to LiICA in tetrahydrofuran at -78°. Addition of 2-chloropropanoyl chloride to the lithium enolate (exothermic) resulted in the precipitation of a small amount of solid, presumably lithium chloride. When acetic acid was added to the mixture, the hydrochloride of cyclohexylisopropyl amine precipitated. After

heating the filtrate (reflux, 1.5 hours), a mixture of chloroketones was obtained, consisting of 40% 2-chloro-4-methyl-3-pentanone (50) and 22% 2-chloro-2-methyl-3-pentanone (51).



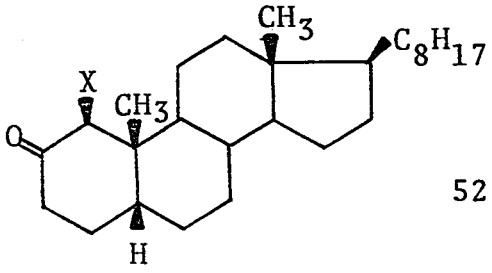
50



51

The formation of the α'-chloroketone 51 probably arises via an isomerization analogous to that observed in the bromination of unsymmetrical ketones as mentioned previously (eq. 46).

Two apparently contradictory reports have appeared concerning the isomerization of α-chloroketones. Satch Horiuchi, and Hogitani [140] have recently studied the isomerization of the bromo and chloro ketones 52(a,b).

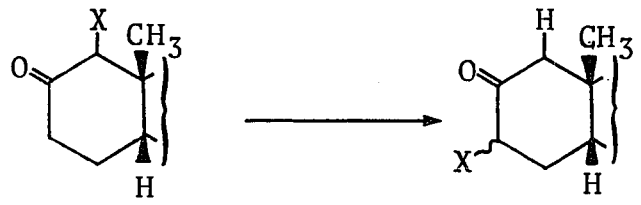


52

a) X = Br

b) X = Cl

They found that both 52a and 52b rearranged on treatment with acidic reagents (acetic acid-hydrogen bromide, acetic acid-hydrogen chloride, and acetic acid alone) as illustrated in the following equation involving partial structures.



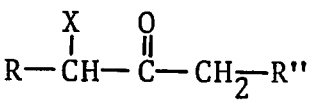
(66)

However, Mehta, Miller, and Tidy [143] have reported that simple α-haloketones such as 1-chloro-2-butanone do not rearrange upon treatment with ethereal hydrogen chloride or concentrated hydrochloric acid in glacial acetic acid under reflux.

As a result, we can draw no firm conclusions regarding the formation of the chloroketone 51 in the previously discussed experiment (the acylation of 49 with 2-chloropropanoyl chloride).

Due to the fact that a mixture of positional isomers was obtained, the preparation of α-chloroketones via the acylation of monoesters was not further investigated.

In summary, α-haloketones were found to be readily prepared by the acylation of bistetrahydropyranyl malonates with α-haloacid halides. The method appears to be mainly advantageous in the preparation of α-haloketones of type A where R" = Alkyl, 53.



The α-chloroketones prepared in this study were found to be relatively stable compounds. By contrast, the α-bromoketones were usually unstable and decomposed readily if stored at room temperature. Furthermore, dehydrobrominated products were found to be present along with the bromoketones as obtained by the thermal decomposition method (Table VI).

EXPERIMENTAL

General Considerations

Infrared (ir) spectra were recorded on a Unicam SP 1000 Infrared Spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were run on a Varian A-60 Spectrometer in the indicated solvents with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ values relative to TMS = 0. The following abbreviations were used in the text: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, and m = multiplet.

Mass spectra were recorded on an AEI Model MS-2 or Model MS-9 Spectrometer.

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

Refractive indices were measured on a Bausch and Lomb Abbé-3L Refractometer.

Analytical gas liquid chromatographic (glc) analysis was performed on a Varian Aerograph Series 1200 gas chromatograph and preparative work on a Varian A-90-P3 gas chromatograph.

All reactions involving sodium hydride were performed under a dry nitrogen atmosphere. Dihydropyran was freshly distilled from sodium metal before use. Benzene was dried over lithium aluminium hydride.

Preparation of Alkylated Malonic Acids.

n-Hexylmalonic acid.[186] Ethyl malonate (155g, 0.97 mole) was added to 0.97mole of sodium ethoxide (from 22.2 g of sodium in 500 ml of absolute ethanol). The solution was warmed to the boiling point and 159 g (0.97 mole) of bromohexane was added dropwise under reflux over 4 hours. The ethanol was distilled and the residue was added to water. The oil was separated and the aqueous layer was extracted with ether. After drying (Na_2SO_4), the combined organic extracts were distilled and afforded 184 g (78%) of diethyl *n*-hexylmalonate, bp 111°(2 mm), $n_D^{23.5}$ 1.4293 [lit.[187] bp 150-155°(20mm), n_D^{21} 1.4278]. The ester was saponified by heating to reflux for 7 hours with 2 moles of potassium hydroxide in 225 ml of an ethanol-water mixture (1:2 by volume). The solvent was partly distilled and the concentrate poured into ice-cold conc. hydrochloric acid. The acid was filtered and recrystallised from benzene, yield: 177 g (79%), mp 105-106° (lit.[187] 103-105°)

Cyclohexylmalonic acid. In a similar way, 67 g (0.4 mole) of bromocyclohexane was reacted during 8 hours with 0.4 mole of diethyl sodiomalonate in ethanol. The reaction yielded 37 g (27%) diethyl cyclohexylmalonate, bp 140° (7 mm) [lit.[187] 151-153° (16 mm)]. The ester was saponified with 0.27 mole of potassium hydroxide in 50 ml of aqueous ethanol as before. After acidification (conc. hydrochloric acid) there was obtained 21 g (83%) of cyclohexylmalonic

acid which was recrystallised from hot water, mp 192.5° (lit.[187] 176-178°dec)

2-Butylmalonic acid. In a similar way, addition of 136 g (0.74 g) of 2-iodobutane to 0.74 mole of diethyl sodiomalonate in ethanol afforded 134 g (83%) of diethyl 2-butylmalonate, bp 84° (2.2 mm) [lit.[187] 245-250° (762 mm)]. The ester was saponified with 1.5 moles of potassium hydroxide in 150 ml of aqueous ethanol as before. There was obtained 68 g (69%) 2-butylmalonic acid which was recrystallised from benzene-heptane, mp 73-74°(lit.[187]76°).

n-Propylmalonic acid. Addition of 51 g (0.30 mole) of iodopropane to 0.30 mole of diethyl sodiomalonate in a similar way, afforded diethyl *n*-propylmalonate, bp 116° (22-24mm) [lit.[187]222-227° (750 mm)]. The ester was saponified with aqueous ethanolic potassium hydroxide (0.65 mole) as before. There was obtained 40 g(91%) of *n*-propylmalonic acid which was recrystallised from benzene-*n*-pentane, mp 92.5-93.0° (lit.[187] 96°).

Phenylmalonic acid. Diethyl phenylmalonate was prepared by the method of Levene and Meyer.[188] Reaction of ethyl oxalate (65.7 g, 0.45 mole) with ethyl phenylacetate (77.8 g, 0.48 mole) in 250 ml of absolute ethanol containing 0.45 mole of sodium ethoxide [from 10.4 g (0.45 g.atom) of sodium] afforded after decarbonylation by pyrolysis 69 g (63%) of product. The ester was saponified with ethanolic aqueous potassium hydroxide (0.6 mole) as before.

There was obtained 48 g (59%) of phenylmalonic acid which was recrystallised from water, then from benzene, mp 146-147° (lit.[187] 143°).

Preparation of α-Haloacid Chlorides.

2-Chloropropanoyl chloride. Commercial 2-chloropropanoic acid (67 g, 0.62 mole) was heated under reflux for 3 hours with 100 g of freshly distilled thionyl chloride. After standing for 18 hours at 25°, the reaction mixture was distilled at atmospheric pressure to remove the excess thionyl chloride. Vacuum distillation of the residue afforded 66 g (86%) of 2-chloropropanoyl chloride, bp 52-54°(100 mm) [lit.[174] 53°(100 mm)],ir (liquid film): 1785 (C=O), 930 cm^{-1} (C—Cl).

2-Bromopropanoyl chloride. In the same manner, 2-bromopropanoic acid (76 g, 0.50 mole) and 55 ml of thionyl chloride afforded 82 g (96%) of 2-bromopropanoyl chloride, bp 72° (95 mm) [lit.[187] 131-133° (760 mm)], ir (liquid film): 1825, 1720, 920 cm^{-1} (C=OCl).

2-Chloro-2-methylpropanoyl chloride.[189] 2-Methylpropanoic acid (52 g, 0.60 mole) was heated under reflux for 3 hours with 200 ml of freshly distilled thionyl chloride. Then 60 ml of freshly distilled sulphuryl chloride was added dropwise to the refluxing solution. The mixture was illuminated for 5 days with a 200 Watt lamp. Fractional distillation at atmospheric pressure (700 mm)

afforded a fraction (bp 110-116) which upon redistillation yielded 41 g (38%) of 2-chloro-2-methylpropanoyl chloride, bp 114-116°(700 mm) [lit.[187] 126-127° (760 mm)], ir (liquid film): 1830, 1775, 960 cm^{-1} (C=OCl); nmr (CCl_4): $\underline{\delta}$ 1.86 (s) $(C\underline{H}_3)_2CCl$.

2-Bromo-2-methylpropanoyl chloride. In the same manner, bromine (0.81 g) was added dropwise to a thionyl chloride solution of 2-methylpropanoyl chloride [from 43 g (0.48 mole) of 2-methylpropanoic acid and 70 ml of thionyl chloride heated to reflux for 2.5 hours]. The reaction mixture was illuminated (200 Watt lamp) while being heated under reflux for 20 hours. Fractional distillation afforded a dark red distillate which could not be decolourised by further redistillation. The organic material was carefully hydrolysed by pouring into ice-water. The aqueous mixture was extracted with ether and the ether layer was washed with dilute sodium hydroxide solution. Acidification (conc. hydrochloric acid) of the base extract, followed by ether extraction afforded after concentration of the organic phase, 23 g of 2-bromo-2-methylpropanoic acid as a white solid, mp 46-48° (lit.[187] 48-49°. Treatment with 20 g of thionyl chloride under reflux for 3 hours gave after fractional distillation, 19 g (22%) of 2-bromo-2-methylpropanoyl chloride, bp 77-78° (95 mm) [lit.[174] 52° (30 mm)], ir (liquid film): 1825, 1725, 960, 825 cm^{-1} (C=OCl); nmr (CCl_4): $\underline{\delta}$ 2.04 (s)

$(C\underline{H}_3)_2CBr$.

Preparation of 2-Chloro-3-decanone. (Bowman Procedure)[172]

n-Hexylmalonic acid (9.4 g, 50 mmole) was added, portion-wise, to 12.6 g (150 mmole) of dihydropyran in 50 ml of dry benzene containing one drop of conc. sulphuric acid, at room temperature. An exothermic reaction occurred. The mixture was kept below 30° by cooling with a cold water bath (20°). After complete dissolution of the acid, the solution was stirred for an additional 30 minutes. Potassium hydroxide pellets (4 g) were added and the mixture stirred for 45 minutes. The liquid was decanted by filtration through a glass wool plug. The filtrate was concentrated by distillation under reduced pressure, keeping the temperature below 25°. The residue was dissolved in 50 ml of benzene and added to 2.19 g of sodium hydride (56.7% oil dispersion) in 100 ml of benzene, at such a rate as to allow a moderate evolution of hydrogen. The clear solution which resulted was cooled to 5° and 6.4 g (50 mmole) of 2-chloropropanoyl chloride was added all at once. On warming to room temperature, sodium chloride precipitated as a gelatinous mass. After 4 hours, 5 ml of glacial acetic acid was added and the mixture was heated to reflux for 2 hours. The solution was cooled and successively washed with 25 ml of water, 25 ml of saturated sodium bicarbonate solution, and 25 ml

of brine solution. After drying (Na_2SO_4) and concentration (rotary evaporator), the residue was fractionally distilled at 1.5-2.0 mm. The first fraction (4.73 g), distilling at 42-51° was tetrahydropyranyl acetate, [lit.[172] bp 42-43°(1 mm)], ir (liquid film): 1742 (C=O), 1240 (C–O ester), 1150-1100 cm^{-1} (C–O–C ether); nmr (CCl_4): $\underline{\delta}$ 1.2-1.8 (m, 6) $-(C\underline{H}_2)_3-$, 2.13 (s, 3) $C\underline{H}_3C=O$, 3.80 (m, 2) $-C\underline{H}_2O-$, 4.03 (br s, 1) $-OC\underline{H}O-$. The second fraction collected (2.76 g) distilled between 65-71°, ir (liquid film): 1725, 1740 cm^{-1} (C=O). The third fraction (76-86°, 2.56 g) was composed mainly of a ketonic component (ir 1725 cm^{-1}) and an acidic impurity (ir 1700, 2600-3500 cm^{-1}) which was not further investigated.

The reaction was repeated as described above. The concentrate was washed alternately with 25 ml of dilute hydrochloric acid and 25 ml of saturated sodium bicarbonate solution (3 times) until the infrared showed the carbonyl absorbtion at 1720 cm^{-1} to predominate. The residue was distilled at 1 mm. Less than 0.8 g was collected below 60°. The main fraction [6.64 g (70%),82-84°] was identified as 2-chloro-3-decanone. Further distillation (micro spinning band) of a sample gave material with the following properties: bp 74° (0.7-0.8 mm) [lit.[172] 70-71° (1 mm)]; n_D^{20} 1.4398 (lit.[172] 1.4512); ir (liquid film): 1723 cm^{-1} (C=O); nmr ($CDCl_3$): $\underline{\delta}$ 0.98 (br t, 3) terminal $C\underline{H}_3$, 1.57 (d, 3, J = 7 cps) $C\underline{H}_3CHCl$, 1.3-1.7 (m, 10) $-(C\underline{H}_2)_5-$

2.65 (complex t, 2, J = 7 cps) $CH_2C\underline{H}_2C{=}O$, 4.35 (q, 1, J = 7 cps) $CH_3C\underline{H}Cl$; mass spectrum m/e (relative intensity): 190 (1.2) $M^+(Cl_{35})$, 192 (0.4) M^+ (Cl_{37}). Anal. Calcd. for $C_{10}H_{19}ClO$: C, 62.98; H, 10.04; Cl, 18.59. Found: C, 62.89; H, 10.14; Cl, 18.68.

Preparation of 3-Chloro-1-cyclohexyl-2-butanone.

Cyclohexylmalonic acid (9.3 g, 50 mmole) was treated according to the Bowman procedure described previously with 12.6 g (150 mmole) of dihydropyran. On stirring the ester solution with potassium hydroxide (4 g) a gelatinous precipitate appeared which rendered filtration difficult. On addition of the crude ester in benzene solution (50 ml) to 2.12 g of sodium hydride (56.7% oil dispersion) in 100 ml of benzene, hydrogen was evolved in 85% yield. Further treatment with 2-chloropropanoyl chloride (6.3 g, 50 mmole) and 6 ml of glacial acetic acid, as described before, yielded, after work-up and fractional distillation, 4.4 g (48%) of 3-chloro-1-cyclohexyl-2-butanone, bp 88° (2.2 mm), n_D^{20} 1.4696; ir (liquid film): 1720 cm^{-1} (C=O); nmr ($CDCl_3$): $\underline{\delta}$ 1.57 (d, 3, J = 7 cps) $C\underline{H}_3CHCl$, 1.1-2.4 (br m, 11) *cyclo*-$C_6\underline{H}_{11}$, 2.53 (d, 2, J = 7 cps) $C\underline{H}_2C{=}O$, 5.31 (q, 1, J = 7 cps) $CH_3C\underline{H}Cl$; mass spectrum m/e (relative intensity): 188(0.03)$M^+(Cl_{35})$ 190(0.01) $M^+(Cl_{37})$ 125(41) 97(62) 55(100) 41(35) 39(20); Anal. Calcd. for $C_{10}H_{17}ClO$: C, 63.65; H, 8.98; Cl, 18.79. Found: C, 63.65; H, 9.04; Cl, 18.95.

Quantitative Nmr Analysis of the Formation of Bistetrahydropyranyl *n*-Hexylmalonate (45).

In benzene (1.5 mole of dihydropyran per carboxylic acid group) Method A. *n*-Hexylmalonic acid (4.71 g, 25 mmole) was treated with 6.31 g (75 mmole) of dihydropyran in 25 ml of benzene containing one drop of conc. sulphuric acid as described in the Bowman procedure. As the acid was added (portion-wise), the temperature of the dihydropyran solution rose quickly. Cooling with a cold water bath (20°) was applied to ensure a temperature between 25 and 30°. After treatment with potassium hydroxide (2 g) for 30 minutes, the mixture was filtered through a glass wool plug. The solid residue was washed with dry benzene. The combined filtrate was concentrated under vacuum (bath temp. at 25°). The residue (8.15 g of a pale yellow viscous oil) displayed ir (liquid film): 1775 cm^{-1} (broad) (C=O); nmr (CCl_4): δ 0.88 (br t, 3) terminal-C$\underline{H}_3$, 1.1-2.1 (m, 22) $-(C\underline{H}_2)_5-$ and $-(C\underline{H}_2)_3-$x2 (tetrahydropyranyl rings), 3.26 (t, 1, J = 7 cps) $CH_2C\underline{H}(CO_2-)_2$, 5.94 (br s, 2) -OC$\underline{H}$O-. A mixture of the diester (0.714 g) and freshly distilled bromoform (1.407 g) was made up to a 2 ml volume with carbon tetrachloride. Nmr analysis of the solution by integration (4 times) of the broad singlet (2$\underline{H}$) at δ 5.94 *versus* the bromoform proton at δ 6.99 revealed 89-92 ±5% ester formation. After 13 days at 0°C, the product was shown, in the same manner, to contain 88±5% ester.

In benzene (1 mole of dihydropyran per carboxylic acid group). *n*-Hexylmalonic acid (1.88 g, 10 mmole) was added portion-wise to 1.77g (21 mmole) of dihydropyran in 10 ml of benzene containing one drop of conc. sulphuric acid. After complete addition, the solution was stirred for 30 minutes at 25°, during which time it turned from pale yellow to orange to green. On addition of 1 g of potassium hydroxide, the solution turned yellow and a gelatinous precipitate formed. As previously described, filtration, concentration, and nmr analysis afforded a yield of ester estimated as 71-79%.

In tetrahydrofuran. To a solution of *n*-hexylmalonic acid (1.87 g, 10 mmole) in freshly distilled tetrahydrofuran (from lithium aluminium hydride) (10 ml) containing one drop of conc. sulphuric acid, was added dropwise 2.52 g (30 mmole) of dihydropyran. After 30 minutes at 23 to 25°, the solution was treated with ca. 1 g of potassium hydroxide pellets. A gelatinous precipitate formed and after 15 minutes the mixture was filtered. The filtrate was concentrated, and the remaining cloudy oil (3.31 g) was shown by nmr analysis to contain 35% ester.

The reaction was repeated. The dihydropyran was added to the acid solution which was heated to reflux. After 30 minutes, the solution was cooled and treated as described above. The residue (3.04 g) showed 69% ester by nmr analysis.

Reaction between Bistetrahydropyranyl *n*-Hexylmalonate(45) and 2-Chloropropanoyl Chloride.

The ester 46 was prepared according to method A as described previously, on a 20 mmole scale from 3.74 g of *n*-hexylmalonic acid and 5.05 g of dihydropyran containing 3.37 g of diphenyl ether as internal standard for glc analysis. The crude ester-diphenyl ether concentrate was dissolved in 50 ml of benzene and added dropwise to 20 mmole of sodium hydride (0.849 g of a 56.7% oil dispersion) in 50 ml of benzene. Quantitative hydrogen evolution resulted at 30-35°. The clear solution thus obtained was cooled to 5° and 1.64 g (20 mmole) of 2-chloropropanoyl chloride in 20 ml of benzene was added all at once. On warming to room temperature, a gelatinous precipitate appeared at 18-20°. The mixture was magnetically stirred. Aliquots (5 ml) were taken at intervals of time given below. Glacial acetic acid (ca. 0.5 ml) was added to each of these aliquots, and the resulting mixtures were heated under reflux for ca. 1.5 hours.
Glc analysis (10% SE-52 on Chromosorb W, 155°) of the mixtures gave the following results (time of acylation, % yield of 2-chloro-3-decanone): 15 min, 94; 1 hr, 94; 3 hrs, 95; 5 hrs,96; 8 hrs, 95; 12 hrs, 92; 24 hrs, 88.

Ketonic Cleavage of the β-Ketodiester obtained from the Reaction of Bistetrahydropyranyl *n*-Hexylmalonate (45) and

2-Chloropropanoyl Chloride.

Aliquots (5 ml) of the mixture obtained in the preceding experiment after a one-hour acylation period were treated as follow. Analysis was done by glc (15% SE-52 on Chromosorb W, 155°) as before.

No acid catalyst. A 5 ml aliquot was heated under reflux for 2 hours. The carbon dioxide evolution was measured over di-*n*-butyl phthalate saturated with carbon dioxide. The gas was evolved at a rate of ca. 0.02 ml per min. After 2 hours, the yield of 2-chloro-3-decanone was estimated as 41% by glc.

Acetic acid catalyst. A 5 ml aliquot (ca. 0.8 mmole of β-ketodiester) was treated with 0.5 ml of glacial acetic acid (ca. 8.5 mmole). A fast and complete carbon dioxide evolution occurred when the mixture was heated to reflux for 1.5 hours. The yield of 2-chloro-3-decanone was estimated as 94% by glc.

A 5 ml aliquot (ca. 0.8 mmole of β-ketodiester) was treated with 15 mg (0.25 mmole) of acetic acid. On heating under reflux, carbon dioxide was evolved at a rate of ca. 0.02 ml per min. After 1.5 hours the yield of 2-chloro-3-decanone was estimated as 58% by glc.

p-Toluenesulphonic acid catalyst. To a 5 ml aliquot of the β-ketodiester solution (ca. 0.8 mmole) was added 0.279 g (1.6 mmole) of anhydrous *p*-toluenesulphonic acid.[185] As the mixture was heated under reflux, it turned dark

orange. After 2 hours, and a variable (0.03-0.05 ml per min.) and incomplete carbon dioxide evolution the yield of 2-chloro-3-decanone was estimated as 46% by glc.

In the same manner, addition of 52 mg (0.30 mmole) of *p*-toluenesulphonic acid (anhydrous) to a 5 ml aliquot also resulted in incomplete and variable slow carbon dioxide evolution. After 2.5 hours of reflux, the yield of 2-chloro-3-decanone was estimated as 36% by glc.

Sulphuric acid catalyst. To a 5 ml aliquot of the β-ketodiester mixture (ca. 0.8 mmole) was added 4 drops of conc. sulphuric acid (ca. 1.7 equiv.). As the mixture was warmed to reflux, a tarry residue formed. A slow (0.03 ml per min.) and incomplete carbon dioxide evolution resulted. After 1.8 hours, a 46% yield of 2-chloro-3-decanone was estimated by glc.

Preparation of 2-Chloro-3-heptanone.

n-Propylmalonic acid (7.3 g, 50 mmole) was converted into the bistetrahydropyranyl ester with dihydropyran (12.6 g, 150 mmole) in 50 ml of benzene containing one drop of conc. sulphuric acid, and treated as described for *n*-hexylmalonic acid in method A. The ester concentrate was dissolved in 50 ml of benzene and added to 50 mmole of sodium hydride in 100 ml of benzene. Hydrogen evolution started on heating to 40°, and continued below 30° as the ester was being added dropwise. After the

hydrogen evolution was completed, 50 mmole of 2-chloropropanoyl chloride in 20 ml of benzene was added all at once to the cooled (5°) pale yellow solution. After stirring for an additional 30 minutes, 15 ml of glacial acetic acid was added and the mixture was refluxed for 1.75 hours. The cooled reaction mixture was washed with 25 ml of water, then alternately with 50 ml of saturated sodium bicarbonate solution and 50 ml of dilute hydrochloric acid (3 times), followed by brine and drying of the organic phase (Na_2SO_4). The crude oil obtained upon concentration (rotary evaporator) was distilled and afforded 6.1 g (82%) of a ketonic fraction boiling at 77-84° (30 mm). Redistillation gave pure 2-chloro-3-heptanone (5.0 g, 62%), bp 82-83°(30 mm), n_D^{20} 1.4335 [lit.[190] 82.5° (31 mm), 1.4335]; ir (liquid film): 1720 cm^{-1} (C=O); nmr (CCl_4): δ 1.55 (d, 3, J = 7 cps) $C\underline{H}_3CHCl$, 0.87 (br t, 3) terminal-$C\underline{H}_3$, 1.1-1.8 (m, 4) -$C\underline{H}_2C\underline{H}_2CH_3$, 2.5-2.8 (m, 2) $C\underline{H}_2C{=}O$, 4.36 (q, 1, J = 7 cps) $CH_3C\underline{H}Cl$; mass spectrum m/e: 148 $M^+(Cl_{35})$, 150 $M^+(Cl_{37})$, 85 (M^+-CH_3CHCl).

Preparation of 2-Chloro-5-methyl-3-heptanone.

In the same manner, 2-butylmalonic acid (8.0 g, 50 mmole) was treated with 12.6 g (150 mmole) of dihydropyran. The resulting diester was reacted with sodium hydride (50 mmole) in 100 ml of benzene at 45°. The

sodium salt of the diester (a pale yellow solution) was treated with 2-chloropropanoyl chloride (50 mmole) as before at 5°. Acetic acid (15 ml) cleavage and work-up as described previously, afforded, after two distillations, 5.6 g (69%) of 2-chloro-5-methyl-3-heptanone, bp 91° (31 mm), n_D^{20} 1.4367, ir (liquid film): 1720 cm^{-1} (C=O); nmr (CCl_4): $\underline{\delta}$ 0.89 (t, 3, J = 7 cps) $C\underline{H}_3CH_2$, 0.91 (d, 3, J = 7 cps) $C\underline{H}_3CH$, 1.1-1.5 (m, 2) $CHC\underline{H}_2CH_3$, 1.7-2.3 (m, 1) $C\underline{H}CH_2$, 1.55 (d, 3,J = 7 cps) $C\underline{H}_3CHCl$, 2.4-2.7 (m, 2) $C\underline{H}_2C=O$, 4.27 (q, 1,J = 7 cps) $CH_3C\underline{H}Cl$; mass spectrum m/e (relative intensity): 162(0.9) $M^+(Cl_{35})$ 164(0.3) $M^+(Cl_{37})$ 99(45) 71(65) 57(21) 43(100) 39(25). Calcd. for M^+ $C_8H_{15}OCl^{35}$: 162.0812. Found: 162.0811. Anal. Calcd. for $C_8H_{15}OCl$: C, 59.08; H, 9.30; Cl, 21.80. Found: C, 59.12; H, 9.48; Cl, 21.85.

Formation of 2-chloro-3-decanone by Elimination of the Potassium Hydroxide Treatment of the Bistetrahyropyranyl Ester.

n-Hexylmalonic acid (1.88 g, 10 mmole) was added portion-wise to 2.62 g (30 mmole) of dihydropyran in 10 ml of benzene containing one drop of conc. sulphuric acid and 1.01 g of diphenyl ether as internal standard for glc analysis. After a 30 minute stirring period below 30°, the pale yellow solution was added to 10.2 mmole of sodium hydride in 15 ml of benzene. Quantitative

evolution of hydrogen was obtained at 25 to 27°. Acylation with 10 mmole of 2-chloropropanoyl chloride as described in the preceding experiment, followed after 1 hour by 15 ml of acetic acid (1.5 hour of reflux) gave a 98% yield of 2-chloro-3-decanone. (glc, 15% SE-52 on Chromosorb W, 155°)

On repeating the reaction as described, the ester solution obtained was a dark red colour. Addition of this solution to sodium hydride resulted in a very fast evolution of hydrogen. The yield of 2-chloro-3-decanone was estimated as 70% by glc, in this experiment.

A second attempt at repeating the reaction as described, led to the formation of a pale orange diester solution. On addition to sodium hydride, hydrogen was evolved immediately at 25°. The yield of 2-chloro-3-decanone in this experiment was estimated as 92% by glc.

Excess sodium hydride (10%). A pale yellow solution of diester (10 mmole) obtained in the manner described was added to 11 mmole of sodium hydride. The resulting solution of sodium salt was treated with 2-chloropropanoyl chloride (10 mmole) as described previously. After cleavage with acetic acid (15 ml), there was formed a 78% yield of 2-chloro-3-decanone, as estimated by glc (15% SE-52 on Chromosorb W, 155°).

General Procedure for the Preparation of α-Haloketones

using *p*-Toluenesulphonic Acid as Catalyst in the Ester Formation Step. (Prodedure A) (Results Tabulated in Table V.)

2-Chloro-3-decanone. To 10 mmole of *n*-hexylmalonic acid as a slurry in 10 ml of benzene containing 2-3 mg of anhydrous *p*-toluenesulphonic acid,[185] was added dropwise, 30 mmole of dihydropyran, at 25°. The mixture was magnetically stirred. A clear colourless solution resulted even when the temperature was allowed to rise above 30°. After 30 minutes of additional stirring, the solution was added dropwise to 10 mmole (0.1 to 0.2 % excess) of sodium hydride in 15 ml of benzene. Gas evolution was very slow at 25°, but increased on warming to 35-40°. The addition was continued at such a rate as to obtain a moderate evolution of hydrogen. After quantitative hydrogen evolution, the clear pale yellow solution was cooled to 5° and 10 mmole of 2-chloropropanoyl chloride was added all at once. Sodium chloride precipitated when the mixture warmed to ambient temperature. After 30 to 60 minutes, the mixture was treated with 5 ml of glacial acetic acid and heated under reflux for 1.5 hours. Alternate acid-base treatment as before yielded a residue which analysed for 100% 2-chloro-3-decanone by glc (15% SE-52 on Chromosorb W, 155°).

3-Chloro-1-cyclohexyl-2-butanone. In the same manner, 5.6 g (30 mmole) of cyclohexylmalonic acid in

30 ml of benzene was treated with dihydropyran (15.2g, 180 mmole). Dissolution of the acid occurred on heating the mixture to 35°. The colourless solution was added to 30 mmole of sodium hydride in 45 ml of benzene. Hydrogen evolved on warming to ca. 60°. The solution was cooled to 5° and 30 mmole of 3-chloropropanoyl chloride in benzene was added all at once. Sodium chloride was precipitated on heating at 55-60° for 30 minutes. The reaction afforded, after acetic acid (15 ml) treatment and work up as before, 19 g of a pale orange oil. Distillation gave 5.47 g (97%) of 3-chloro-1-cyclohexyl-2-butanone, bp 90-92° (4.0-4.5 mm), n_D^{20} 1.4700, which was identical spectroscopically to the material previously prepared by the Bowman procedure.

2-Chloro-5-methyl-3-heptanone. 2-Butylmalonic acid (8.0 g, 50 mmole) was treated with 12.6 g (150 mmole) of dihydropyran in the manner described previously, affording a colourless ester solution at 25°. Addition of this solution to sodium hydride (50 mmole) in benzene resulted in hydrogen evolution at 40°. After cooling to 5°, 2-chloropropanoyl chloride (50 mmole) was added all at once. After stirring for 30 minutes at room temperature, the mixture was treated with acetic acid (15 ml) and worked up as before. There was obtained a yellow oil which afforded upon distillation 6.54 g (81%) of 2-chloro-5-methyl-3-heptanone, bp 77-79° (19 mm),

n_D^{20} 1.4367, which was identical spectroscopically to the material prepared by the previous method.

2-Chloro-3-heptanone. In the same manner, *n*-propylmalonic acid (3.48 g, 30 mmole) was reacted successively with dihydropyran (90 mmole), sodium hydride (30 mmole), and 2-chloropropanoyl chloride (30 mmole) in benzene. After acetic acid (10 ml) treatment and work up as before, there resulted 14 g of crude reaction product. Distillation gave 6.7 g of a ketonic fraction [60-80° (15-20 mm)] which was chromatographed on silica gel using a water-cooled column, and *n*-pentane:ether (20:1 by volume) as eluant. Pure 2-chloro-3-heptanone was eluted as the second component, (2.71 g, 61%), bp 83.5-84.0° (29 mm), n_D^{20} 1.4339, and was identical spectroscopically to the material prepared by the previous method.

2-Bromo-3-heptanone. Addition of 2-bromopropanoyl chloride (5.2 g, 30 mmole) to the solution of bistetrahydropyranyl sodio-*n*-propylmalonate [prepared as above from *n*-propylmalonic acid (30 mmole), dihydropyran (90 mmole), and sodium hydride (30 mmole)],afforded after the usual acetic acid treatment and work up, 15 g of an orange oil. After distillation, all fractions boiling below 75° at 7.5 mm (9 g) were chromatographed on silica gel as in the preceding experiment. 2-Bromo-3-heptanone (4.66 g, 81%) was obtained as a colourless

liquid (*Lachrimatory!*), bp 73.5-74.0° (9 mm), n_D^{20} 1.4580, ir (liquid film): 1720 cm^{-1} (C=O); nmr (CCl_4): δ 0.91 (br t, 3) terminal-CH_3, 1.1-1.9 (m, 4) $CH_2CH_2CH_3$, 1.73 (d, 3, J = 7cps) CH_3CHBr, 3.5-3.9 (m, 2) $CH_2C=O$, 4.36 (q, 1, J = 7 cps) CH_3CHBr; mass spectrum m/e (relative intensity): 192(1.6) $M^+(Br_{79})$ 194(1.6) $M^+(Br_{81})$ 109(2.5) 107(2.6) 85(80) 57(100) 41(56) 39(16). Anal. Calcd. for $C_7H_{13}BrO$: C, 43.55; H, 6.78; Br, 41.38. Found: C, 43.39; H, 6.92; Br, 41.06.

Addition of 6.5 g (30 mmole) of 2-bromopropanoyl bromide (instead of 2-bromopropanoyl chloride) produced reaction with the sodium salt solution of the ester below 18°, with precipitation of sodium bromide. The crude product (11 g), after distillation and chromatography over silica gel, afforded 3.93 g (68%) of 2-bromo-3-heptanone, identical to the material obtained from 2-bromopropanoyl chloride.

2-Chloro-2-methyl-3-heptanone. To the sodium salt solution of bistetrahydropyranyl *n*-propylmalonate (30mmole) obtained as described previously, cooled to 5°, was added, all at once, a benzene solution of 4.3 g (30 mmole) of 2-chloro-2-methylpropanoyl chloride. Upon warming to 60° sodium chloride precipitated. After 30 minutes at this temperature, 15 ml of acetic acid was added and the mixture reflux for 1.5 hours. Upon work up, as before, the yield of 2-chloro-2-methyl-3-heptanone was

estimated as 13% by glc analysis (15% SE-30 on Chromosorb W, 130°). Distillation of the crude reaction product afforded material which boiled over a wide range [from 70° (30 mm) to 100° (10 mm)], which contained (by ir analysis) an acidic component. The distillate was washed with cold saturated sodium bicarbonate solution. The residue analysed (by glc) for 27% chloroketone. A sample of 2-chloro-2-methyl-3-heptanone purified by preparative glc (15% STAP, 75°) displayed the following properties: n_D^{20} 1.4325; ir (liquid film): 1720 cm^{-1} (C=O); nmr (CCl_4): δ 0.94 (br t, 3) terminal-CH_3, 1.1-1.6 (m, 4) $CH_2CH_2CH_3$, 1.62 (s, 6) $(CH_3)_2Cl$, 2.71 (t, 2, J = 7 cps) $CH_2CH_2C=O$; mass spectrum m/e(relative intensity): 164(0.25) $M^+(Cl_{37})$ 162(0.7) $M^+(Cl_{35})$ 85(60) 57(100) 41(66) 39(20). Anal. Calcd. for $C_8H_{15}ClO$: C, 59.08; H, 9.30; Cl, 21.80. Found: C, 59.01; H, 9.45; Cl, 21.46.

2-Bromo-2-methyl-3-heptanone. To the sodium salt solution of bistetrahydropyranyl *n*-propylmalonate (30 mmole), obtained as described previously, cooled at 5°, was added, all at once, a benzene solution of 5.5 g (30 mmole) of 2-bromo-2-methylpropanoyl chloride. The mixture was warmed to 65° for 30 minutes. Acetic acid treatment and work-up, as before, afforded 11.7 g of a yellow-green oil. Vacuum distillation at 10 mm, followed by chromatography over silica gel (*n*-pentane:ether,

20:1 by volume) of all fractions (6.8 g) distilling below 80°, gave 0.55 g (9 %) of bromoketone. The product was shown by glc to contain a minor impurity. Preparative glc (15% XF-1150, 115°) afforded pure 2-bromo-2-methyl-3-heptanone, ir (liquid film): 1710 (C=O), 1368, 1484 cm^{-1}(methyl groups); nmr (CCl_4): $\underline{\delta}$ 0.94 (br t, 3) terminal-C$\underline{H}_3$, 1.1-1.8 (m, 4) C$\underline{H}_2$C$\underline{H}_2$CH$_3$, 1.82 (s, 6) (C$\underline{H}_3$)$_2$CBr, 2.73 (t, 2, J = 7 cps) CH$_2$C$\underline{H}_2$C=O; mass spectrum m/e: 206 $M^+(Br_{79})$, 208 $M^+(Br_{81})$, 85 M^+-$(CH_3)_2CBr$. This bromoketone was found to darken readily if stored at room temperature. The minor component (isolated by preparative glc) was tentatively assigned the structure 2-methyl-1-hepten-2-one, ir (liquid film): 1675 (C=C—C=O), 3090, 1731, 1628, 930 cm^{-1} (CH_2=C); nmr (CCl_4): $\underline{\delta}$ 0.91 (br t, 3) terminal-C$\underline{H}_3$, 1.1-1.8 (m, 4) C$\underline{H}_2$C$\underline{H}_2$CH$_3$, 1.80 (d, 3, J = 1 cps) C$\underline{H}_3$C=CH, 2.55 (t, 2, J = 7 cps) CH$_2$C$\underline{H}_2$C=O, 5.71 (br s, 1) and 5.73 (q, 1, J = 1 cps) C$\underline{H}_2$=CCH$_3$.

3-Chloro-1-phenyl-2-butanone. Phenylmalonic acid (3.6 g, 20 mmole) in 20 ml of benzene was treated with 10.2 g (120 mmole) of dihydropyran at 30° and magnetically stirred for 1 hour. Addition of the colourless solution of ester to 20 mmole of sodium hydride in 40 ml of benzene resulted in hydrogen evolution when the mixture was warmed to 50-55°. A white precipitate was formed. To this slurry, cooled to 5°, was added, all at

once, a benzene solution of 2-chloropropanoyl chloride (2.6 g, 20 mmole). The mixture was allowed to warm up to room temperature. After 18 hours, acetic acid (15 ml) was added to the gelatinous mixture which was then heated to reflux (1.5 hours). Work-up, as before, afforded a crude reaction product which was chromatographed over silica gel (*n*-pentane:ether, 20:1 by volume). The second component (1.98 g, 55%) to elute was the desired 3-chloro-1-phenyl-2-butanone, obtained as a colourless liquid, bp 96.5-97.0° (2.5 mm), n_D^{20} 1.5246 (lit.[191] n_D^{25} 1.5204), ir (liquid film): 1725 (C=O), 745, 700 cm^{-1} (monosubstituted phenyl); nmr (CCl_4): δ 1.48 (d, 3, J = 7 cps) $C\underline{H}_3CHCl$, 3.86 (s, 2) $C\underline{H}_2C{=}O$, 7.17 (s, 5) $C_6\underline{H}_5$; mass spectrum m/e: 182 $M^+(Cl_{35})$, 184 $M^+(Cl_{37})$, 119 $M^+ - CH_3CHCl$.

3-Bromo-1-phenyl-2-butanone. To the sodium salt of bistetrahydropyranyl phenylmalonate (10 mmole) (obtained from 10 mmole of phenylmalonic acid and 60 mmole of dihydropyran as described previously) was added a benzene solution of 2-bromopropanoyl chloride (10 mmole). After 18 hours at room temperature, the mixture was treated with 10 ml of acetic acid and refluxed over 1.5 hours. After work-up as before, there was obtained a crude product which was chromatographed over silica gel (*n*-pentane:ether, 20:1 by volume). 3-Bromo-1-phenyl-2-butanone (0.27 g, <2%) was isolated as a yellow oil which

darkened within one hour at room temperature. Ir (liquid film): 1725 cm^{-1} (C=O); nmr (CCl_4): $\underline{\delta}$ 1.60 (d, 3, J = 7 cps) $C\underline{H}_3CHBr$, 3.90 (s, 2) $C\underline{H}_2C{=}O$, 4.40 (q, 1, J = 7 cps) $CH_3C\underline{H}Br$, 7.25 (s, 5) $C_6\underline{H}_5$; mass spectrum m/e: 226 $M^+(Br_{79})$, 228 $M^+(Br_{81})$, 119 $M^+ - CH_3CHBr$.

Preparation of 2-Chloro-2-methyl-3-heptanone by Pyrolytic Cleavage of the β-Ketodiester 47. General Method for the Preparation of α-Haloketones listed in Table VI (Procedure B).

The β-ketodiester 47 obtained as a mixture with sodium chloride in benzene by procedure A [from the acylation of the sodium salt of bistetrahydropyranyl *n*-propylmalonate (30 mmole) with 2-chloro-2-methylpropanoyl chloride (30 mmole)] was filtered through a coarse sintered glass funnel to remove the precipitated sodium chloride. the salt was washed three times with 10 ml portions of dry benzene, then with a 10 ml portion of *n*-pentane. The filtrate was concentrated (rotary evaporator) and afforded 11.7 g of a viscous cloudy oil. The concentrate was transferred to a distilling apparatus which was then immersed in a preheated oil bath (ca. 165°) and slowly evacuated. The first fraction to distill was identified as dihydropyran. As the pressure reached 25 mm, a colourless liquid (3.69 g), boiling between 75 and 83°, was obtained which contained an acidic component [Ir (liquid film): 1700 br (C=O), 2700-3500 cm^{-1} br (bonded OH)]. The

liquid was dissolved in *n*-pentane and extracted with ice-cold dilute sodium hydroxide. After drying (Na_2SO_4) the organic phase and removal of the solvent (rotary evaporator), the residue (3.42 g, 74%), a colourless oil, was distilled, bp 87.5-89.0° (32 mm), n_D^{20} 1.4329, and was shown to be identical (spectroscopically) to 2-chloro-2-methyl-3-heptanone obtained by procedure A.

Preparation of 2-Bromo-2-methyl-3-heptanone by Procedure B.

The β-ketodiester obtained as a mixture with sodium chloride in benzene by procedure A [from the acylation of the sodium salt of bistetrahydropyranyl *n*-propylmalonate (30 mmole) with 2-bromo-2-methylpropanoyl chloride (30 mmole)] was treated as described previously. Pyrolysis of the β-ketodiester concentrate (17.5 g) in a preheated oil bath (170-180°) under vacuum (15 mm) in the manner described in procedure B, afforded a fraction boiling between 70 and 100° (6.05 g). The product mixture was washed with ice-cold dilute sodium hydroxide and yielded 4.32 g of neutral material, ir (liquid film): 1710 (C=O), 1685 cm^{-1} (C=C-C=O). Glc analysis (15% SE-30, 150°) showed the presence of 56% 2-bromo-2-methyl-3-heptanone and 21% 2-methyl-1-hepten-3-one.

Preparation of 3-Chloro-1-phenyl-2-butanone by Procedure B.

The mixture obtained from the acylation of bis-tetrahydropyranyl phenylmalonate (30 mmole) with 2-chloropropanoyl chloride (30 mmole) (as described in procedure A) was filtered. The filtrate was concentrated and yielded 26 g of crude β-ketodiester. Pyrolysis of the β-ketodiester in a distillation apparatus [held in a preheated oil bath (130°) and evacuated to 2 mm] afforded a fraction boiling between 70 and 100°. It was dissolved in *n*-pentane and washed with ice-cold dilute sodium hydroxide. After drying (Na_2SO_4), the organic phase was concentrated. The residue, a colourless oil, (3.08 g, 57%) was shown to be identical (spectroscopically) to the material obtained by procedure A.

Preparation of 3-Bromo-1-phenyl-2-butanone by Procedure B.

The mixture obtained from the acylation of bis-tetrahydropyranyl phenylmalonate (30 mmole) with 2-bromopropanoyl chloride (30 mmole) (as described in procedure A) was filtered. The filtrate was concentrated and yielded 24 g of crude β-ketodiester. The latter was decomposed in a distillation apparatus held in an oil bath at 150-170° in the manner described previously. This procedure yielded 5.36 g of a fraction distilling at 70-111° (3.5 mm). The neutral component of this fraction, obtained by ice-cold dilute sodium hydroxide

wash as described before, was distilled. The material obtained (2.51 g, 37%), bp 104-111° (3.5 mm), n_D^{20} 1.5346 (lit.[191] n_D^{25} 1.5395) was spectroscopically identical to 3-bromo-1-phenyl-2-butanone prepared by procedure A. The material obtained (2.5 g, 54%) by acidification of the base wash with conc. hydrochloric acid, and extraction with ether was identified as 2-bromopropanoic acid, bp 78-80° (2.5 mm) [lit.[187] 96° (10 mm)], $n_D^{22.5}$ 1.4752, ir (liquid film): 1700-1740 (C=O), 2500-3500 cm^{-1} (bonded OH); nmr (CCl_4): $\underline{\delta}$ 1.86 (d, 3, J = 7 cps) $C\underline{H}_3CHBr$, 4.41 (q, 1,,J = 7 cps) $CH_3C\underline{H}Br$, 12.33 (br s, 1) $COO\underline{H}$.

Attempted Preparation of 3-Chloro-3-methyl-1-phenyl-2-butanone by Procedure B.

The sodium salt of the bistetrahydropyranyl phenylmalonate, prepared on a 10 mmole scale (as in procedure A) as a slurry in benzene, was treated at 5° with 1.6 g (12 mmole) of 2-chloro-2-methylpropanoyl chloride in 10 ml of benzene. The mixture was heated during 5 hours at 65°, then left for 19 hours at ambient temperature (25-27°). After filtration of the solid material, the filtrate was concentrated (rotary evaporator). The residue (9.23 g) was decomposed in a distillation apparatus held in an oil bath at 150-170° in the manner described previously. All material boiling below 115° (1.5 mm) was collected. The neutral component (after

dilute sodium hydroxide wash of the distillate as before) was shown to contain no ketonic material by ir analysis. Acidification of the base-wash with conc. hydrochloric acid and ether extraction, afforded 1.05 g (76%) of 2-chloro-2-methylpropanoic acid, n_D^{20} 1.4302 (lit.[76] 1.4380), ir (liquid film): 1700-1740 (C=O), 2500-3500 cm^{-1} (bonded OH); nmr (CCl_4: $\underline{\delta}$ 1.85 (s, 6) $C\underline{H}_2CCl$, 11.73 (s, 1) $COO\underline{H}$; mass spectrum m/e: no M^+, 87 M^+- Cl, 77 79 M^+- CO_2H.

Attempted Preparation of 3-Bromo-3- methyl-1-phenyl-2-butanone by Procedure B.

The sodium salt of the bistetrahydropyranyl phenylmalonate, prepared on a 24 mmole scale (as in procedure A) as a slurry in benzene, was treated at 5° with 4.5 g (25 mmole) of 2-bromo-2-methylpropanoyl chloride in 25 ml of benzene. After 6 hours at 65° and 18 hours at ambient temperature (25-27°), the mixture was filtered. The filtrate was concentrated (rotary evaporator) and the residue obtained (13.4 g) was decomposed in a distillation apparatus held in an oil bath at 165-180° in the manner described previously. Evacuation to 2 mm provided a distillate which upon extraction (as a solution in $\underline{n}$-pentane) with dilute sodium hydroxide, and acidification (with conc. hydrochloric acid) of the base-wash as described previously, afforded 3.15 g (78%) of

2-bromo-2-methylpropanoic acid, mp 38.5-41.0°, identical spectroscopically to the authentic acid prepared by bromination of 2-methylpropanoic acid.

Preparation of di-*t*-butyl malonate.

Malonic acid (20 g, 20 mmole) in 40 ml of ether was shaken with 50 ml of 2-methylpropene and 2 ml of conc. sulphuric acid in a pressure bottle for 7 hours according to the method of McCloskey and coworkers.[192] The procedure yielded 20 g (48%) of di-*t*-butyl malonate as a colourless liquid, bp 109-110° (20 mm) [lit.[192] 112-115° (31 mm)].

Preparation of di-*t*-butyl *n*-hexylmalonate.

Bromohexane (7.43 g, 45 mmole) in 10 ml of dry *t*-butyl alcohol was added to a solution of di-*t*-butyl sodiomalonate, prepared from 19 g (89 mmole) of di-*t*-butyl malonate and 2.8 g of sodium hydride (57% oil dispersion) 67 mmole) in 50 ml of *t*-butyl alcohol as described by Fonken and Johnson.[173] After stirring for 48 hours at 65°, the mixture was cooled and poured into 150 ml of water. The organic layer was separated and the aqueous layer was extracted three times with ether. The combined extracts and organic layer were dried over anhydrous potassium carbonate. After removal of the ether and *t*-butyl alcohol by distillation at atmospheric

pressure, a trace of magnesium oxide was added and the liquid was distilled in alkali-washed equipment. The distillation yielded 13 g of a fraction boiling at 89-112° (1 mm). Redistillation afforded 11 g (80%) of pure di-*t*-butyl *n*-hexylmalonate, bp 111-112° (0.3 mm), n_D^{20} 1.4259, ir (liquid film): 1730 (C=O), 1365 (methyl), 1150 cm^{-1} (C-O-C ester); nmr ($CDCl_3$): δ 0.88 (br t, 3) terminal-C*H*$_3$, 1.1-1.5 (m, 10) -(C*H*$_2$)$_5$-, 1.35 (s, 18) C(C*H*$_3$)$_3$ x2, 3.13 (t, 1, J = 7 cps) $CH_2CH(CO_2-)_2$; mass spectrum m/e (relative intensity): no M^+, 244(2) 189(13) 188(11) 171(13) 160(12) 144(23) 57(100). Anal. Calcd. for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 67.83; H, 10.64.

Reaction between 2-Chloropropanoyl Chloride and the Sodium Salt of Di-*t*-butyl *n*-Hexylmalonate.

Di-*t*-butyl *n*-hexylmalonate (4.6 g, 12 mmole) in 25 ml of benzene was added to 13 mmole of sodium hydride (10% excess) in 75 ml of benzene and heated under reflux according to the method of Johnson and Fonken[173] during 4.5 hours (92% of the theoretical amount of hydrogen was evolved). A solution of 2-chloropropanoyl chloride (1.52 g, 12 mmole) in 10 ml of benzene was added. Heating for 1 hour resulted in the precipitation of sodium chloride. Anhydrous *p*-toluenesulphonic acid (0.17 g, 1 mmole) was added to neutralize the excess sodium hydride. The

mixture was filtered and the filtrate was concentrated (rotary evaporator). The residue (4.43 g) was added to 50 ml of glacial acetic acid containing 2% (by volume) acetic anhydride and 0.1 g anhydrous *p*-toluenesulphonic acid and heated under reflux for 2 hours. The yield of 2-chloro-3-decanone in the resulting solution was estimated as 27% by glc (10% FFAP, 160°).

Preparation of Tetrahydropyranyl 2-Methylpropanoate(49).

To 88 g (1 mole) of freshly distilled 2-methylpropanoic acid in 500 ml of benzene containing 10 mg of anhydrous *p*-toluenesulphonic acid[185] was added dropwise, during 45 minutes, 126 g (1.5 mole) of dihydropyran at 25°. After stirring for 30 minutes, 16 g of potassium hydroxide was added, and the mixture was left standing for 18 hours. Filtration and concentration of the filtrate (rotary evaporator) afforded a concentrate which was distilled under vacuum. The ester (143 g, 83%) was obtained as a colourless liquid, bp 90-92° (8.3 mm), n_D^{20} 1.4347, ir (liquid film): 1740 (C=O), 1200-800 cm^{-1} (C-O-C ether and ester); nmr (CCl_4): δ 1.20 (d, 6, J = 7 cps) $(C\underline{H}_3)_2CH$, 1.4-1.9 (m, 6) $-(C\underline{H}_2)_3-$, 2.60 (sep, 1, J = 7 cps) $(CH_3)_2C\underline{H}$, 3.5-4.0 (m, 2) $C\underline{H}_2$-O, 5.97 (br s, 1) O-C$\underline{H}$-O; mass spectrum m/e (relative intensity): no M^+ 84(30) 73(27) 56(24) 55(57) 41(100) 39(69). Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found:

C, 62.99; H, 9.27.

Reaction between the Lithium Salt of Tetrahydropyranyl 2-Methylpropanoate and 2-Chloropropanoyl Chloride.

Under an atmosphere of dry nitrogen, 2.83 g (20 mmole) of cyclohexylisopropylamine in 20 ml of tetrahydrofuran (distilled from lithium aluminium hydride) was cooled to -45°. Addition of 13.3 ml of 1.5M hexane solution of *n*-butyllithium, during 5 minutes, resulted in the formation of a clear colourless solution. After a 15 minute stirring period, the solution was cooled to -78° and 3.2 g (19 mmole) of tetrahydropyranyl 2-methylpropanoate in 5 ml of tetrahydrofuran was added dropwise, followed, after 10 minutes, by 2.6 g (20 mmole) of 2-chloropropanoyl chloride. A white precipitate formed. which redissolved as the mixture was warmed to 25°. After 2 hours of additional stirring, 5 ml of glacial acetic acid was added. A white precipitate formed. The gelatinous mass was diluted with 15 ml of dry tetrahydrofuran and filtered. The solid (2.8 g) was identified as the hydrochloride of cyclohexylisopropyl amine, mp 209.0-209.5°. Treatment with sodium hydroxide solution regenerated the free amine whose ir was identical to that of a commercially available sample. Treatment with hydrogen chloride in ether gave back the hydrochloride salt, mp 210°, ir (nujol mull): 2700-2250, 2035, 1575 cm^{-1}

(ammonium bands); nmr (D_2O): $\underline{\delta}$ 1.34 (d, 6, J = 6.5 cps) $(C\underline{H}_3)_2CH$, 3.39 (s, 1, J = 6.5 cps) $(CH_3)_2C\underline{H}$, 0.9-2.3 and 2.2-3.1 (m, 11) *cyclo*-$C_6\underline{H}_{11}$. The filtrate was heated under reflux for 1.5 hours, then partially concentrated by distillation of the solvent at atmospheric pressure. The residue was poured into ice-cold 2N hydrochloric acid, saturated with sodium chloride, and extracted with *n*-pentane. The organic extract was washed with saturated sodium bicarbonate solution, then brine, and dried over anhydrous sodium sulphate. The solution was concentrated by distillation of the solvent at atmospheric pressure. The residue (4.4 g) was shown to contain two major components which were separated by glc (15% XF-1150, 110°). The first component (40% by glc) was identified as 2-chloro-4-methyl-3-pentanone (50), ir (liquid film): 1720 (C=O), 1445, 1465 cm^{-1} (gem dimethyl); nmr (CCl_4): $\underline{\delta}$ 1.12 (d, 6, J = 7 cps), $(C\underline{H}_3)_2CH$, 1.54 (d, 3, J = 6.5 cps) $C\underline{H}_3CHCl$, 3.08 (sep, 1, J = 7 cps) $(CH_3)_2C\underline{H}$, 4.35 (q, 1, J = 6.5 cps) $CH_3C\underline{H}Cl$; mass spectrum m/e: 134 $M^+(Cl_{35})$, 136 $M^+(Cl_{37})$, 71 $M^+ - CH_3CHCl$. The second component (22% by glc) was identified as 2-chloro-2-methyl-3-pentanone (51), ir (liquid film): 1720 cm^{-1} (C=O); nmr (CCl_4): $\underline{\delta}$ 1.04 (t, 3, J = 7 cps) $C\underline{H}_3CH_2$, 1.63 (s, 6) $(C\underline{H}_3)_2CCl$, 2.73 (q, 2, J = 7 cps) $CH_3C\underline{H}_2C=O$; mass spectrum m/e: 134 $M^+(Cl_{35})$, 136 $M^+(Cl_{37})$, 59 $M^+ - (CH_3)_2CCl$.

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