THE SYNTHESIS OF SOME CYCLOBUTYLCARBINYL KETONE DERIVATIVES AND AN INVESTIGATION OF THE INTERACTION OF 4-MEMBERED RINGS WITH ADJACENT CARBANION CENTERS

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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Doctor of Philosophy in Chemistry.

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ABSTRACT

THE SYNTHESIS OF SOME CYCLOBUTYLCARBINYL KETONE DERIVATIVES AND AN INVESTIGATION OF THE INTERACTION OF 4-MEMBERED RINGS WITH ADJACENT CARBANION CENTERS

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Ph.D. in Chemistry

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In the introductory section the olefinic properties of the three- and four- membered rings have been discussed. Due to the high degree of p character in their C-C bonds these rings (especially cyclopropyl groups) are known to stabilize adjacent carbocation centers. Relatively little is known, however, about the interaction of cyclopropyl groups with the adjacent carbanion centers and no data is available in the literature* about such interaction of four- membered rings.

In this work, a series of phenyl cyclobutylcarbinyl ketones have been synthesized to observe the effect of the cyclobutyl ring on the base-catalyzed rate of enolization of these ketones by means of H-D exchange experiments, carried out under standardized conditions using pyridine/D_2O/OD^-, as medium of exchange. The results have been compared to those of an earlier study[2] with phenyl cyclopropylcarbinyl ketones and other phenyl alkylcarbinyl ketones that have also been synthesized. The conclusion has been that the four- membered rings stabilize the transition states leading to the enolate anions but that this stabilization is much smaller than that rendered by the cyclopropyl groups. Indeed, in some experiments such stabilization by the four-membered ring could not be clearly detected. A search for the homoconjugative interaction of the four-membered ring with a carbanion center β- to the ring has been carried out using 3-cyclobutyl-1-phenyl-1-propanone and other suitable model compounds. No such effect of the cyclobutyl group has been detected. The detailed synthesis of some novel cyclobutylcarbinyl ketones have also been described.

As a further extension of this work, the relative kinetic acidities of the methine hydrogens of cyclopropyl, cyclobutyl, and isopropyl phenyl ketones

have been determined with the base system that has been used through this work. This comparison had already been done in the literature with varying base systems and with conflicting results. Our results agree with most of them, in that the methine hydrogen in cyclopropyl phenyl ketone resists base-catalyzed H-D exchange.

(* See, however, ref.[1], which partly stems from the work in this thesis)

Keywords: Cyclobutyl, cyclobutylcarbinyl, carbanion.

Science Code: 405.02.01

ÖZ

BAZI SİKLOBÜTİLKARBİNİL KETON TÜREVLERİNİN SENTEZİ VE DÖRTLÜ HALKALARIN KOMŞU KARBANYON MERKEZLERİ İLE ETKİLEŞİMLERİNİN İNCELENMESİ

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Haziran 1992, 155 sayfa.

Giriş kısmında üçlü ve dörtlü halkaların olefinik özelliklerine ait bazı bilgiler tartışılmıştır. Karbon-karbon bağlarındaki yüksek derecedeki p karakterinden dolayı bu halkaların komşu artı yük merkezlerini (özellikle üçlü halkaların) kararlı hale koyduğu bilinmektedir. Komşu eksi yük merkezleri ile üçlü halkaların etkileşimine ilişkin bilgiler ise çok az olup dörtlü halkaların bu türden etkileşimlerine ait bilgiler ise literatürde yoktur*. Bu çalışmada bir dizi fenil siklobütilkarbinil keton sentezlenerek dörtlü halkaların bu ketonlarda, piridin/D_2O/OD^- sistemi kullanılarak tayin edilen baz katalizli enolleşme

hızlarına etkisi H-D değiş-tokuşu deneyleri ile incelenmistir. Bu deneyler sonunda daha önceki bir çalışmadaki[2] fenil siklopropilkarbinil ketonlarla ve sentezlenen diğer fenil alkilkarbinil ketonlarla alınan sonuçlar karşılaştırılmış ve sonuç olarak dörtlü halkaların enolat anyonlarının oluşmasındaki geçiş halini (transition state) bir miktar kararlı hale koyduğunu fakat bu etkinin üçlü halkaların etkisinden oldukça daha zayıf olduğu kanısına varılmıştır. Bazı deneylerde dörtlü halkanın herhangi bir kararlılaştırıcı etkisi açıkça gözlenememiştir. Dörtlü halkanın β- konumundaki bir karbanyon merkezi ile de homokonjugative etkileşimini incelemek üzere 3-siklobutil-1-fenil-1-propanon ve uygun model bileşikler üzerinde de deneyler yapılmış fakat böyle bir etki gözlenememiştir. Ayrıca, ilk defa hazırlanan fenil siklobütilkarbinil ketonların sentezleri de ayrıntılı olarak verilmiştir.

Bu çalışmanın diğer bir uzantısı olarak da siklopropil, siklobütil ve izopropil fenil ketonların metin hidrojenlerinin kinetik asitlikleri bu çalışmada kullanılan baz sistemi ile karşılaştırılmıştır. Bu kıyaslamaların çeşitli baz sistemleri ile önceden yapılmış olmasına rağmen literatürdeki sonuçları çelişkilidir. Bu çalışmada erişilen sonuçlar literatürdeki sonuçların çoğunluğu ile uygunluk içinde

olup, siklopropil ketonlardaki metin hidrojeninin baz katalizli H-D değiş-tokuşuna direnç gösterdiği yönündedir.

(* Bu konuda, bu tezdeki çalışmaların da katkısıyla yazılan bir makale basılmıştır, Bkz. ref [1]).

Anahtar kelimeler: Siklobütil, siklobütilkarbinil, karbanyon.

Bilim Dalı Sayısal Kodu: 405.02.01

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INTRODUCTION

1.1. Olefinic Properties of the Four-Membered Rings

The olefinic properties of the three-membered ring is well known and recently reviewed by Wong[3]. Models showing bonding in the three-membered ring have also been proposed[4] for the four-membered ring to explain these olefinic properties. Properties similar to those of the three-membered ring have been seen although to a lesser extent, in the literature for the cyclobutane ring.

1.1.1. Bonding in the Cyclobutane Ring:

Among the important models describing bonding in the four-membered ring, the trigonally-hybridized and bent-bond models are briefly described below.

1.1.1.1. The Trigonally Hybridized Model[5] (Walsh Model)

In this model, in a planar cyclobutane ring, all C atoms are sp^2 hybridized. All the sp^2 orbitals on each carbon have their axes in a plane perpendicular to the plane of the four-membered ring. The C-H bonds utilize sp^2 hybridized carbon atomic orbitals and are thus in a plane at right angles to the plane of the ring. The remaining sp^2 carbon atomic orbitals are directed toward

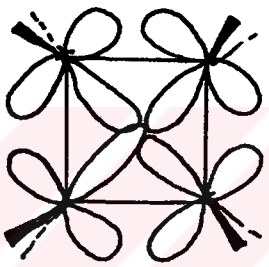


Figure 1. The Walsh Model of Cyclobutane

the center of the ring and overlap intraannularly with each other. The pure 2p orbitals on each carbon atom have their axes in the plane of the ring and overlap to some extent with each other. In this model, overlapping 2p orbitals form π- charactered molecular orbitals similar to olefins. For conjugation, the plane of the four-membered ring must be parallel to the axis of the neighboring 2p atomic orbitals. 2p atomic orbitals on neighboring carbon atoms overlap to give a delocalized

molecular orbital. In cyclobutane, localization is greater than that in cyclopropane and the "four center unsaturation" is less[6] than the three center unsaturation in the three-membered ring.

1.1.1.2. The Bent-Bond Model:

Coulson and Moffitt[7] have used the perfect-pairing approximation to describe the bonding in highly strained small ring hydrocarbons. They applied their bent-bond model to cyclobutane as well as cyclopropane. The carbon-carbon bonds of the ring are

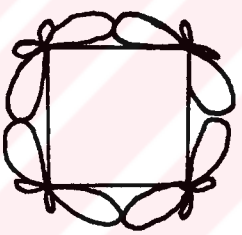


Figure 2. The Bend-Bond Model of Cyclobutane

constructed by overlapping of hybrid atomic orbitals inclined outward from the internuclear line, producing "bent" bonds. The sp^3 hybrids give less effective overlap than the C-C bond of ethane. For this reason, the bonds are referred to as "bent". Maksic, Klasinc and Randic[8] have found the $sp^{4.35}$ and $sp^{2.19}$ hybrids for

carbon atomic orbitals forming carbon-carbon and carbon-hydrogen bonds, respectively, for cyclobutane. The greater p- character in the C-C σ- bonds is frequently invoked to explain the similarity of cyclobutane (and cyclopropane) chemistry to that of olefins. Calculated degree of "bent bonding" for cyclobutane is about one-third of that calculated for cyclopropane[9].

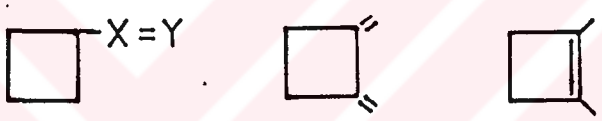
1.1.2. The Olefinic Properties of Cyclobutane Ring and Stabilization of Carbonium Ions by Cyclobutyl Groups:

The olefinic character of the four-membered ring is not as well documented in the literature as that of the three-membered ring. Although cyclopropane with certain reagents gives addition products, for example it is slowly attacked by bromine yielding 1,3-dibromopropane, cyclobutane, in contrast, yields substitution products if any reaction occurs at all. HBr converts only cyclopropane into propyl bromide[10].

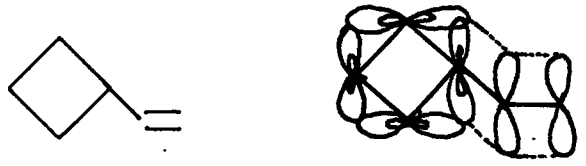
The facile ring opening of cyclopropane with bromine and the more reluctant ring opening that results upon catalytic hydrogenation of cyclopropane and cyclobutane are well-known examples of ethylene-like

behavior[11].

Experimental work has not revealed any striking indication of conjugative power by a cyclobutane ring. There is some evidence, however, which suggests that such an effect is not negligable. The UV spectra[12] of three types of unsaturated cyclobutane compounds reveal auxochromic effects attributable to the cyclobutane ring, due to the increased delocalization of sp^3 electrons in the following strained cyclobutane systems.



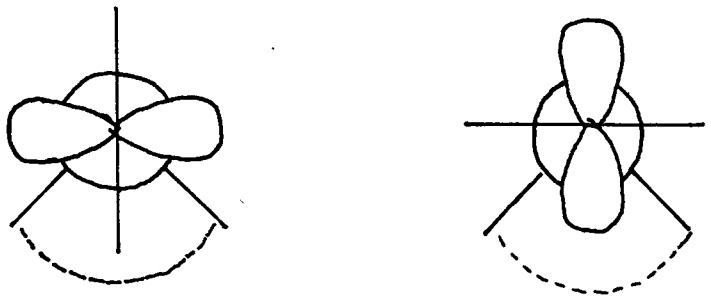
Wilson and Goldhamer[13] in their work dealing with the spectral properties of conjugated systems have discussed the possible conjugation of cyclobutane with olefinic systems, invoking "π-like character" in the bent bonds of the ring.



On the other hand, early extended Huckel calculations indicated no special conjugative ability for the cyclobutane ring[14].

Yonezawa, Shimizu and Kato[15] point out that the energy of the lowest vacant molecular orbital (LUMO) becomes higher as the size of the ring increases. Cyclobutane, as well as cyclopropane, has relatively low LUMO energy and therefore can accept electrons easily. The partial atomic bond populations of the lowest vacant orbital in cyclobutane, as in cyclopropane, are localized only in C-C bonds and are zero in C-H bonds. The odd electron of the cyclopropane and cyclobutane anion radical is localized in the ring and not in the C-H bonds.

Wiberg[16] has performed CNDO calculations on the cyclobutylcarbinyl cation. A bisected conformation is prefered over the perpendicular one by 7.4 kcal/mole, which is significantly smaller than the 25.1 kcal/mole barrier computed for the cyclopropylcarbinyl cation.



Bisected Perpendicular

Figure 3. Two conformations of Cyclobutylcarbinyl cation

According to Radom and Pople[17], when the C-C bonds are "bent", increasing their p character, their C-C hyperconjugative ability increase, but the enhancement in the rotational barrier only becomes really large when a 3-membered ring is present. Ab-initio calculations yield barriers of 17.5 kcal/mole for cyclopropylcarbinyl cation and 4.1 kcal/mole for cyclobutylcarbinyl cation.

Hoffmann and Davidson[18] have investigated the behavior of cyclobutylcarbinyl system in terms of Walsh orbitals of cyclobutane. The highest occupied molecular orbitals of cyclobutane are a degenarate pair with symmetries which permit stabilization of adjacent cationic centers in both perpendicular and bisected conformations; the stabilizing interaction, however is

indicated to be greater in the latter case.

Heilbronner[19] has reached similar conclusions regarding the ability of the cyclobutane ring to interact with adjacent π- deficient centers from an analysis of the photoionization spectrum of cyclobutyl bromide.

Radom,Pople and Schleyer[20] have compared the ethyl cation stabilization energies and found +7.5 kcal/mole, +12.2 kcal/mole and 18.3 kcal/mole for isobutyl, cyclobutylcarbinyl & cyclopropylcarbinyl respectively, as would be expected because of enhanced C-C hyperconjugation in the strained ring compounds. A positive ethyl cation stabilization energy indicates a greater substituent stabilization in the substituted ethyl cation than in ethyl cation according to the following equation.

$$RCH_2CH_2^+ + CH_3CH_3 \longrightarrow RCH_2CH_3 + CH_3CH_2^+$$

R = isopropyl, cyclobutyl, cyclopropyl

Hehre[21] explained substituent effects on the relative energies of the vinylcyclobutane conformers as small but significant by using ab-initio MOT minimal STO-3G basis set. They considered the interaction between the valence orbitals of cyclobutane and an adjacent p function again of unspecified occupation. The

degree of interaction between the cyclobutane valence functions and the p orbital is not expected to be greatly different in the two (bisected & perpendicular) conformations. It was concluded that both cyclopropyl and cyclobutyl rings interact with ethylene to a degree between that characteristic for formally saturated and unsaturated substituents.

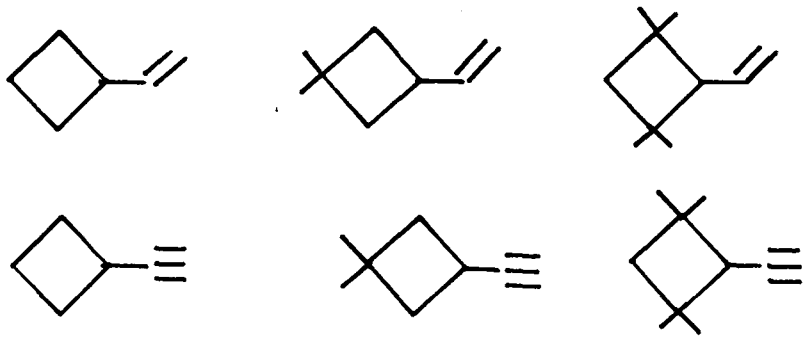
Shanshal[22] applied a 2nd order PMO method to the cyclobutylcarbinyl cation. Both conformations, bisected and perpendicular; are found to be equally conjugated with the ring.

Radom, Pople and Schleyer[20] state that both the perpendicular and bisected conformations of the cyclobutylcarbinyl cations are strongly stabilized according to ab-initio MOT STO-3G calculations. Same authors[23] have found stabilization energies [energy of the formal rxn: RCH_2(+ or .) + $CH_3CH_3 \longrightarrow RCH_3 + CH_3CH_2$ (+ or .)] +12.2 kcal/mole and +0.2 kcal/mole for cyclobutylmethyl cation and radical, respectively, according to ab-initio MO calculations STO-3G basis set. According to their work, the conformational preferences are accompanied by a strong hyperconjugative interaction between the β- carbon and the formally vacant 2p orbital at the positive carbon

(measured by the electron population of that orbital). The corresponding 2p orbital in the radicals is no longer vacant and the hyperconjugative interaction is much weaker. Consequently, the rotational barriers should be smaller in the radicals than those in the cations.

Mollere[24] investigated 3-oxetanylcarbinyl cation system. According to him, the preference of 3-oxetanylcarbinyl cation for the bisected conformation is greater than that of the cyclobutyl analog by a factor of 1.5-2.0 . He used photoelectron spectroscopy , along with the theoretical calculations (CNDO, EHT).

Bruckmann & Klessinger[25] have analyzed the photoelectron spectra of methylene, cyclopropyl and cyclobutyl substituted vinyl, cyclopentenyl and phenyl compounds within the HMO approximation. They found that the conjugative interaction between two π orbitals in the double bonds is 1.98 and 1.14 times more, compared to that between a Walsh orbital of cyclobutane and a π orbital of a double bond; and a Walsh orbital of cyclopropane and an olefinic π orbital respectively. They have also synthesized the following compounds in



order to analyze the conjugative properties of cyclobutane. From the PE spectra of these compounds, as well as of related model compounds, the interaction term H_{RS} = - 0.54 eV to describe the conjugation between cyclobutane and a π system was obtained within the frame work of a LCBO model. They have found that the conjugative interaction does not depend on the conformation in the ethynyl substituted cyclobutanes; and that methyl substitution, which lowers the energy difference between cyclobutane and π orbitals enhances the conjugative power of cyclobutane; in addition to the fact that the influence of the cyclobutane on the π system exceeds that of an alkyl substitution of comparable size.

Jorgensen and Borden[26] have investigated the chemical consequences of orbital interactions in hydrocarbons containing unsaturatively bridge small rings and in ethylene and butadiene bridged polycyclic hydrocarbons containing three- and four- membered rings.

They showed that the stability of molecules vary with the type of orbital interactions between the ring and the bridge.

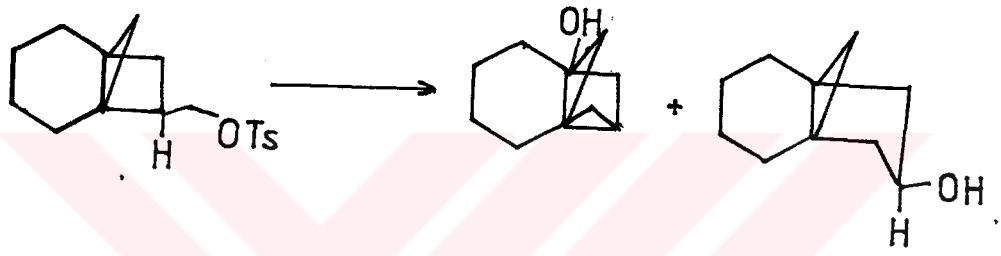
Haddon[27] have investigated the participation of the cyclobutane ring in homoaromatic conjugation, but he could not find any proof.

Jorgensen[28] have also investigated the homoconjugative interactions in the cyclobutyl fused compounds; the conclusion was that they were negligable.

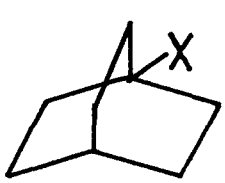
The comparison of the rate of solvolysis reactions with model compounds has an important role in the investigation of the stability of cyclopropylcarbinyl cations[29]. In experimental studies, although the rates of solvolysis of cyclobutylcarbinyl systems, similar to cyclopropylcarbinyl systems are appreciably accelarated, this accelaration has generally been attributed to the relief of steric strain via σ- participation leading to cyclopentyl products. Thus, it is difficult to differenciate experimentally between the rate enhancement

in cyclobutylcarbinyl systems due to ring enlargement and enhanced hyperconjugation.

The following solvolysis reaction is an example to the ring enlargement. Gassmann & Armour[30] report a stereospecific rearrangement of a cyclobutylcarbinyl cation which involves the ring expansion of the four-membered ring of the tricyclo[4.2.1.0]nonane skelaton.

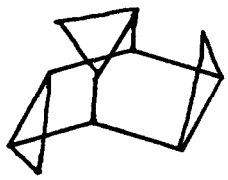


Erden & Meijere[31] have investigated the cyclobutyl neighboring group effect on the stability of bicyclo[2.2.2]octyl bridgehead carbenium ions. Solvolysis of the bridgehead cyclobutylmethyl chloride proceeds without skelatal rearrangement. They have compared the rates of solvolysis of the following compounds.

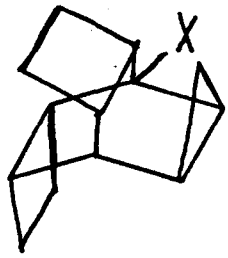


(1)

(2)



(3)

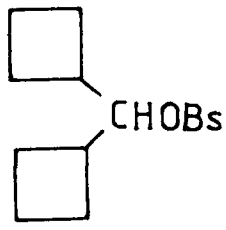


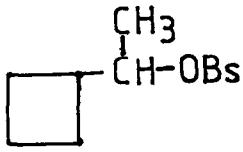
(4)

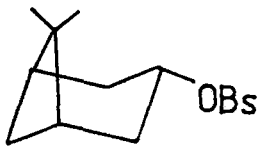
The relative rate of compound (4) compared to compounds (1) and (2) shows significant ability of the cyclobutyl group to stabilize an adjacent positively charged center.

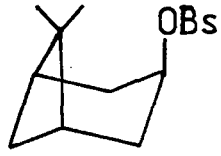
Winstein & Holness[32] state that the rates of acetolysis of dicyclobutylcarbinyl- and cyclobutylmethylcarbinyl p-bromobenzenesulfonates are much accelarated compared with those of the nopinyl derivatives, they give the following sequence at 25° . The result has been explained by the effect of four-membered ring, on ionization during the solvolysis.

Nopinyl Derivatives



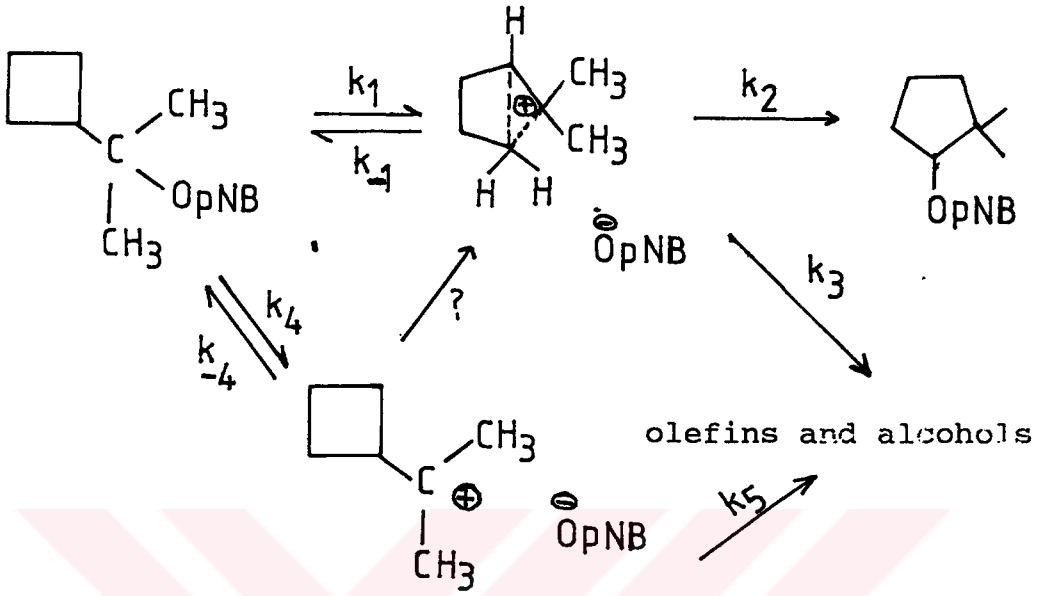






k_{rel}=16800 3900 6 1

Wilcox & Mesirow[33] have studied the solvolysis of dimethylcyclobutylcarbinyl p-nitrobenzoate (OpNB) and related systems.

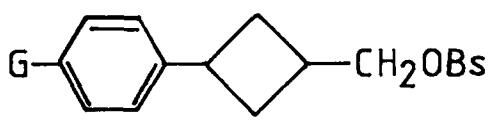


From the consideration of the products formed, it was concluded that dimethylcyclobutylcarbinyl p-nitrobenzoate formed a bridged nonclassical ion and that the driving force was primarily a relief of strain and not a polarizability stabilization.

The solvolysis rates of cyclobutylcarbinyl (4-OBs) and some other brosylates have been determined in a series of solvents by Roberts & Wu[34]. Neighboring group participation involving ring expansion has been postulated for the solvolysis of cyclobutylcarbinyl

derivatives. Release of strain energy in going from the starting material to transition state complex was expected to accompany σ- bond participation by the cyclobutane ring.

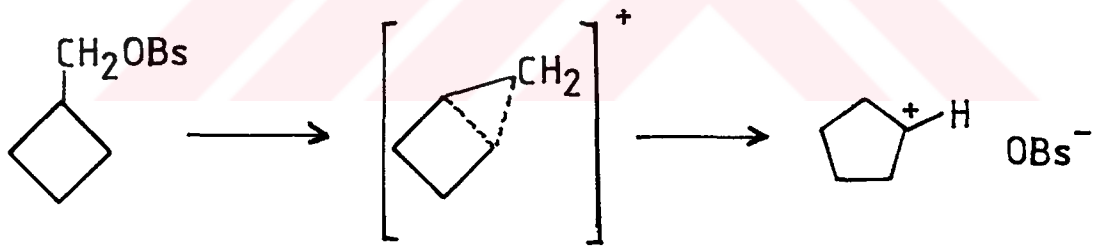
Wilt & Roberts[35] have studied the solvolysis of 4-Ar substituted cyclobutylcarbinyl brosylates. In this



4-Ar

G = -NO2 , CH3O-

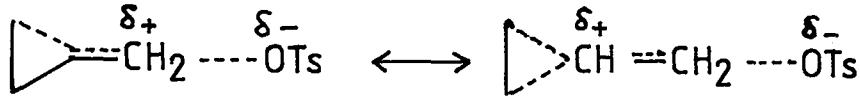
study little direct conjugation was shown between the p-substituent and the developing cationic center.



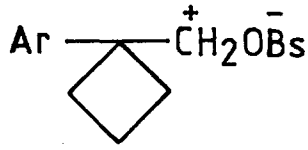
In this, the acetolysis of cyclobutylcarbinyl p-bromobenzenesulfonate was anchimerically assisted and led to cyclopentene and cyclopentyl acetate.

Traylor[36] has proposed that strained σ- bonds,

such as those in cyclopropylcarbinyl substrates, can afford stabilization of neighboring cationic centers via



σ-π conjugation. This affords an interesting possibility

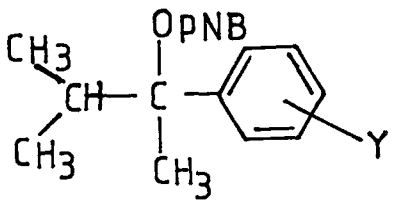


(5)

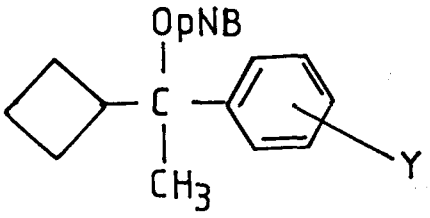
for the structure of (5) in a study by Roberts[37] on cyclobutylcarbinyl p-bromobenzenesulfonate solvolysis. There it was suggested that "1-arylcyclobutylcarbinyl brosylate was stabilized by σ-π conjugation between the cyclobutyl group and the neighboring cationic center where little movement of the cyclobutyl group toward the developing cationic centre occurred; i.e., vertical stabilization took place in which the σ bond was delocalized without changing its bond length or angle significantly".

Peter[38] has investigated the rates and products

of solvolysis of arylmethylcyclobutylcarbinyl p-nitrobenzoates. He found increasing stabilization of the carbenium ion system with increasing electron demand. According to this study, the rate increases must reflect increases in the electron supply by the cyclobutyl group under increasing demand of the cationic center.



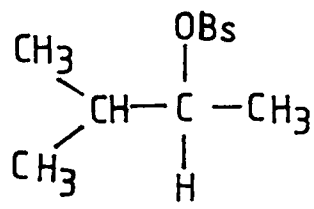
(6)

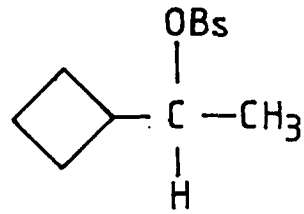


(7)

Y	Rel. Rates	
	6	7
p-CH_3O	1.0	1.0
p-H	1.0	5.7
p-CF_3	1.0	9.0
m,m-$(CF_3)_2$	1.0	17.6

In another study, methylcyclobutylcarbinyl brosylate undergoes acetolysis 86 times faster than a model system. This rate enhancement is attributable to





Rel.Rate (25°)	1.0	85.5

stabilization of the developing carbenium ion by the strained σ bonds in the adjacent cyclobutyl group[32]

1.1.3. Stabilization of Carbanions by Cyclobutyl Groups:

There is no study about the stabilization of adjacent carbanion centers by cyclobutyl group except a recent one[1], which partly stems from the work in this thesis. Greenberg[39] has studied theoretically the 1-bicyclobutylcarbinyl cation and related molecules. According to his result, if rotational barriers are employed as measures of the π conjugation of unsaturated systems with the substituents investigated, then it appears that the central bond in bicyclobutane is comparable to the vinyl group in its ability to stabilize a carbocationic center, but quite inferior in its ability to stabilize a carbanionic center. They have applied ab-initio MO calculations using STO-3G basis set in the

Gaussian 70 series of programs to a study of idealized structures of 1-bicyclobutylcarbinyl cation and related molecules.

Hoz & Levy[40] have studied the cyclobutane-bicyclobutane system, together with the conformation and stability of 1-bicyclobutylcarbinyl anion. They investigated the ability of a bicyclobutyl moiety to stabilize a negative charge at an α- position by analyzing the two conformers (parallel & orthogonal) of 1-bicyclobutylcarbinyl anion.

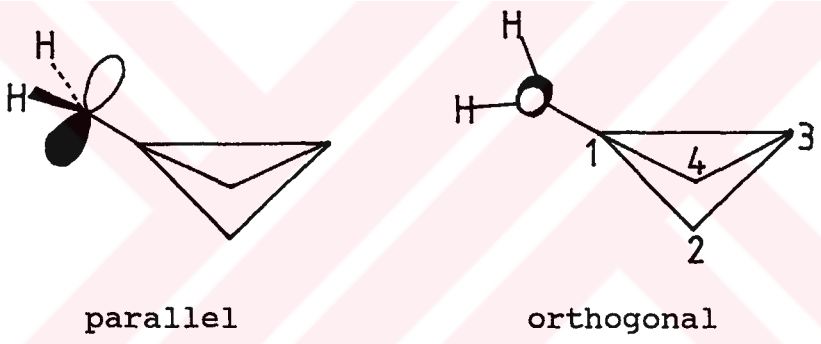


Figure 4. Conformations of 1-Bicyclobutylcarbinyl Anion

The structure and energy of the two conformers of the 1-bicyclobutylcarbinyl anion, the parallel and orthogonal, were calculated using the HONDO program with a 4-31G basis set employing the gradient optimization procedure. A study at a 4-31G level reveals that the two conformers are equally stabilized by the ring. According

to the paper, a carbanion placed at an α position to the bridgehead carbon as in the above figure (4) can not only interact with the central bond in an allylic-like fashion within the plane of symmetry but can also, when rotated by 90°, be effectively stabilized by the side carbon-carbon bonds of the molecule. Thus, the molecule as a whole can, like acetylene display reactivity in two orthogonal planes.

1.1.4. Stabilization of Radicals by Cyclobutyl Groups:

Kemball, Walton & Ingold[41] have suggested that the conformational preferences of the radicals are governed by steric factors, except for cyclobutylmethyl, where the bisected conformation is favored by C-C hyperconjugation involving C. and the two C_α-C_β bonds. C-C hyperconjugation will be important in cyclobutylmethyl radical because of the increased p character of the C-C bonds in the ring. They used E.S.R. spectroscopy, MNDO and INDO semi-emperical SCF MO methods.

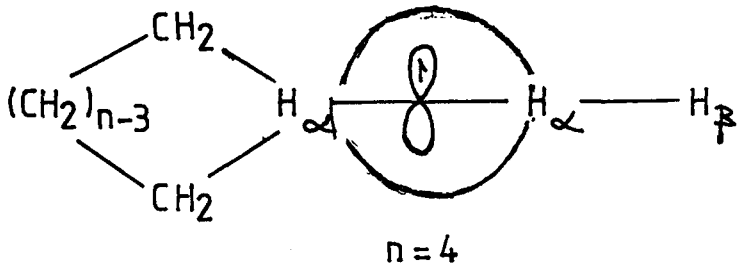


Figure 5. Bisected Conformation of Cyclobutylcarbinyl radical.

1.2. Aim of the Work:

The cyclobutylcarbinyl system has been the subject of theoretical and experimental studies[32,21,18,33,35,37,42], and it is generally agreed that the cyclobutyl group stabilizes an adjacent cationic center much less than a cyclopropyl group. But, there is virtually no study about the interaction of the cyclobutyl group with an adjacent carbanionic centre in the literature[1]. According to Yonezawa, Shimizu & Kato's[15] studies, the energy of the lowest vacant orbital becomes higher as the size of the ring increases; cyclobutane, similar to cyclopropane has relatively low energy LUMO, which might accept electrons easily. Experimental studies[43] related with the three-membered

ring adjacent carbanion center interaction have indicated the possibility of this kind of interaction. Perkins and coworkers[43] have investigated the base-catalyzed rate of enolization of a series of cyclopropylcarbinyl ketones. In this work, an extension of the previous study[43], a series of phenyl cyclobutylcarbinyl ketones have been synthesized to observe the effect of the cyclobutyl ring on the base-catalyzed rate of enolization of these ketones. The main aim of this work is to compare the interaction of the three- and four- membered rings with the adjacent (-) charged centers. In addition to this, the effect of the cyclobutyl group on the carbanion centers β- to it (homoconjugative interaction) have also been investigated. As a further extension of this work, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone and isopropyl phenyl ketone have also been subjected to base-catalyzed enolization using our base system (OD^-/D_2O/pyridine), in which we have carried out all our base-catalyzed enolizations. The methine hydrogen connected to the cyclopropyl group is expected to be the most acidic one what with the increased s character of the exocyclic carbon atomic orbital. On the other hand enolization of a cyclopropyl ketone is expected to be inhibited by the increased I-strain in its enolate form. These two opposing effects have yielded conflicting results in the literature, where different

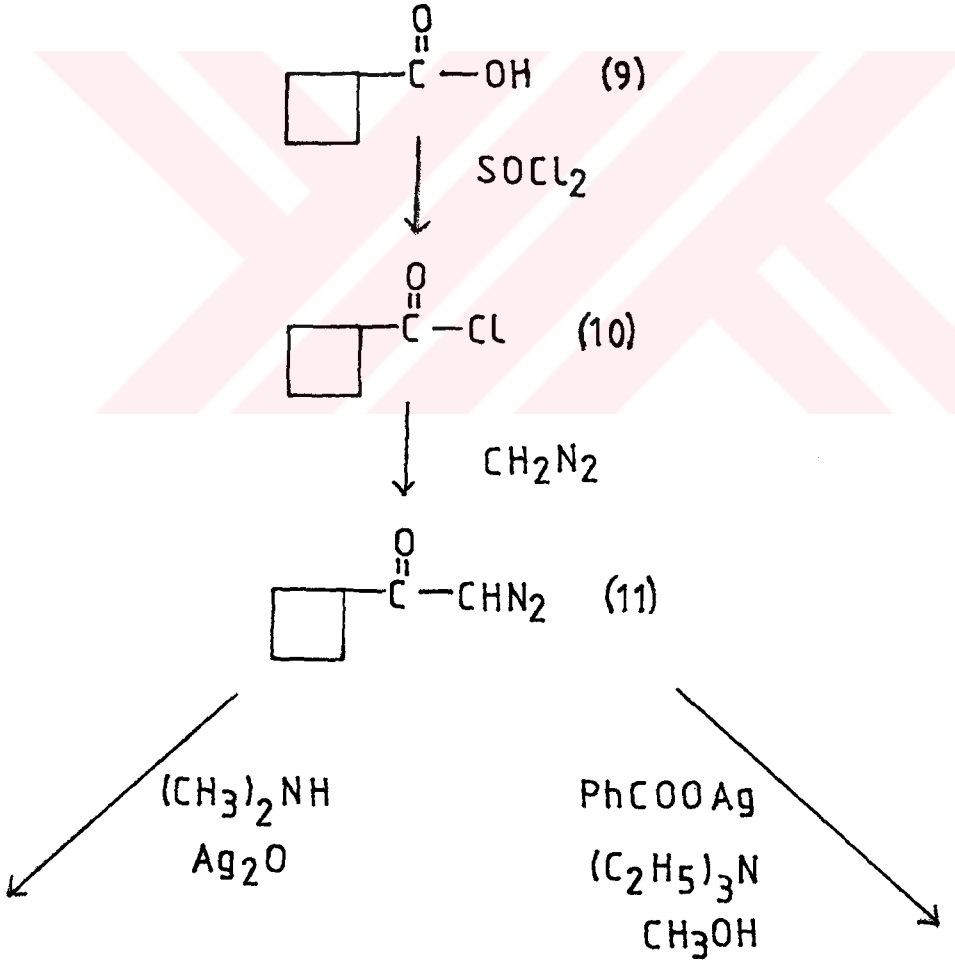
base systems have been used. A last minor aim of this work has therefore been to compare the acidity of the methine-H of cyclopropyl phenyl ketone with those of cyclobutyl (where the s character of the exocyclic carbon atomic orbitals are less than those in the three-membered ring) and isopropyl phenyl ketones.

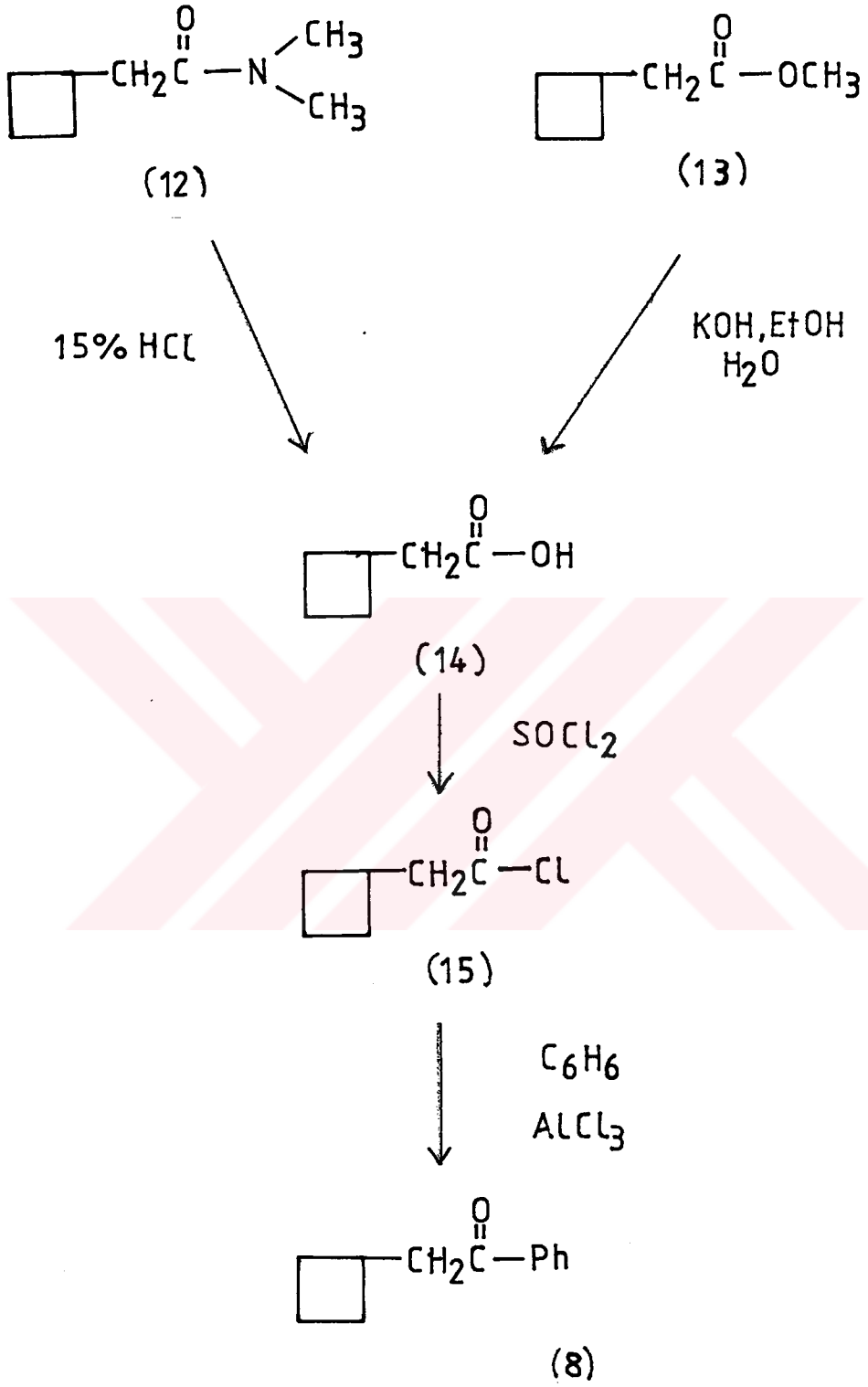
CHAPTER II

RESULTS AND DISCUSSIONS

2.1. Synthesis of Ketones for Kinetic Studies.

2.1.1. Cyclobutylcarbinyl Phenyl Ketone (8):




CH2C(=O)N(CH3)2
(12)
CH2C(=O)OCH3
(13)
15% HCl
KOH, EtOH
H2O
CH2C(=O)OH
(14)
SOCl2
CH2C(=O)Cl
(15)
C6H6
AlCl3
CH2C(=O)Ph
(8)

Cyclobutanecarboxylic acid (9) was chlorinated to cyclobutanecarbonyl chloride (10) with $SOCl_2$. (10) was treated with CH_2N_2 to give cyclobutyl diazomethyl ketone (11) according to Arndt-Eistert reaction. (11) was treated with dimethylamine and silver oxide as catalyst to give N,N-dimethylcyclobutylacetamide (12). In another approach, (11) was turned to its homologated methyl ester (13) using silver benzoate, triethyl amine and methanol. The amide (12) was acidified with 15% HCl to give cyclobutylacetic acid (14). On the other way, the ester 13 was saponified with KOH, to give acid (14). (14) was chlorinated using $SOCl_2$ to cyclobutylacetyl chloride (15), which (15) was treated with $AlCl_3$ and benzene to give cyclobutylcarbinyl phenyl ketone (8) according to Friedel-Crafts reaction.

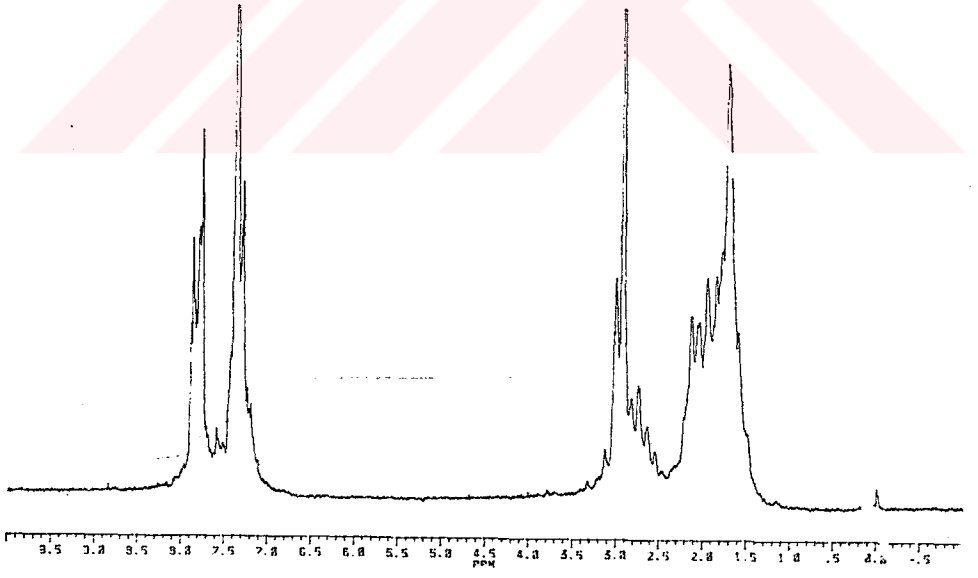


Figure 6. ^{1}H-NMR Spectrum of Cyclobutylcarbinyl Phenyl Ketone (8) in $CDCl_3$.

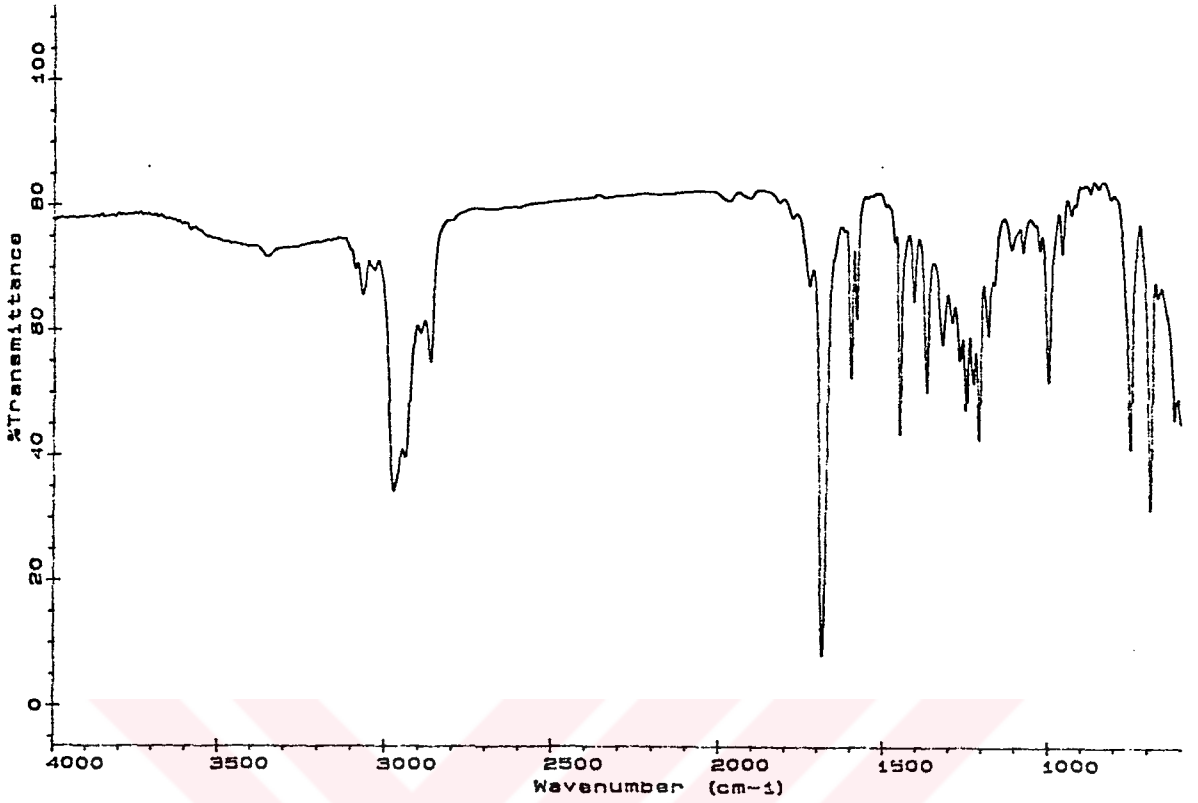


Figure 7. IR Spectrum of Cyclobutylcarbinyl Phenyl Ketone (8) as neat.

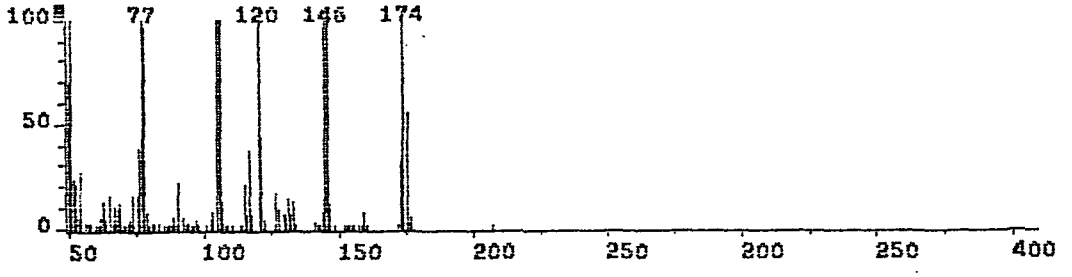


Figure 8. Mass spectrum of Cyclobutylcarbinyl Phenyl Ketone (8) .

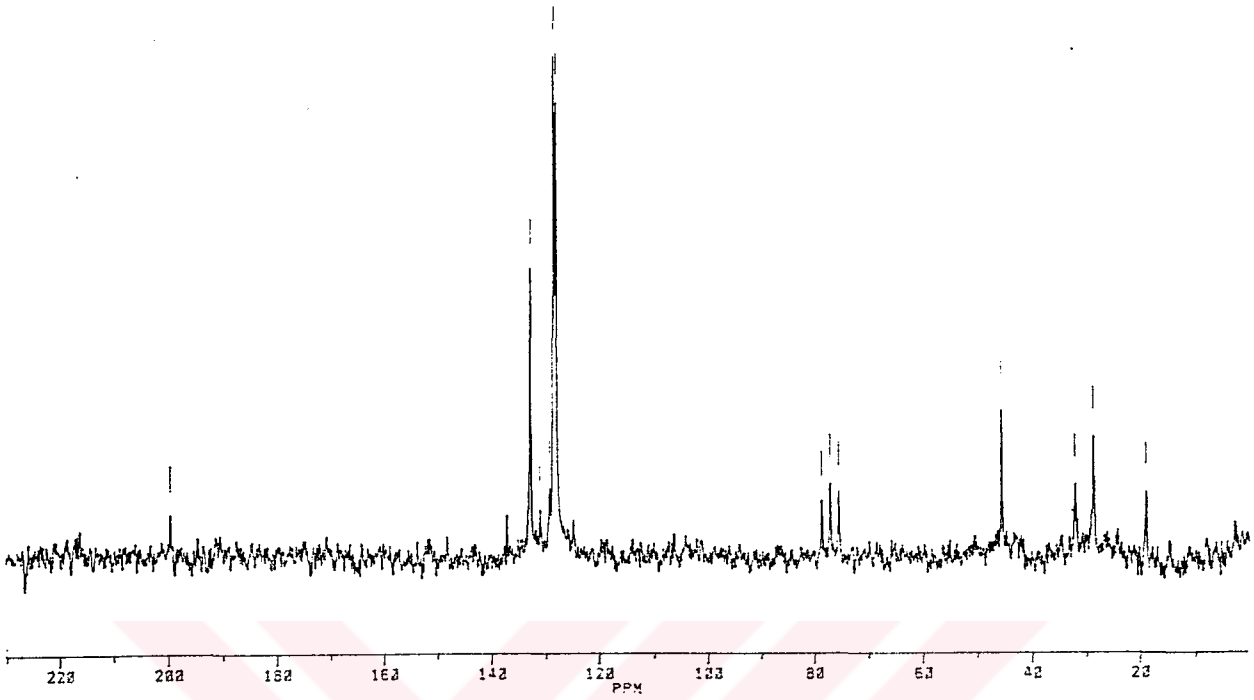
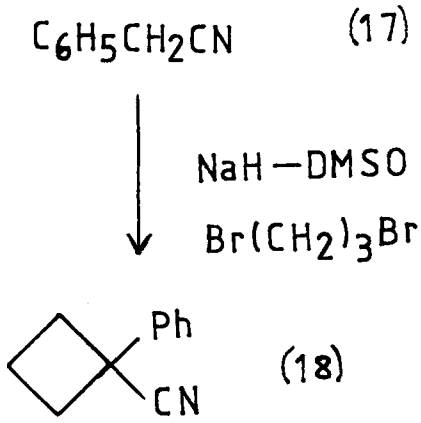
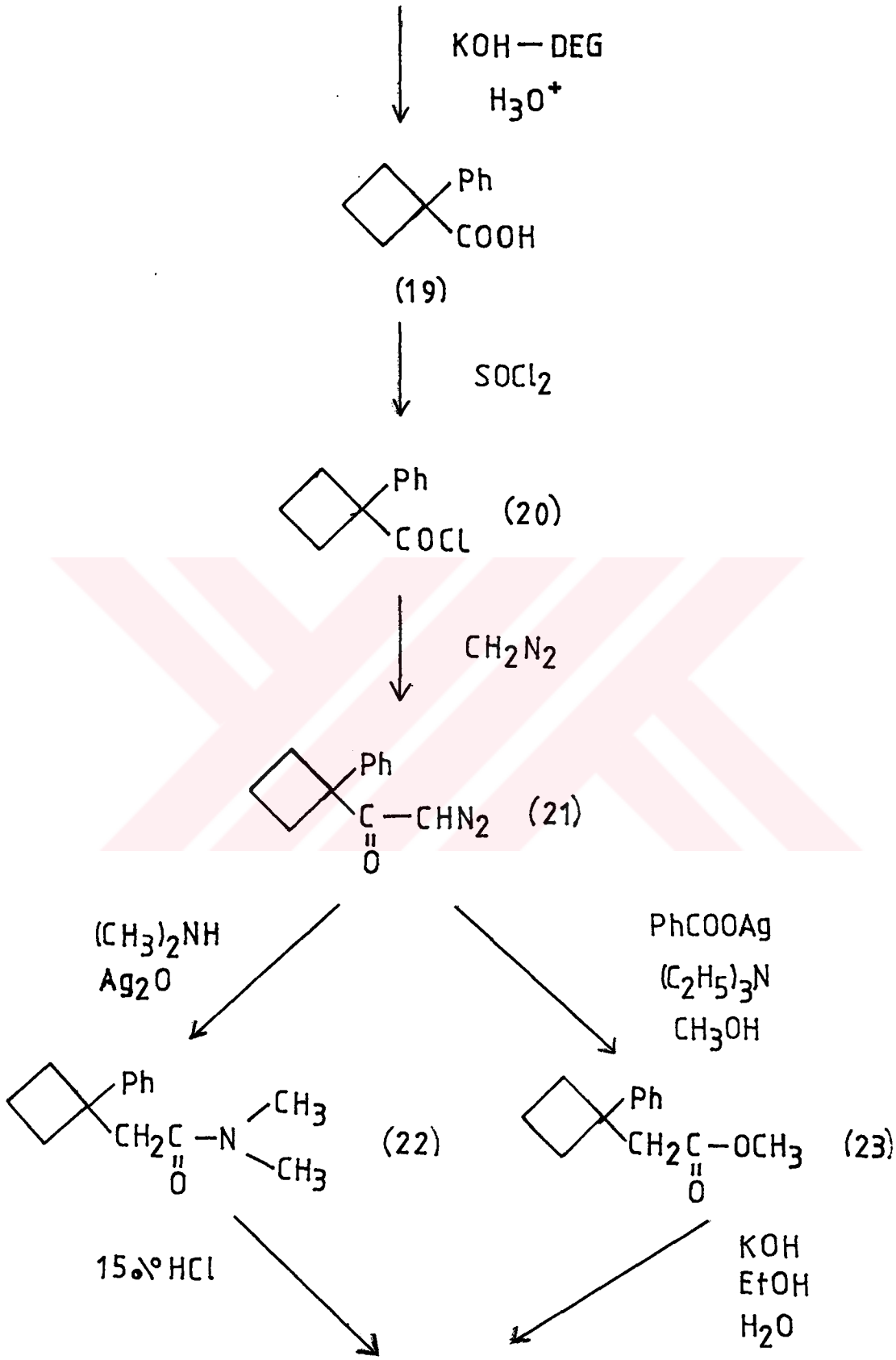
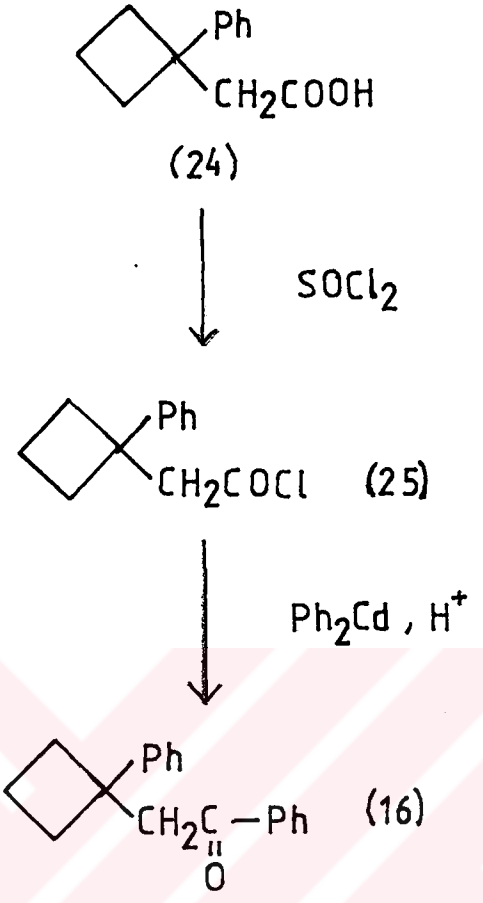


Figure 9. ^{13}C-NMR Spectrum of Cyclobutylcarbinyl Phenyl Ketone (8) in $CDCl_3$.

2.1.2. 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16):




KOH — DEG
H_3O^+
Ph
COOH
(19)
$SOCl_2$
Ph
COCL
(20)
CH_2N_2
Ph
C — CHN_2
O
(21)
$(CH_3)_2NH$
Ag_2O
PhCOOAg
$(C_2H_5)_3N$
CH_3OH
Ph
CH_2C — N
O
CH_3
CH_3
(22)
Ph
CH_2C — OCH_3
O
(23)
15% HCl
KOH
EtOH
H_2O



Benzyl cyanide (17) was treated with sodium hydride in dimethyl sulfoxide and 1,3-dibromopropane to give 1-phenylcyclobutanecarbonitrile (18), which was then treated with KOH, diethylene glycol, and H_2O to give 1-phenylcyclobutanecarboxylic acid (19). The acid (19) was chlorinated to 1-phenylcyclobutanecarbonyl chloride (20) using $SOCl_2$. The acid chloride (20) was treated

with CH_2N_2 to give diazoketone (21). (21) was converted to both (22) and (23) as in the case of (12) and (13). The yield of (23) was much higher than (22). (22) was acidified with 15% HCl to the acid (24) form. (23) was saponified with KOH to 1-phenylcyclobutylacetic acid (24). The acid (24) was chlorinated with $SOCl_2$ to 1-phenylcyclobutylacetyl chloride (25), which was subsequently reacted with diphenylcadmium to give 1-phenylcyclobutylcarbinyl phenyl ketone (16).

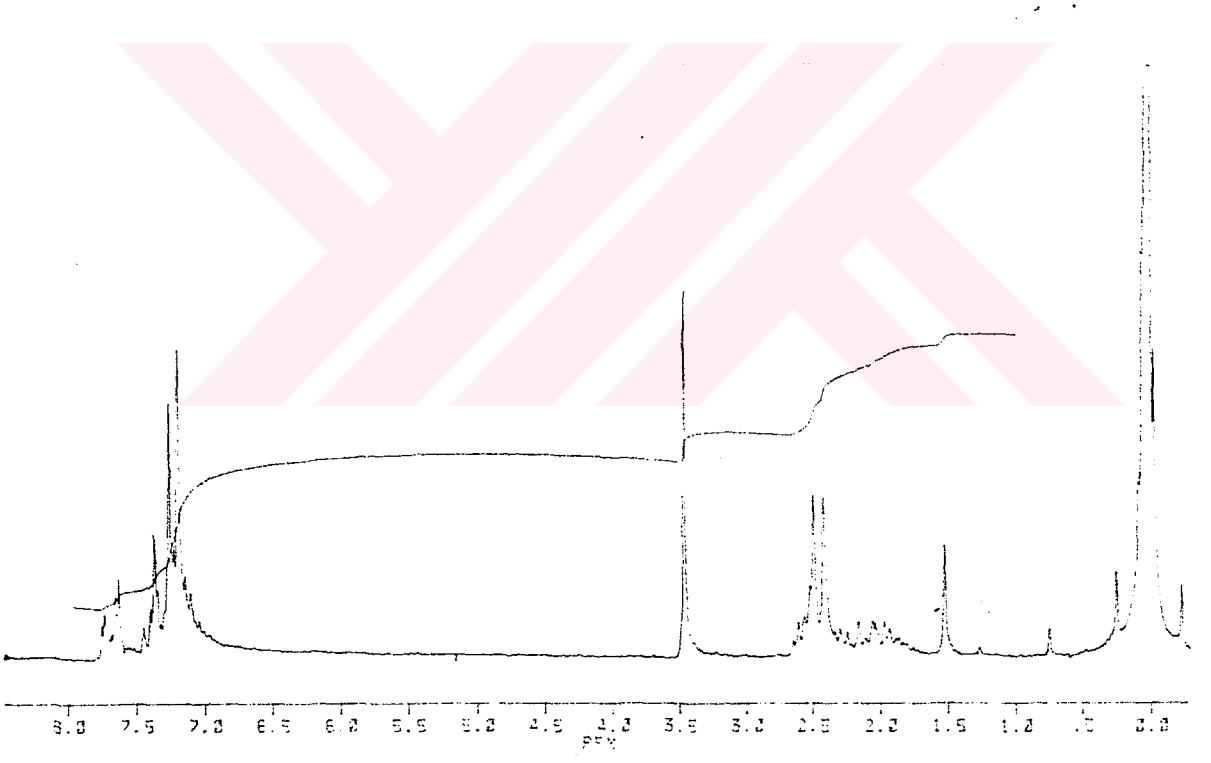


Figure 10. ^{1}H-NMR Spectrum of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) in $CDCl_3$.

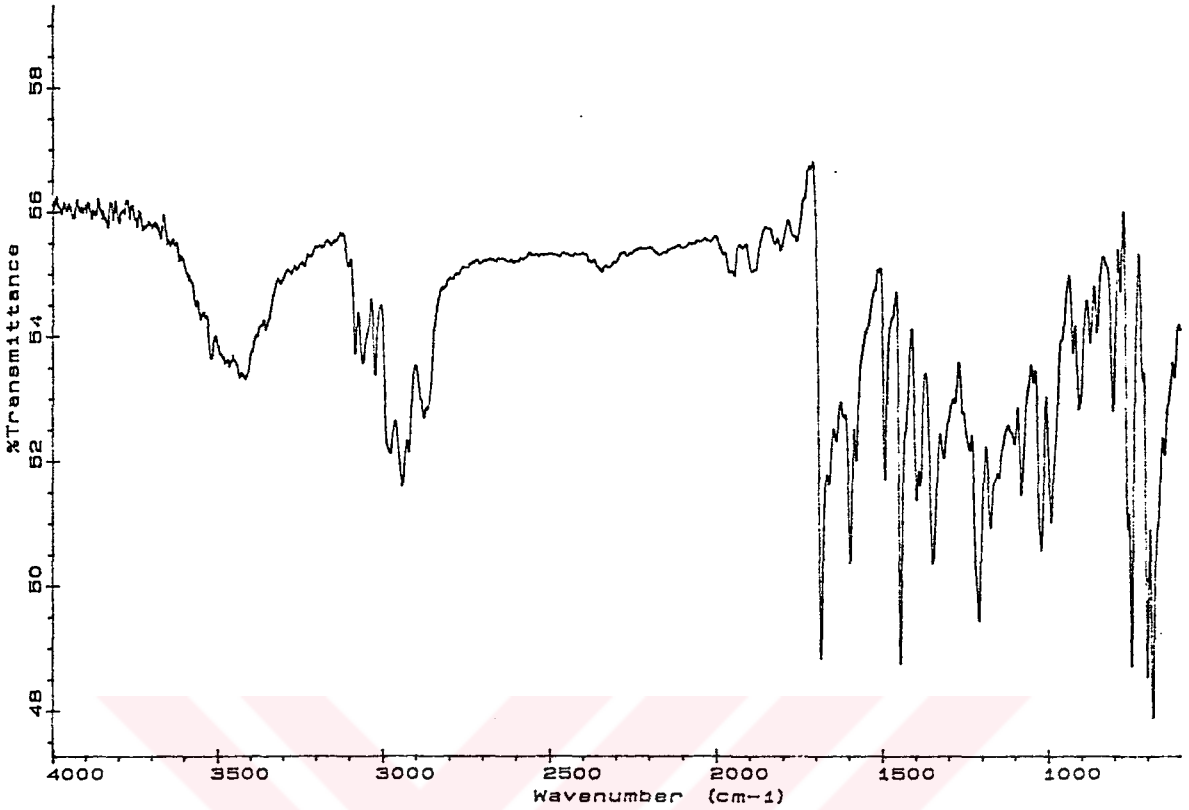


Figure 11. IR Spectrum of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) as KBr pellets.

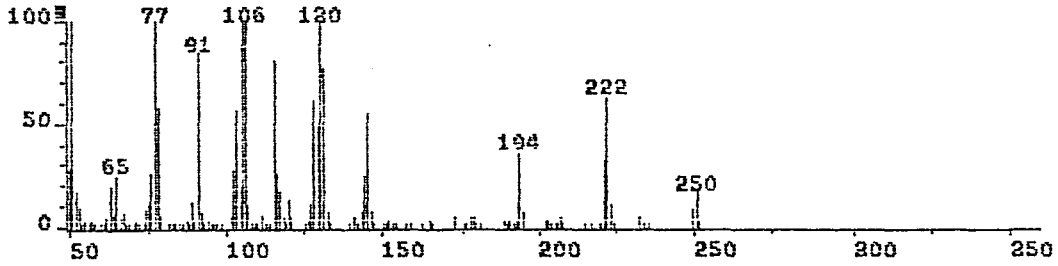


Figure 12. Mass Spectrum of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

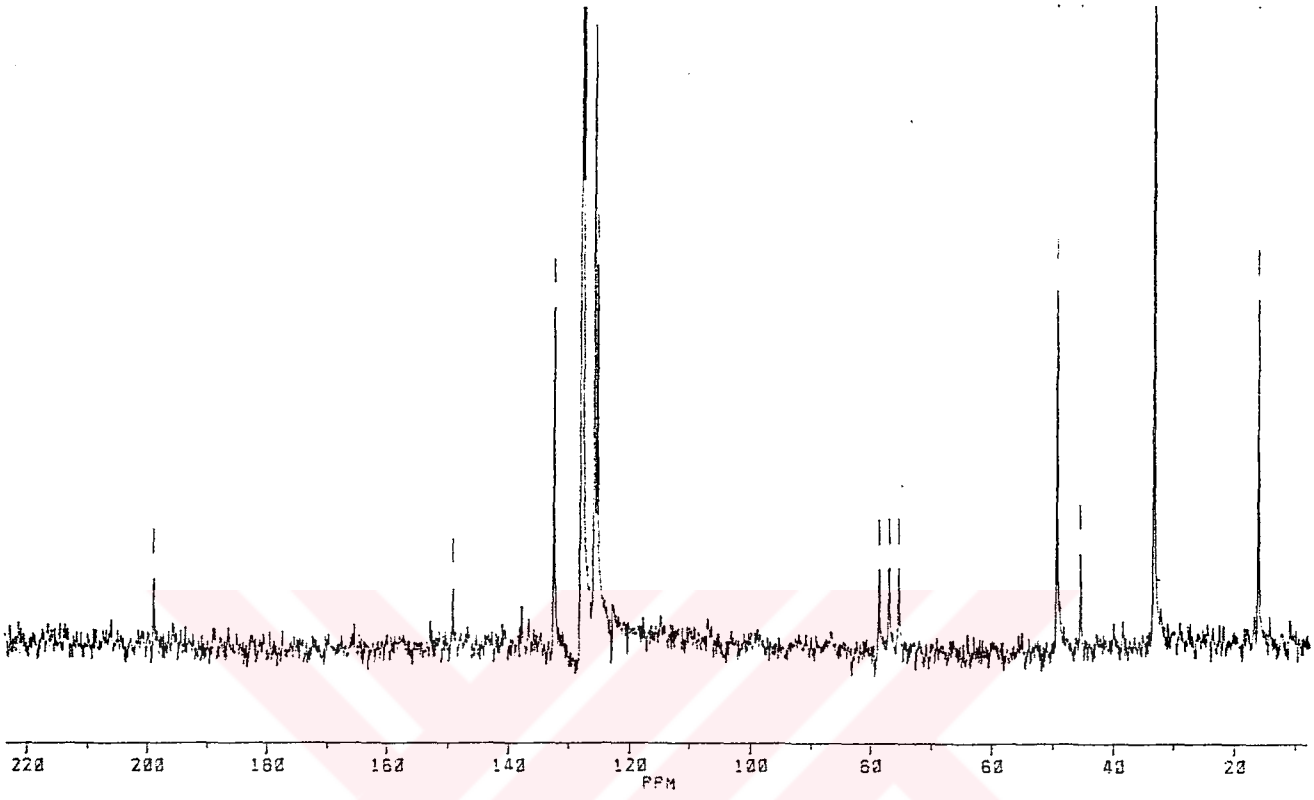
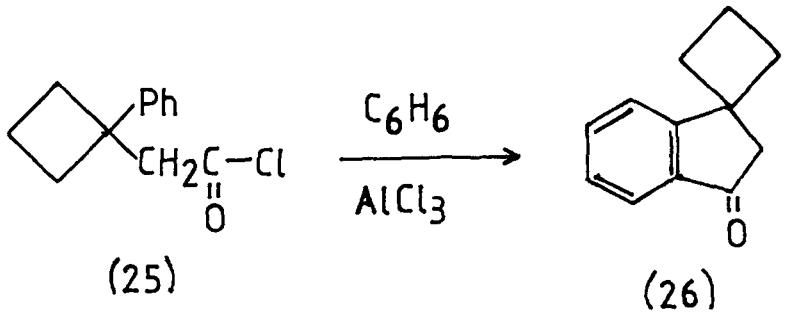


Figure 13. ^{13}C-NMR Spectrum of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) in $CDCl_3$.

2.1.3. 3,3-Trimethylene-1-indanone (26):

1-Phenylcyclobutylacetyl chloride (25) was subjected to Friedel-Crafts reaction using benzene and aluminium chloride to yield 3,3-trimethylene-1-indanone (26).



(25) (26)

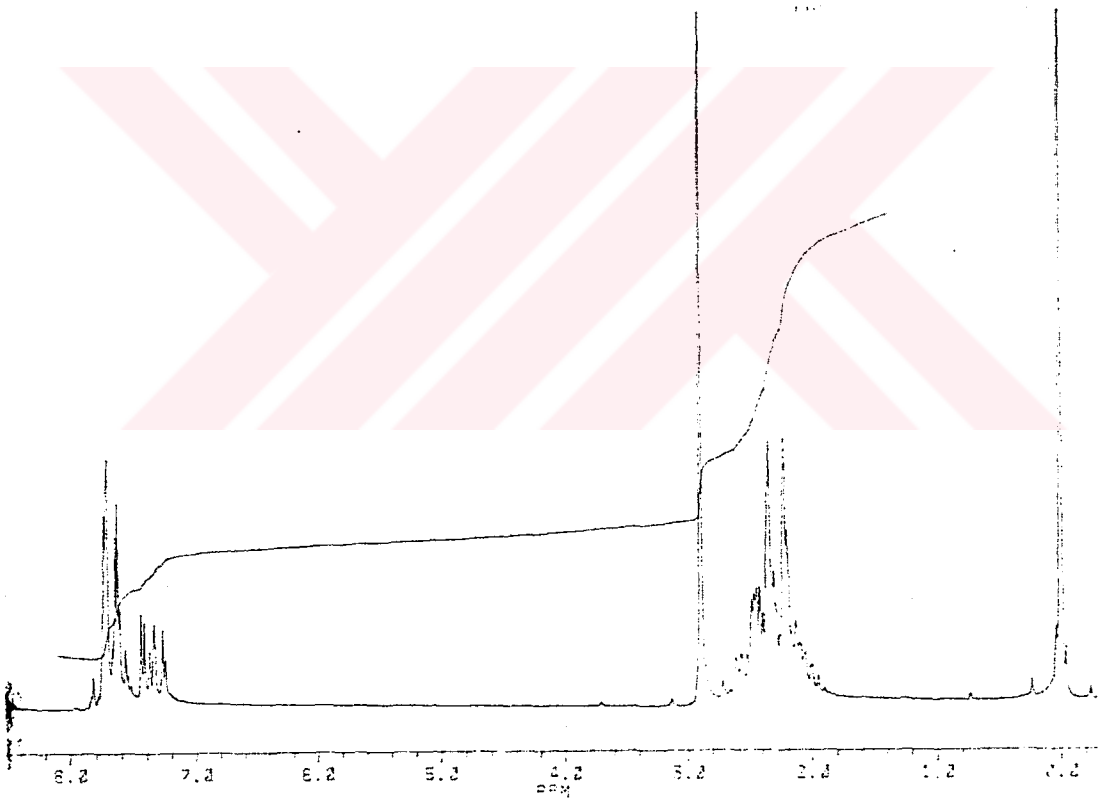


Figure 14. ^{1}H-NMR Spectrum of 3,3-Trimethylene-1-indanone (26) in $CDCl_3$.

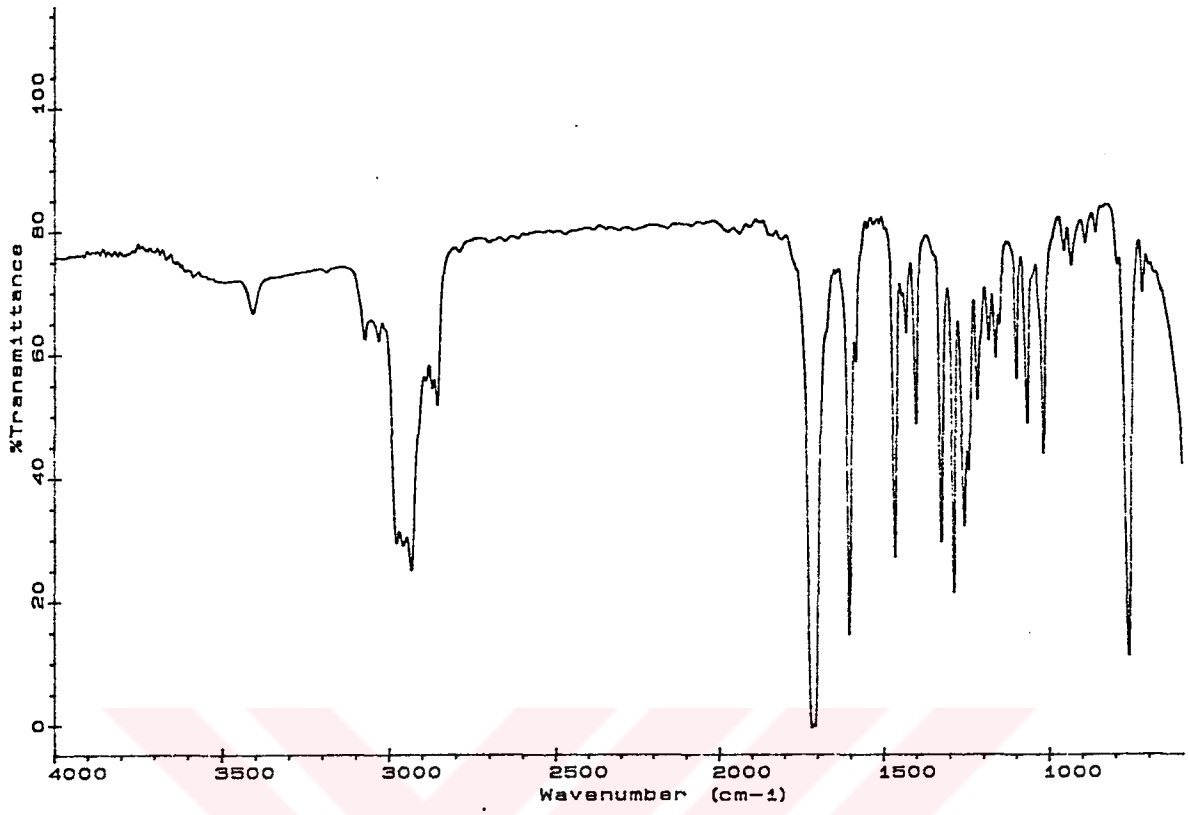


Figure 15. IR Spectrum of 3,3-Trimethylene-1-indanone (26) as neat .

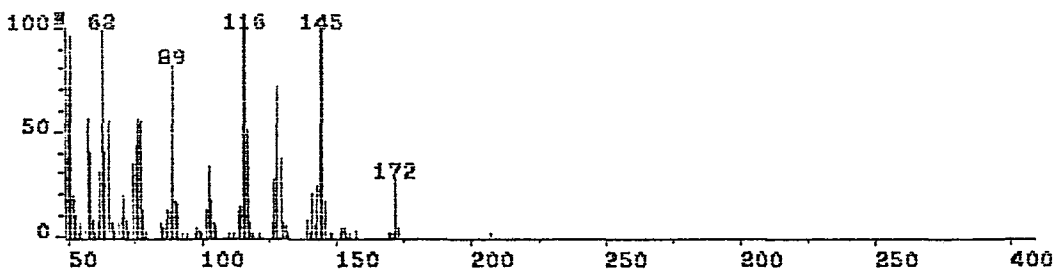


Figure 16. Mass Spectrum of 3,3-Trimethylene-1-indanone (26) .

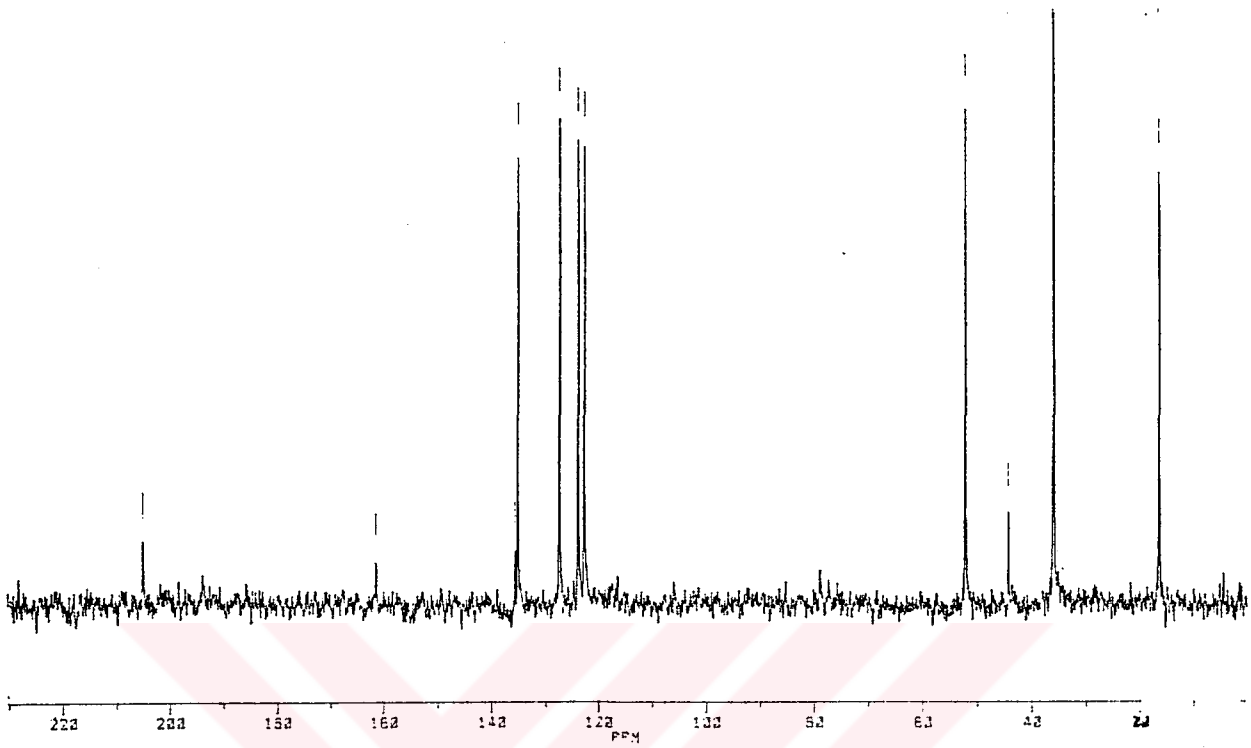
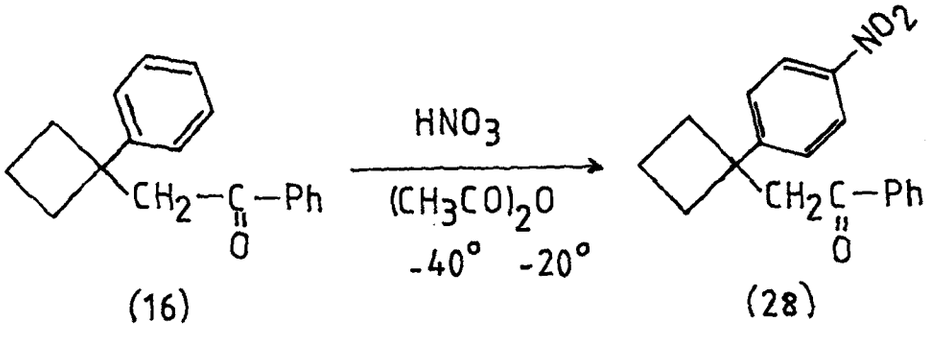


Figure 17. ^{13}C-NMR Spectrum of 3,3-Trimethylene-1-indanone (26) in $CDCl_3$.

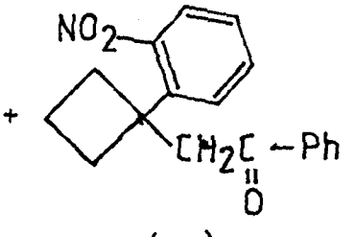
2.1.4. o- and p-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (27) and(28):

1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) was nitrated by fuming HNO_3 in acetic anhydride at -40° to -20° to give a mixture of products. Ortho- (27) and para- (28) nitrated products were isolated by preparative

tlc. The products were identified from their proton nmr splitting patterns in the aromatic region.



(16) (28)



(27)

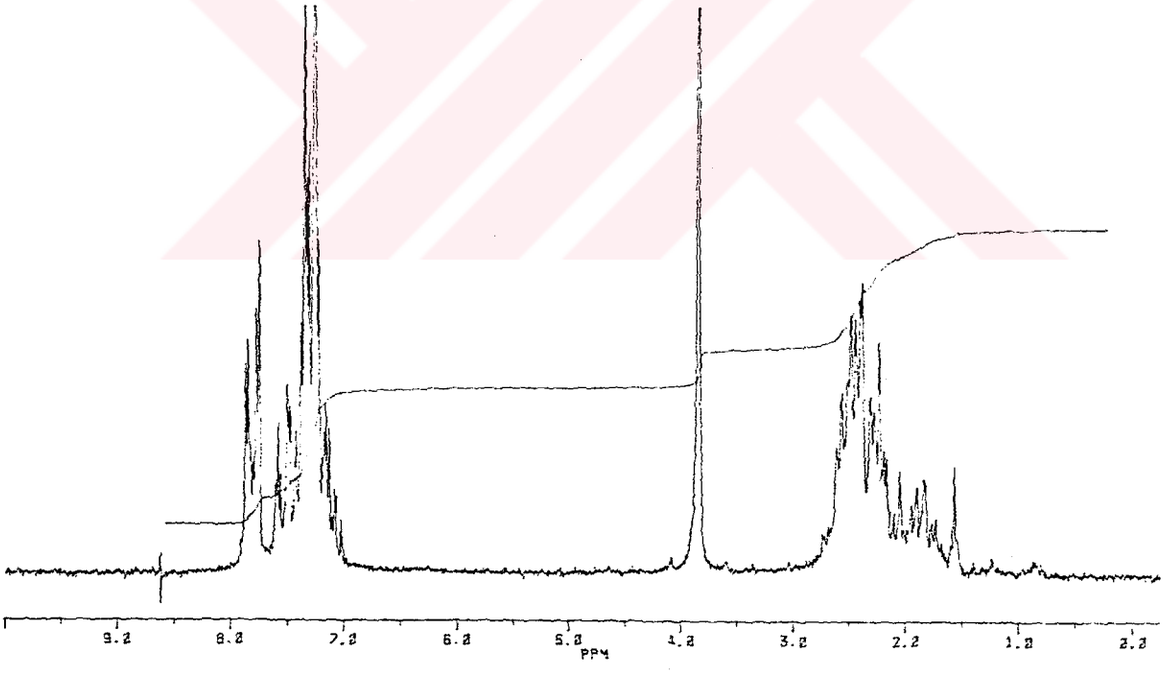


Figure 18. ^{1}H-NMR Spectrum of o-Nitro-1-Phenylcyclobutyl-carbinyl Phenyl Ketone (27) in $CDCl_3$.

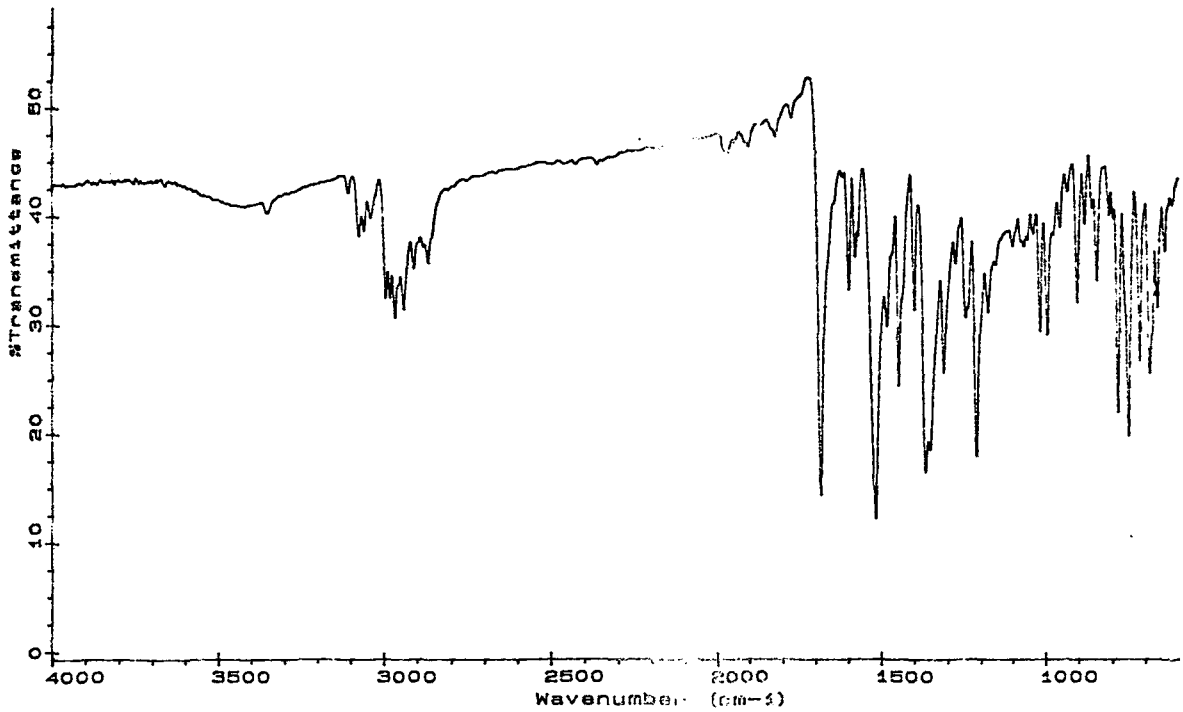


Figure 19. IR Spectrum of o-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (27) as KBr pellet.

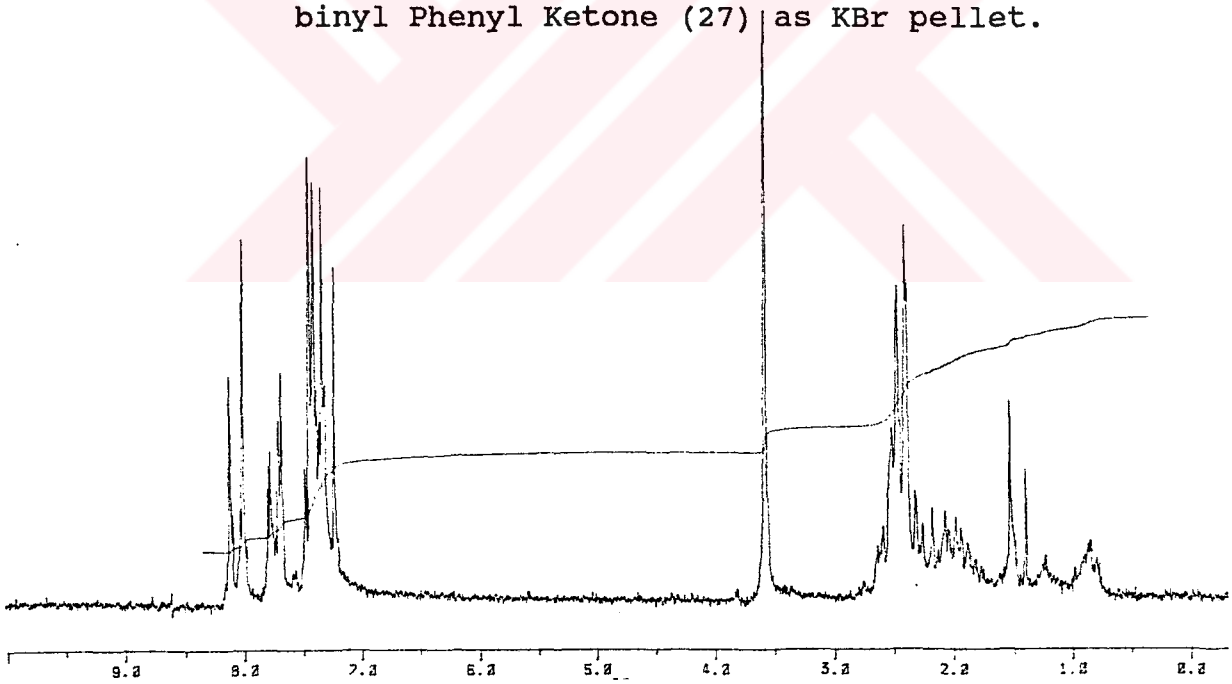


Figure 20. ^{1}H-NMR Spectrum of p-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (28) in $CDCl_3$.

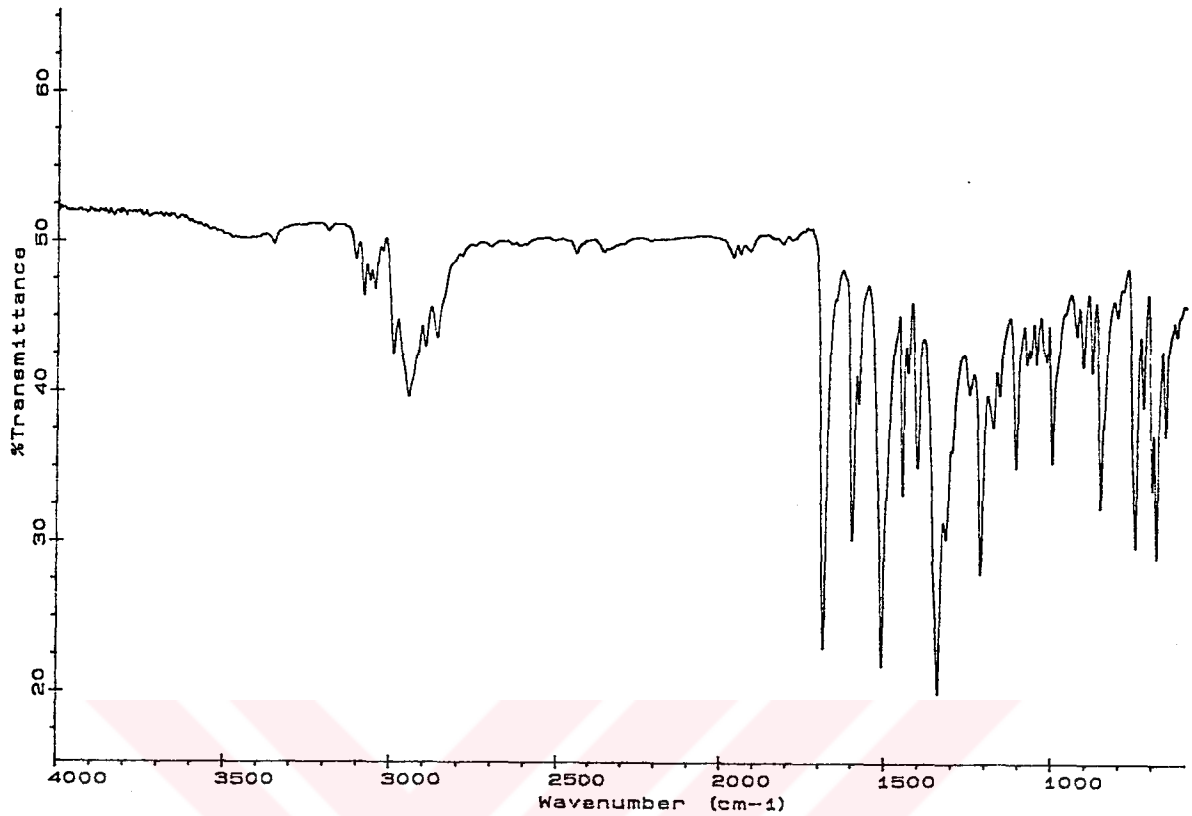


Figure 21. IR Spectrum of p-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (28) as KBr pellet.

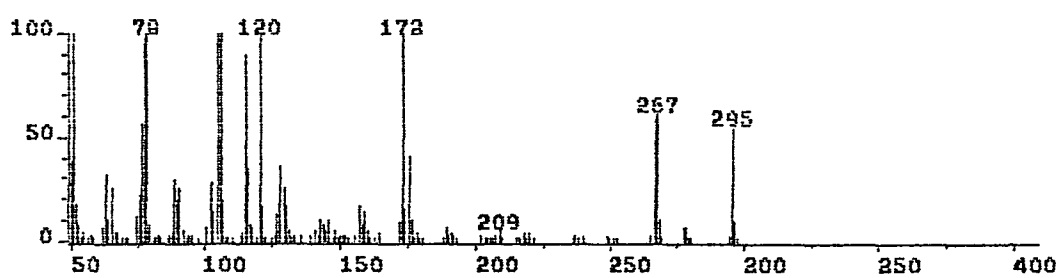


Figure 22. Mass Spectrum of p-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (28) .

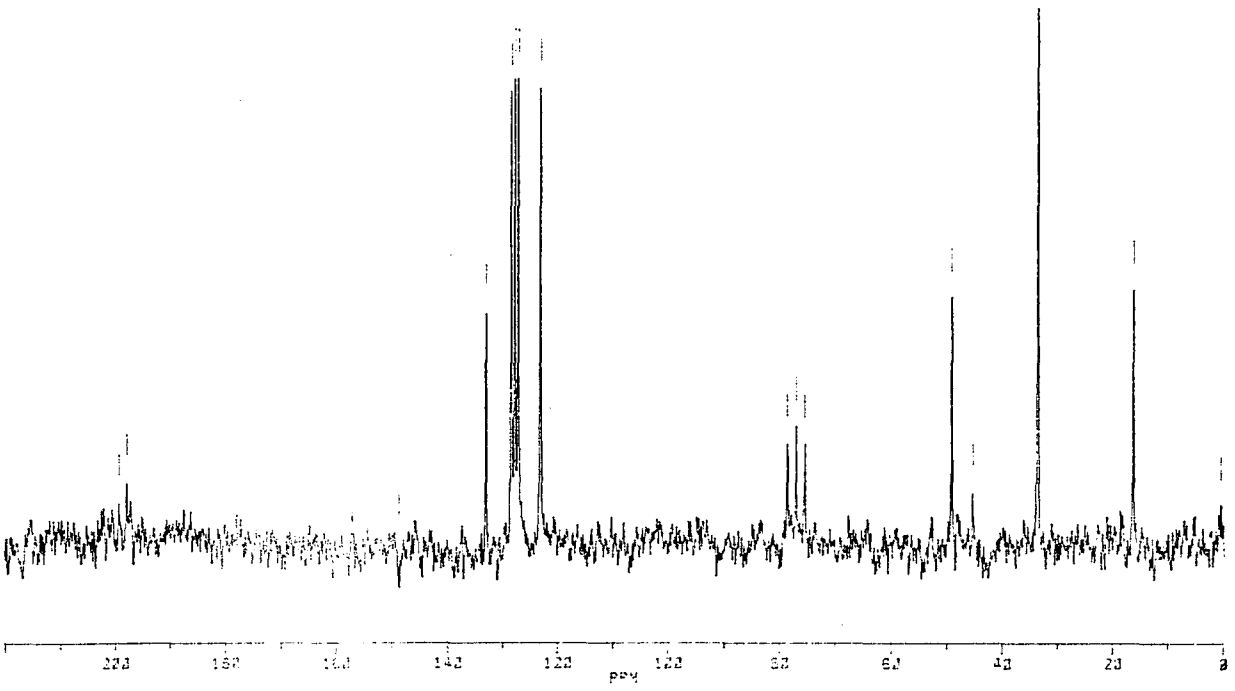
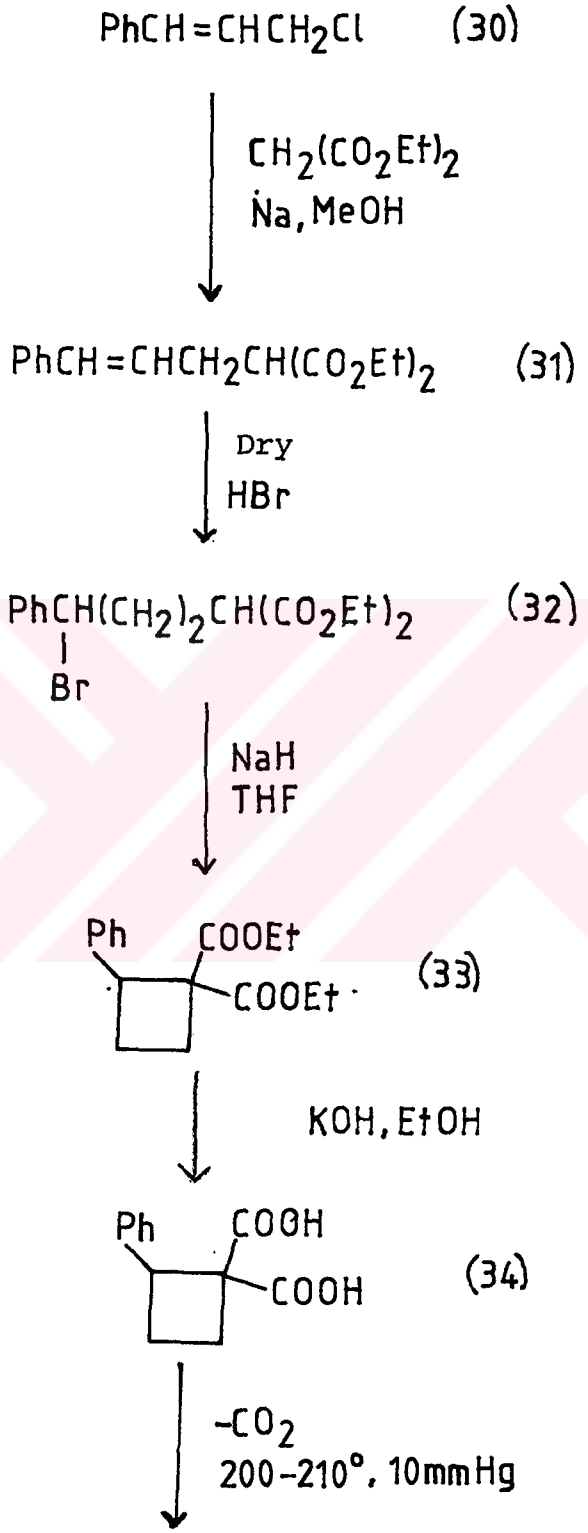
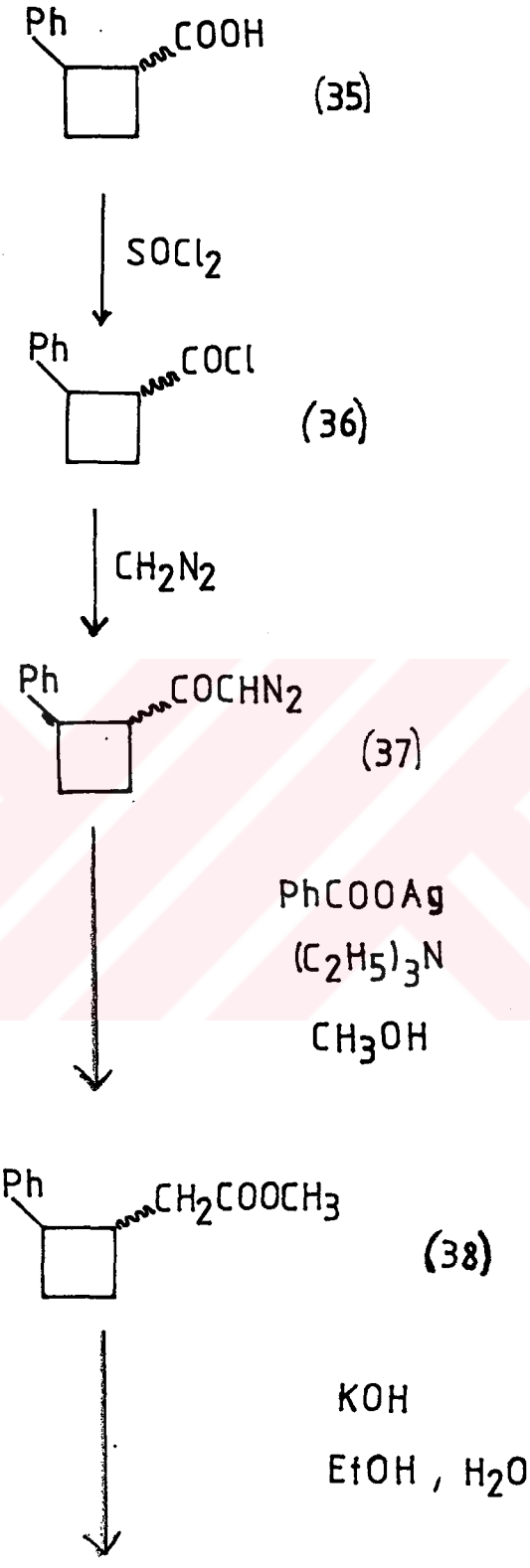
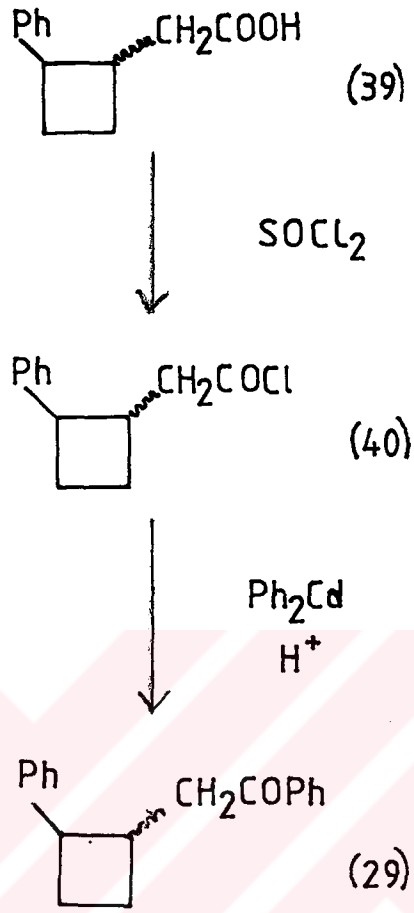


Figure 23. ^{13}C-NMR Spectrum of p-Nitro-1-Phenylcyclobutyl carbinyl Phenyl Ketone (28) in $CDCl_3$.

2.1.5. 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29)*:




Ph
COOH
(35)
SOCl2
Ph
COCl
(36)
CH2N2
Ph
COCHN2
(37)
PhCOOAg
(C2H5)3N
CH3OH
Ph
CH2COOCH3
(38)
KOH
EtOH , H2O



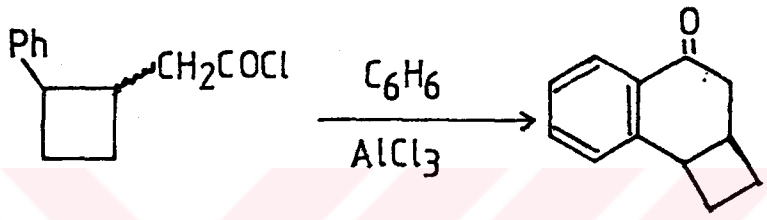
As seen in the ^{1}H-NMR spectrum of (29) (p.49, Fig.30) the α-methylene protons are masked by the rest of the aliphatic protons. Compound (29) , therefore, could not be included in the series of cyclobutylcarbinyl ketones in the kinetic measurements (see p.75).

Ethyl malonate and sodium in methanol were

reacted with cinnamyl chloride (30) to give ethylcinnamyl malonate (31), which was then converted to diethyl(3-bromo-3-phenylpropyl) malonate (32) by passing dry HBr through (31). The malonate (32) was then reacted with sodium hydride in THF to yield the 2-phenylcyclobutanediethylcarboxylate (33) which was finally saponified with KOH and EtOH to yield 2-phenylcyclobutanedicarboxylic acid (34). The decarboxylation of (34) by heating at reduced pressure yields 2-phenylcyclobutanecarboxylic acid (35) as a cis-trans mixture. After obtaining (35), the remaining steps to synthesize the ketone (29) were carried out similar to those in the synthesis of 1-phenylcyclobutylcarbinyl phenyl ketone (16).

In ref.[53], there are three important peaks in the fingerprint region (697, 730, 787 cm^{-1}) of the IR spectrum of cis-2-phenylcyclobutanecarboxylic acid, and two important peaks in the trans form of the acid (700, 753 cm^{-1}) . In 2-phenylcyclobutylcarbinyl phenyl ketone (29), obtained in this work there are three important peaks (698, 752, 794 cm^{-1}). A small scale reaction of 2-phenylcyclobutylacetyl chloride (40) obtained in this work with $AlCl_3$ and benzene according to F.C.reaction gives a product, whose NMR spectrum implies the cyclic ketone (40a). In view of the impossibility of using (29)

in the kinetic measurements (see p.75) and poor yields of the reactions in obtaining compounds (40a) and (29), the identification of (40a) and the stereochemistry of (29) has not been pursued any further, although the structure of (29) is drawn as cis throughout. The ketone (29) is most probably in the cis form. We obtained 2-phenylcyclobutylcarbinyl phenyl ketone (29) according to the reaction of (40) with Ph_2Cd.



(40) (40a)

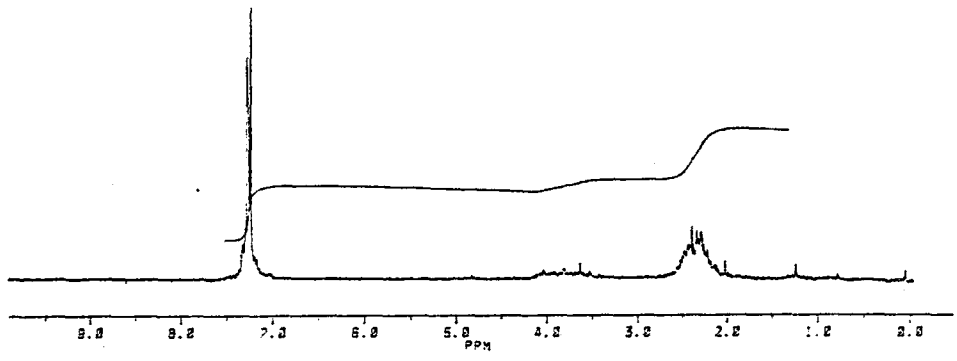


Figure 24. ^{1}H-NMR Spectrum of 2-Phenylcyclobutanecarbonyl Chloride (36) in $CDCl_3$.

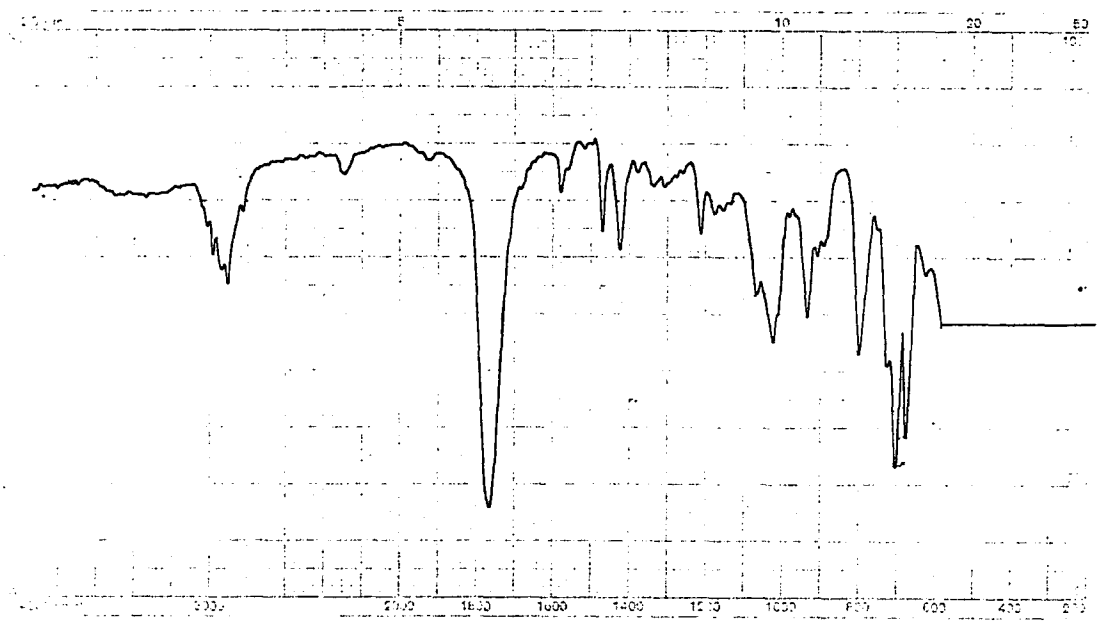


Figure 25. IR Spectrum of 2-Phenylcyclobutanecarbonyl Chloride (36) as neat.

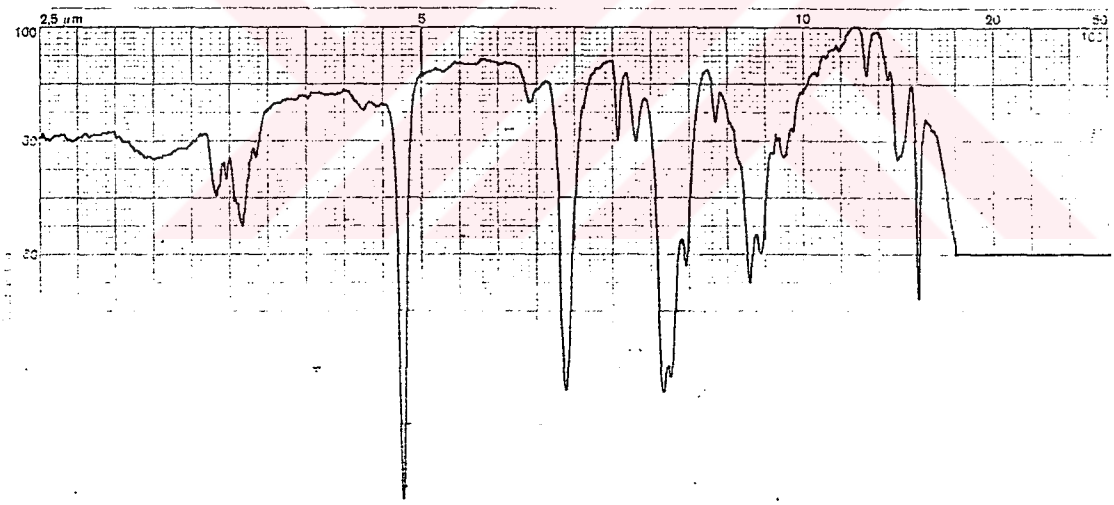


Figure 26. IR Spectrum of 2-Phenylcyclobutyl Diazomethyl Ketone (37) as neat.

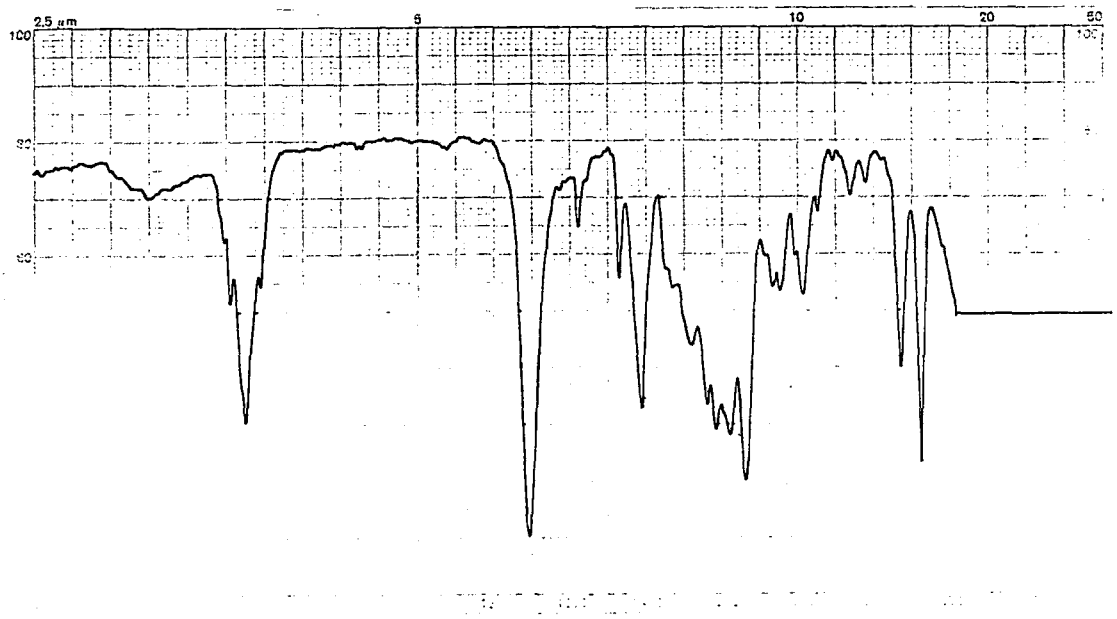


Figure 27. IR Spectrum of Methyl (2-phenylcyclobutyl)-acetate (38) as neat.

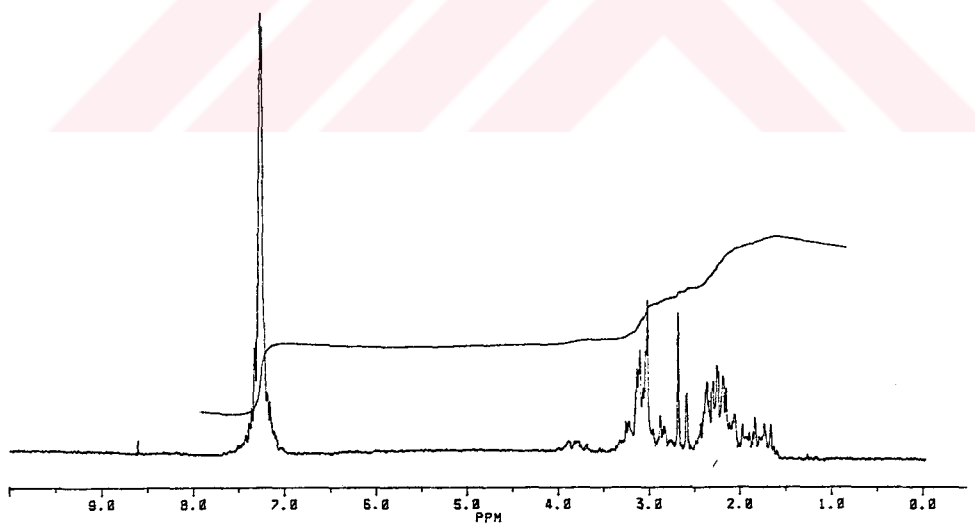


Figure 28. ^{1}H-NMR Spectrum of 2-Phenylcyclobutylacetyl Chloride (40) in $CDCl_3$.

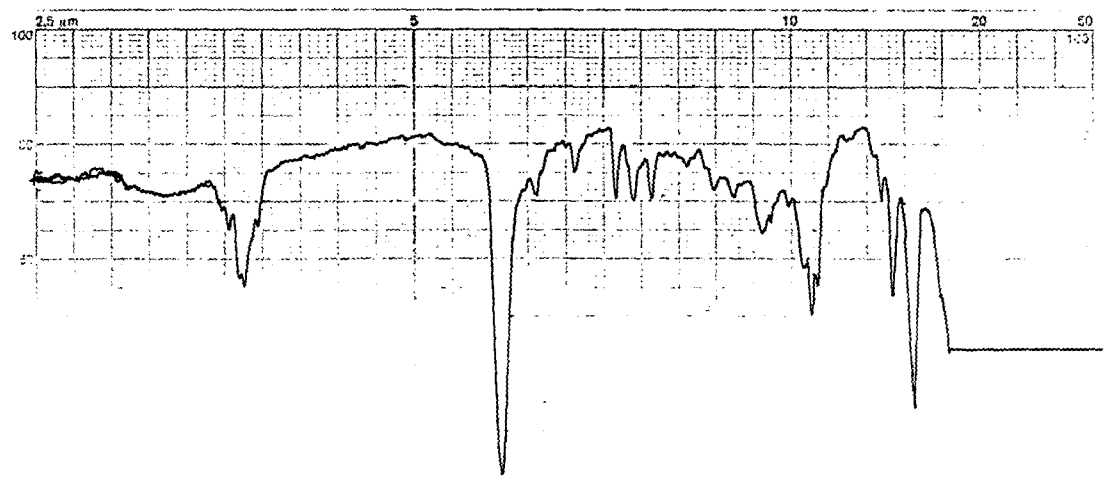


Figure 29. IR Spectrum of 2-Phenylcyclobutylacetyl Chloride (40) as neat.

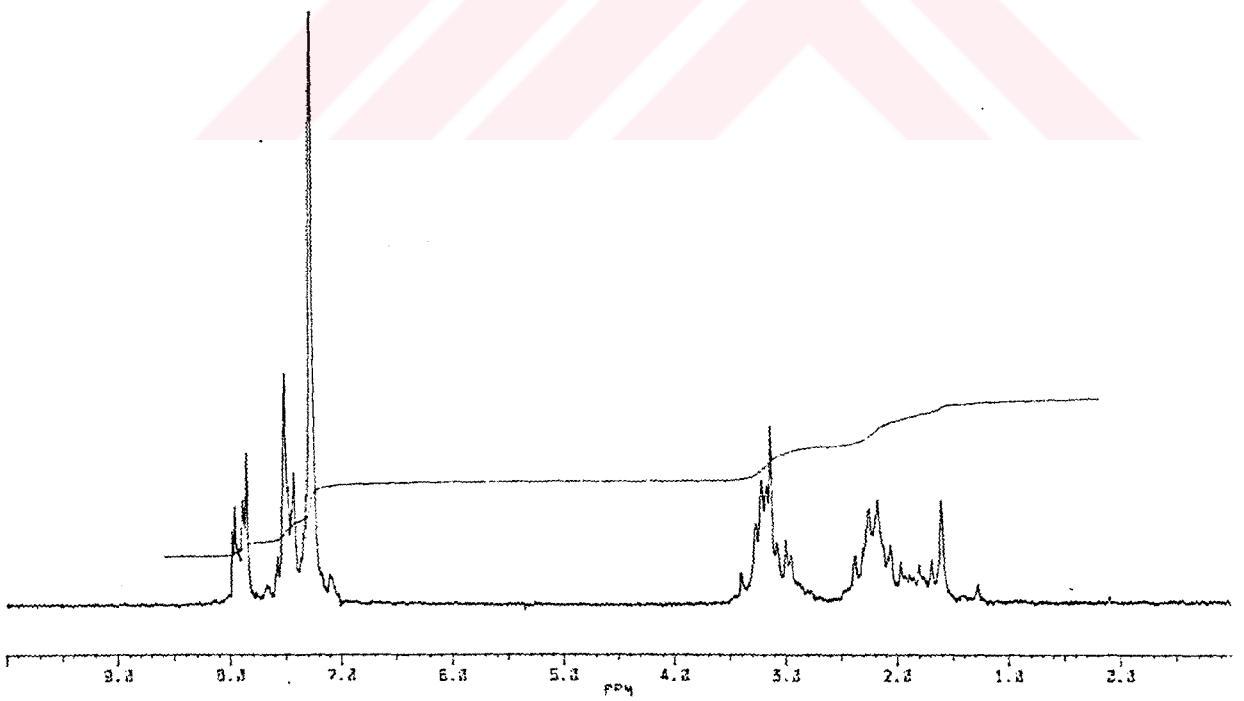


Figure 30. ^{1}H-NMR Spectrum of 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) in $CDCl_3$.

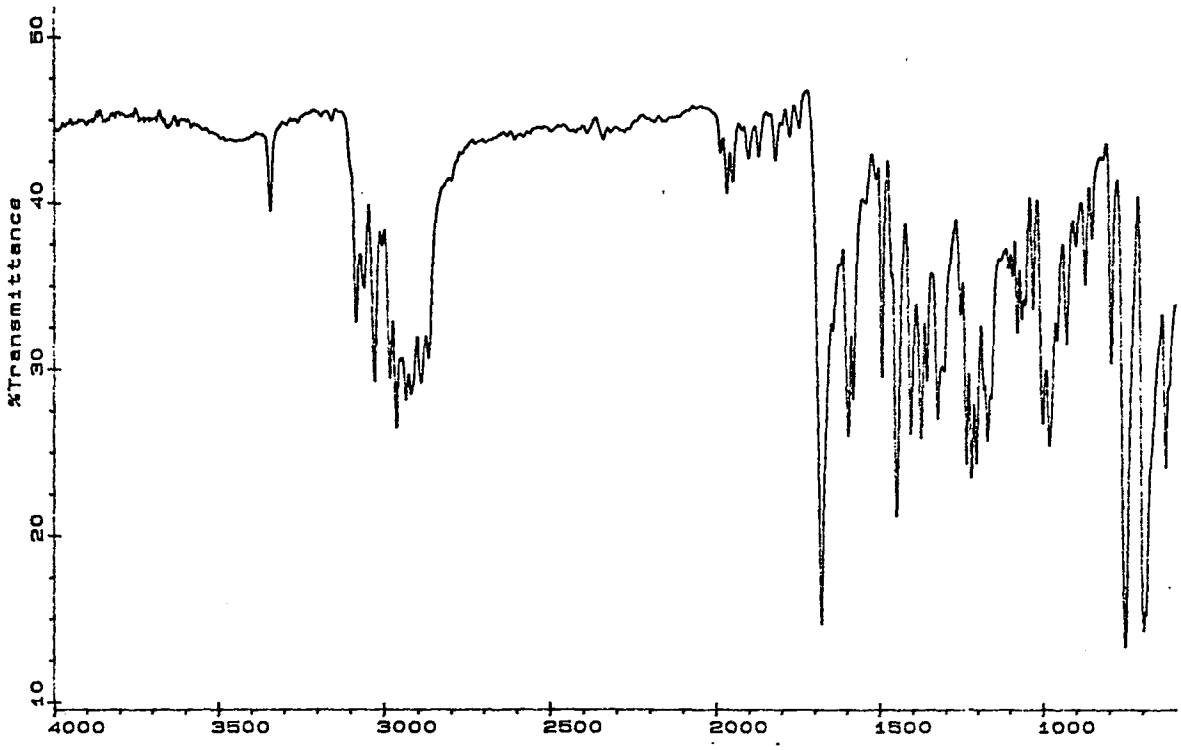


Figure 31. IR Spectrum of 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) as KBr pellet.

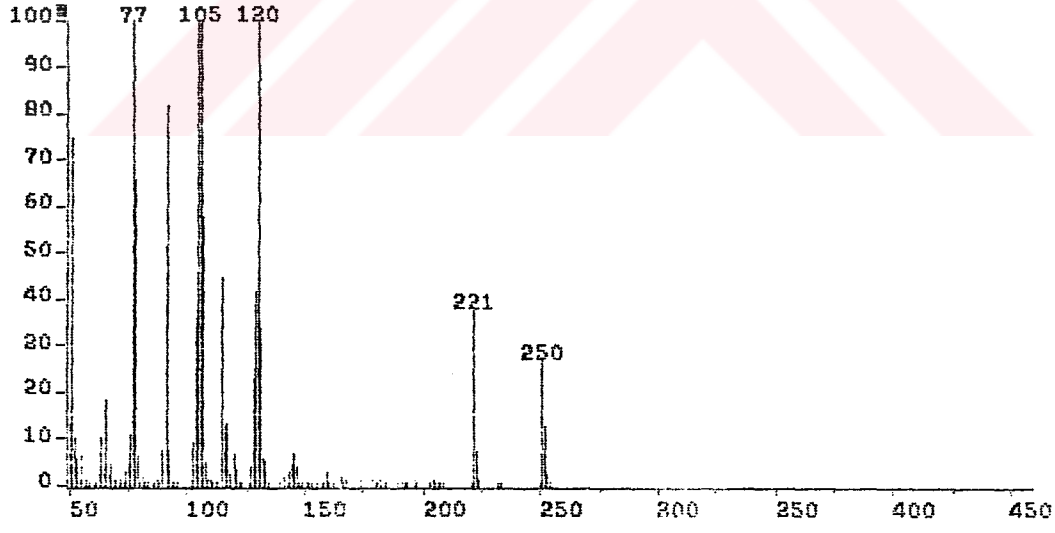


Figure 32. Mass Spectrum of 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) .

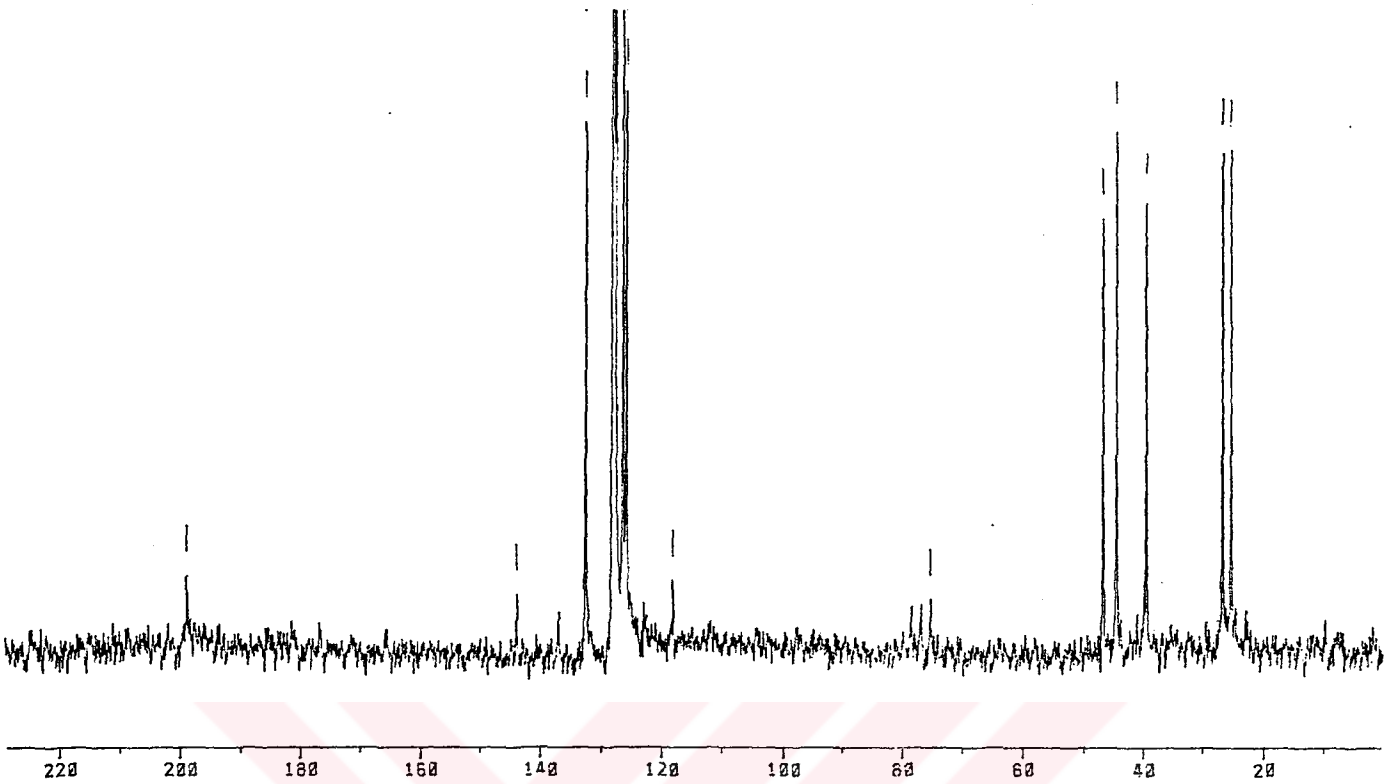


Figure 33. ^{13}C-NMR Spectrum of 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) in $CDCl_3$.

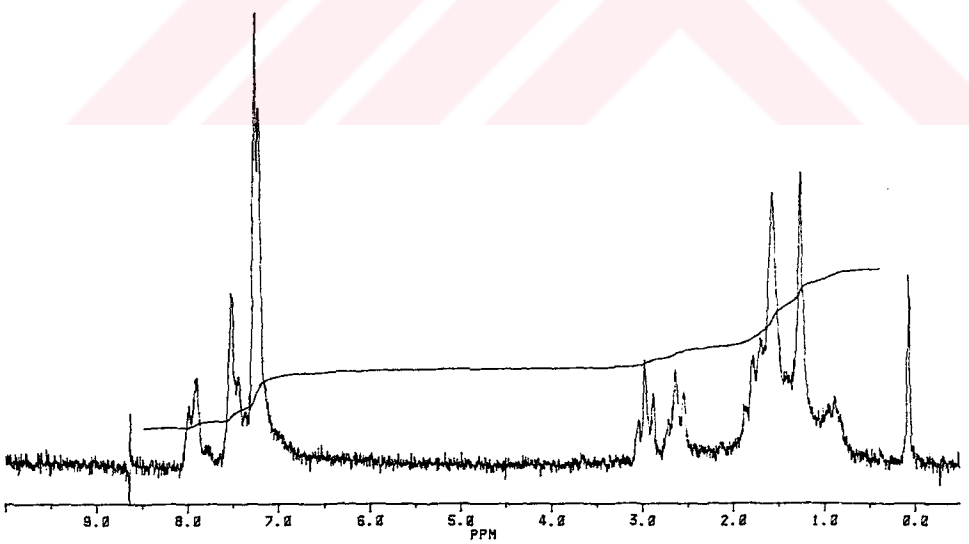
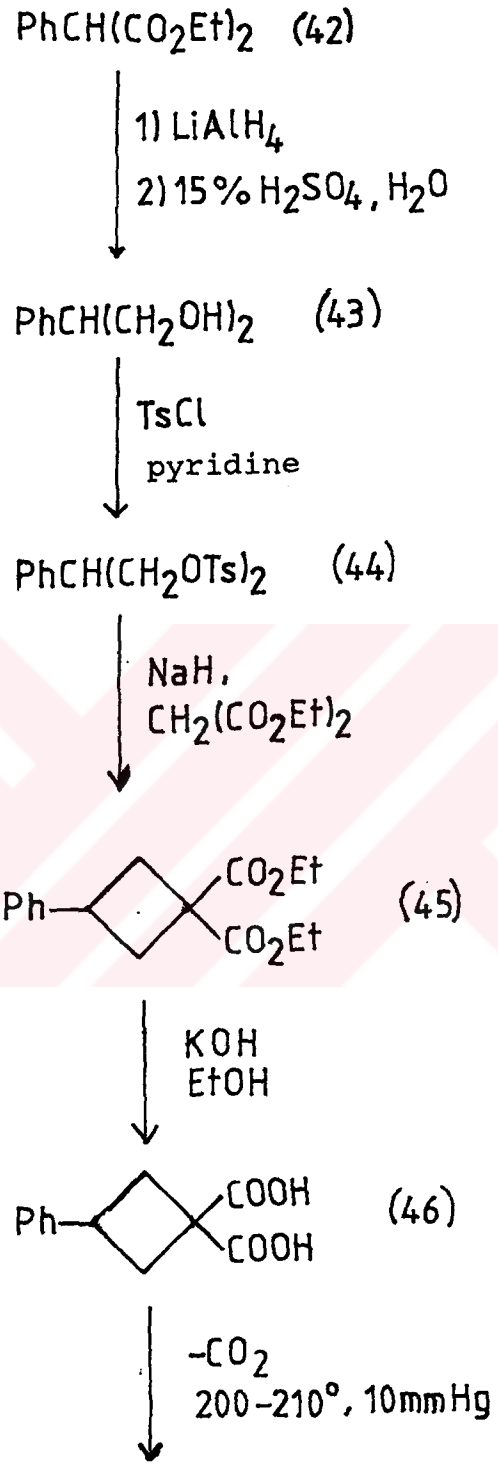
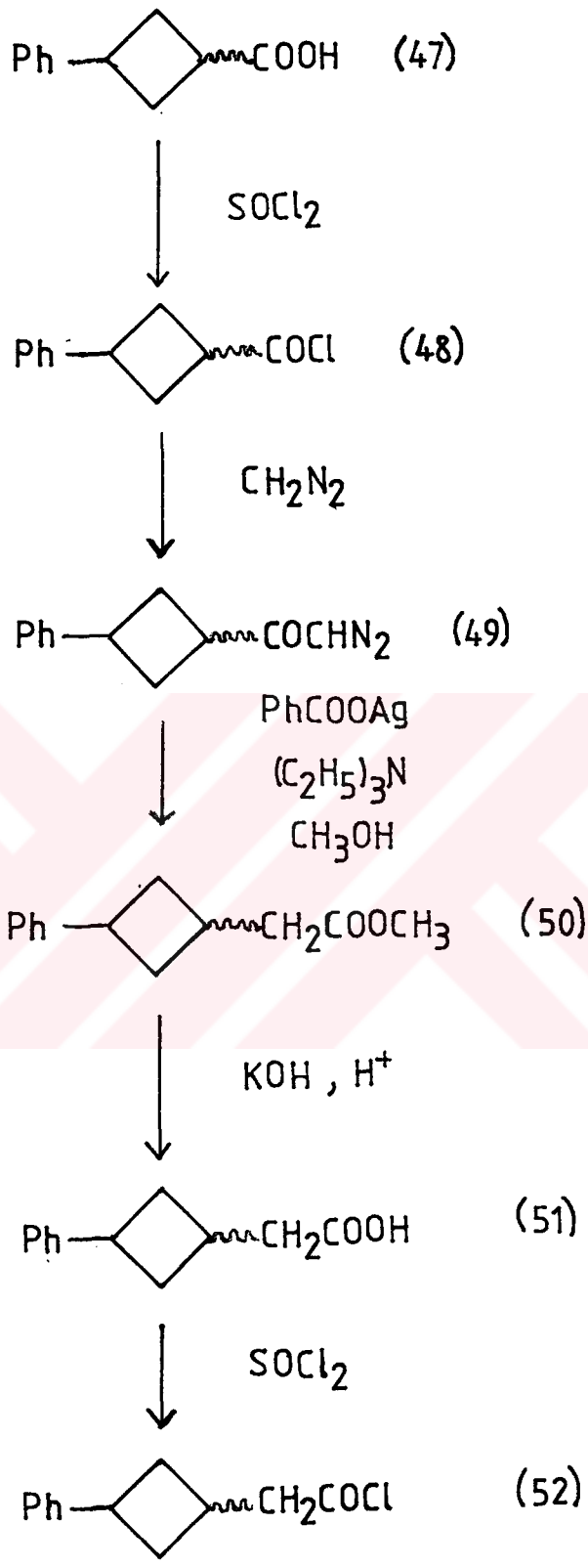
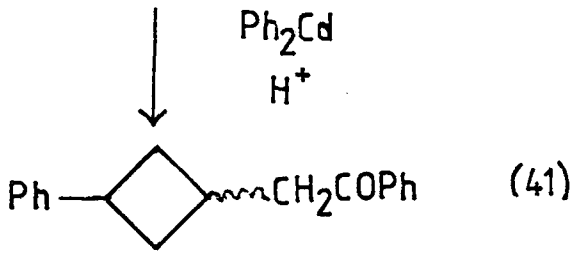


Figure 34. ^{1}H-NMR Spectrum of 3,4-Dimethylene-1-tetralone (40a) in $CDCl_3$.

2.1.6. 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41):




Ph
COOH
(47)
$SOCl_2$
Ph
COCl
(48)
CH_2N_2
Ph
$COCHN_2$
(49)
PhCOOAg
$(C_2H_5)_3N$
CH_3OH
Ph
CH_2COOCH_3
(50)
KOH , H^+
Ph
CH_2COOH
(51)
$SOCl_2$
Ph
CH_2COCl
(52)



(41)

Diethyl phenylmalonate (42) was reduced to the 2-phenylpropane-1,3-diol (43) with $LiAlH_4$. The diol (43) was then tosylated with p-toluenesulfonylchloride in pyridine, to obtain the ditosylate (44). Treatment of (44) with diethyl malonate and NaH in dioxane yielded diethyl-3-phenylcyclobutane-1,1-dicarboxylate (45). (45) was then saponified with KOH to obtain the 3-phenyl-1,1-cyclobutanedicarboxylic acid (46). (46) was then decarboxylated by heating to obtain 3-phenylcyclobutanecarboxylic acid (47) as a cis-trans mixture. (47) was chromatographed on a 70-230 mesh column using ether-hexane mixture (1:10). "Trans" acid[55] was separated as a white solid*. After obtaining the acid (47), the remaining steps to synthesize the ketone (41) were made similar to those in the synthesis of 1-phenyl-cyclobutylcarbinyl phenyl ketone (16).

* The trans-acid is reported to be a solid in the literature[55], whereas the cis-isomer is an oil.

Trans-3-Phenylcyclobutylacetyl chloride (52) gave trans-3-phenylcyclobutylcarbinyl phenyl ketone according to both F.C. and Grignard reactions although formation of any cyclic ketone in the Friedel-Crafts reaction of (52) is not observed with benzene and $AlCl_3$. The ^{13}C-NMR spectrum of (41), however, reveals extra peaks in the aliphatic region. The compound seems to be still contaminated with cis isomer despite the attempted separation at the 3-phenylcyclobutanecarboxylic acid stage.

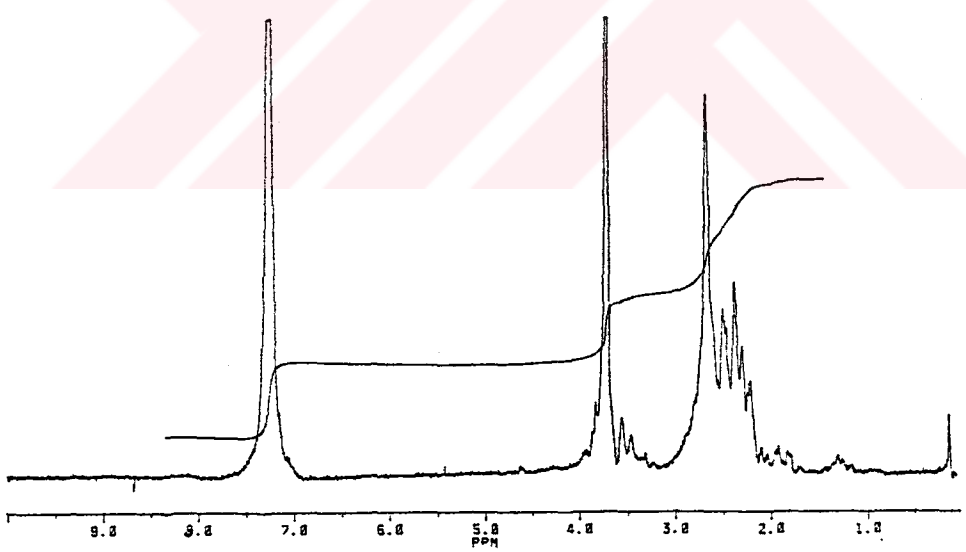


Figure 35. ^1H-NMR Spectrum of Methyl (3-phenylcyclobutyl) -acetate (50) in $CDCl_3$.

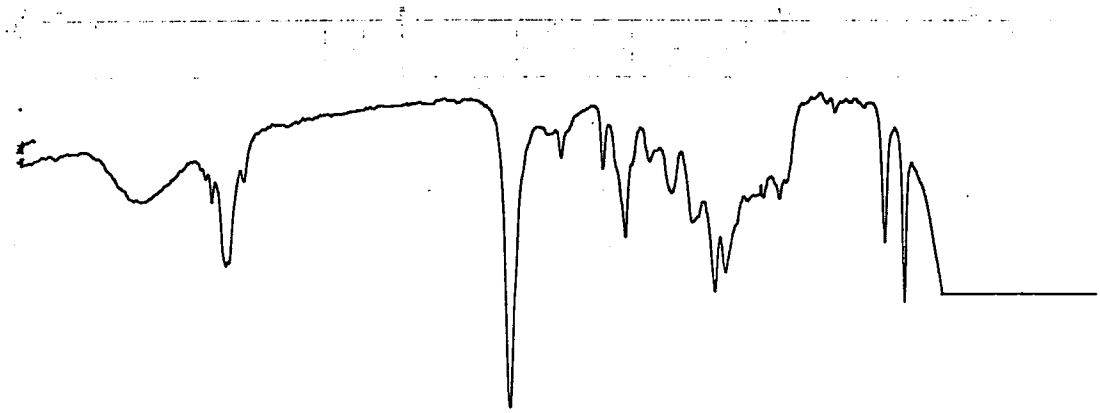


Figure 36. IR Spectrum of Methyl (3-phenylcyclobutyl) -acetate (50) as neat.

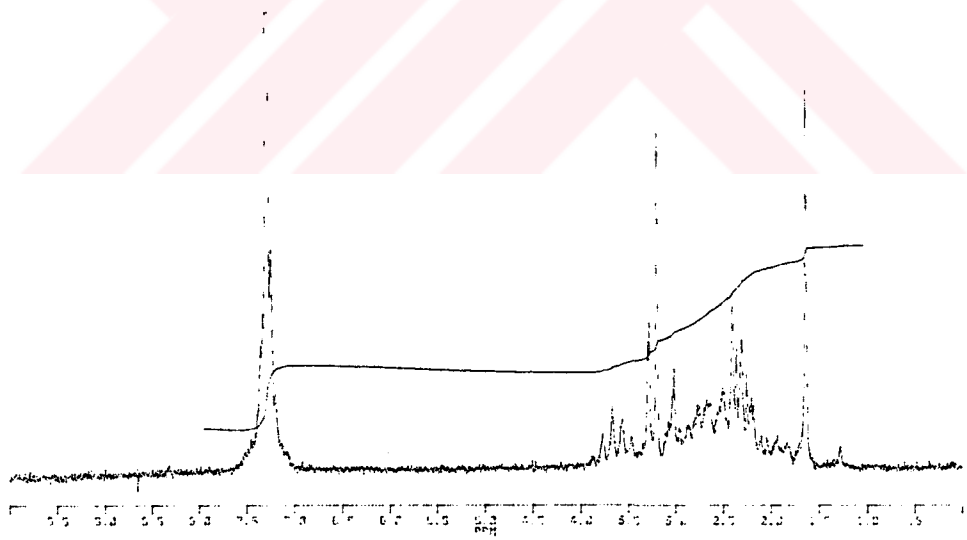


Figure 37. ^{1}H-NMR Spectrum of 3-Phenylcyclobutylacetyl Chloride (52) in $CDCl_3$.

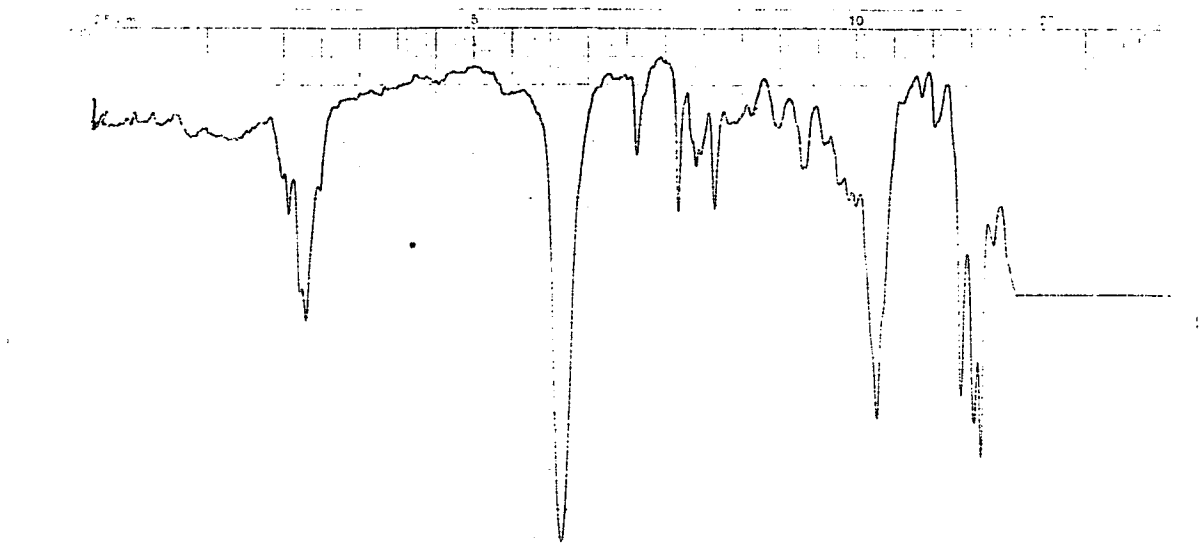


Figure 38. IR Spectrum of 3-Phenylcyclobutylacetyl Chloride (52) as neat.

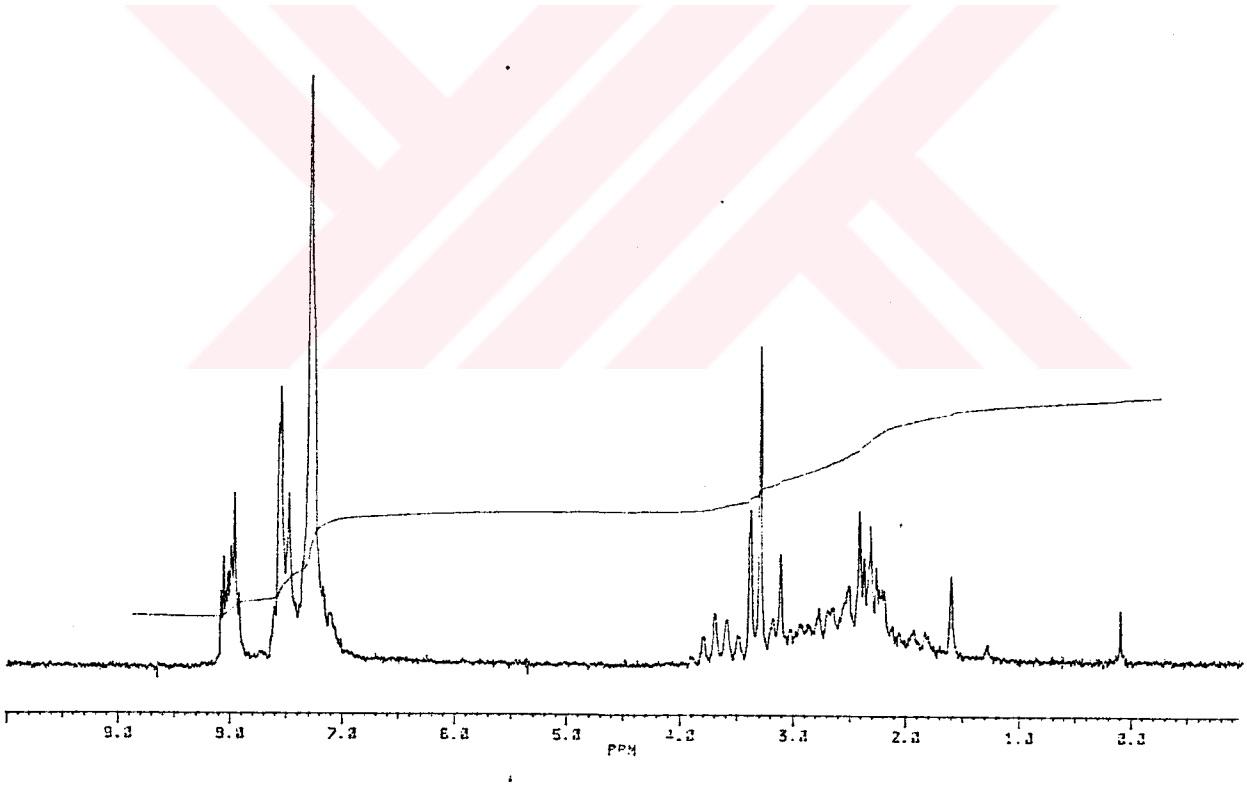


Figure 39. ^{1}H-NMR Spectrum of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) in $CDCl_3$.

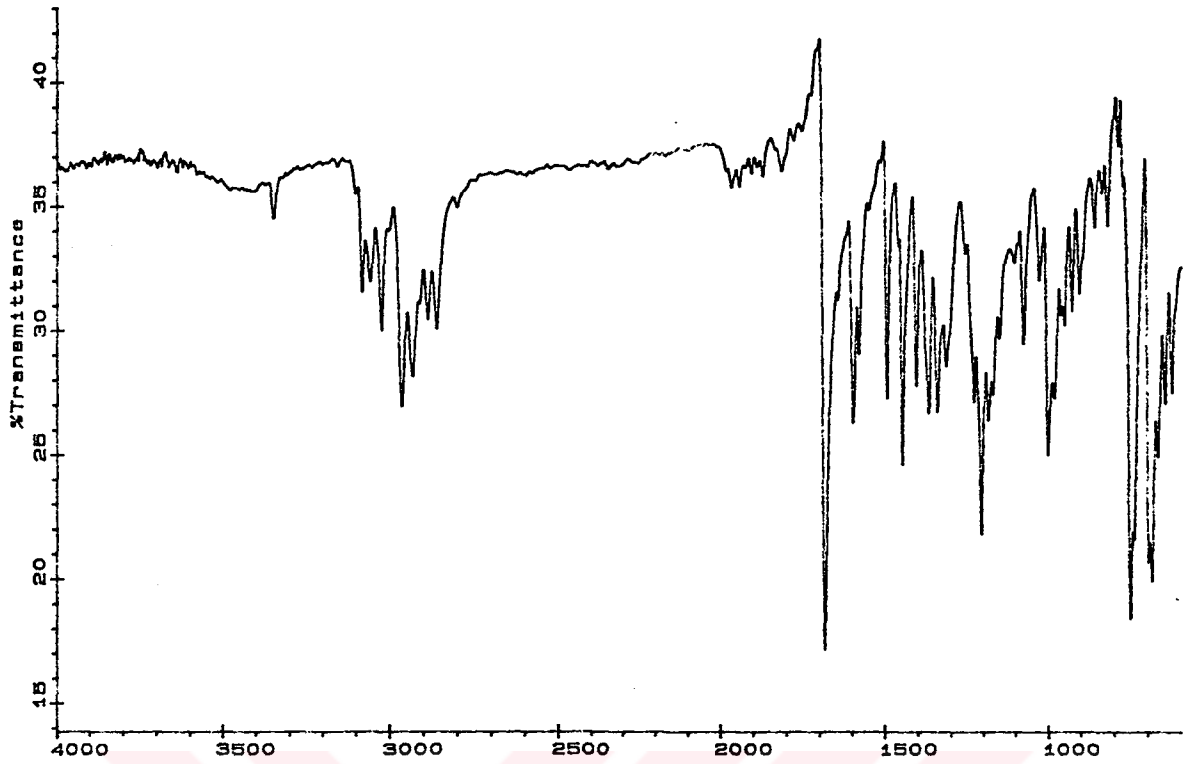


Figure 40. IR Spectrum of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) as KBr pellet.

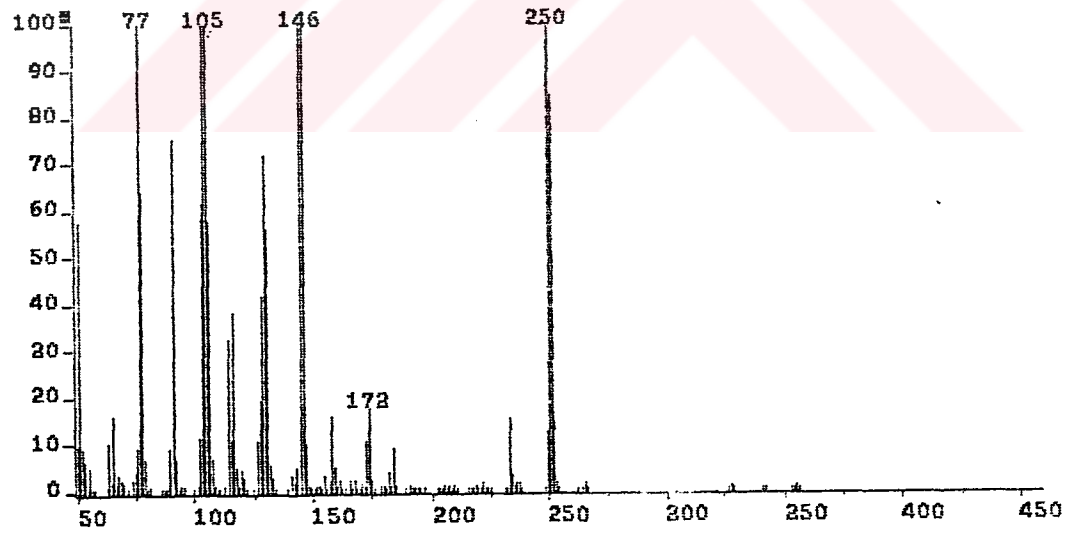


Figure 41. Mass Spectrum of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41).

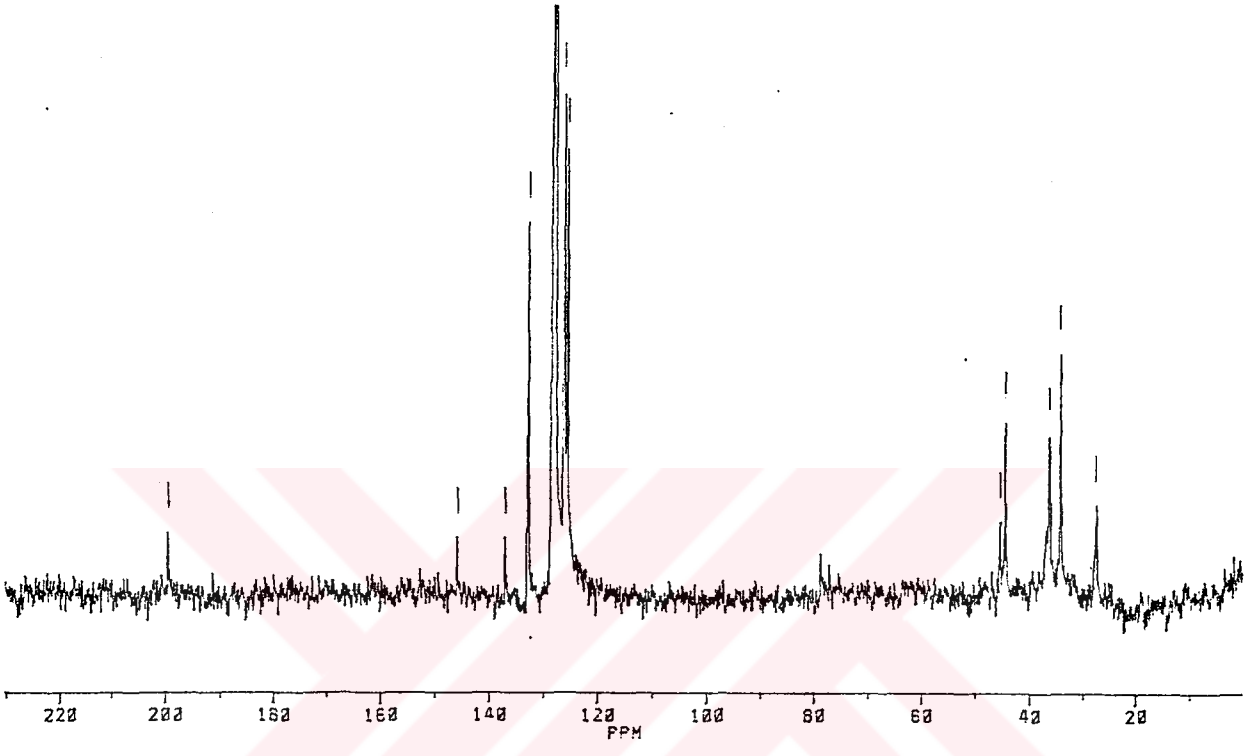
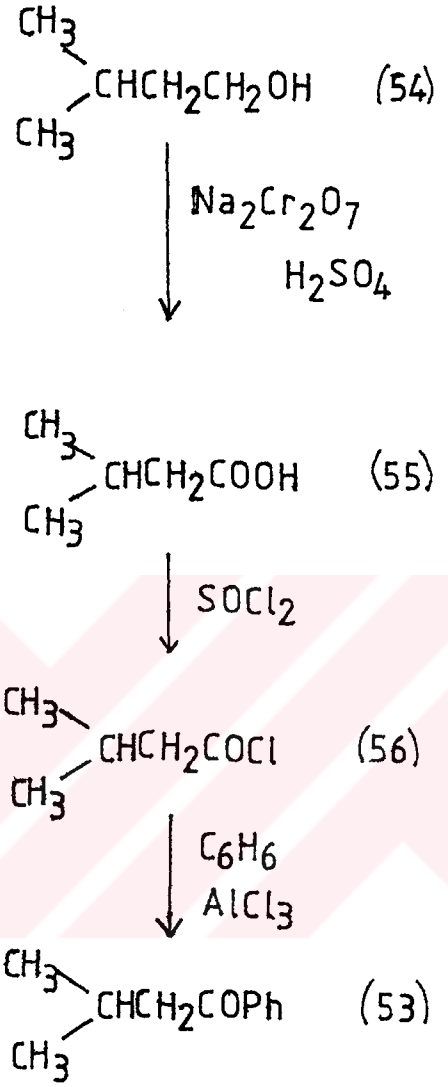


Figure 42. ^{13}C-NMR Spectrum of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) in $CDCl_3$.

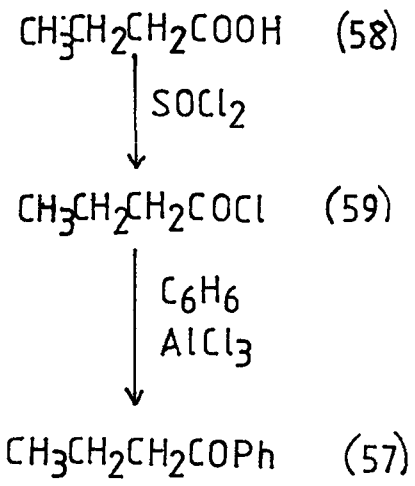
For kinetic studies, isovalerophenone and butyrophenone were synthesized as model compounds.

2.1.7. Isovalerophenone (53):



Isoamyl alcohol (54) was oxidized to isovaleric acid (55) by using $Na_2Cr_2O_7$ and dil. H_2SO_4. Treatment of the acid (55) with $SOCl_2$ yielded isovaleryl chloride (56) which gave isovalerophenone (53) with benzene and $AlCl_3$.

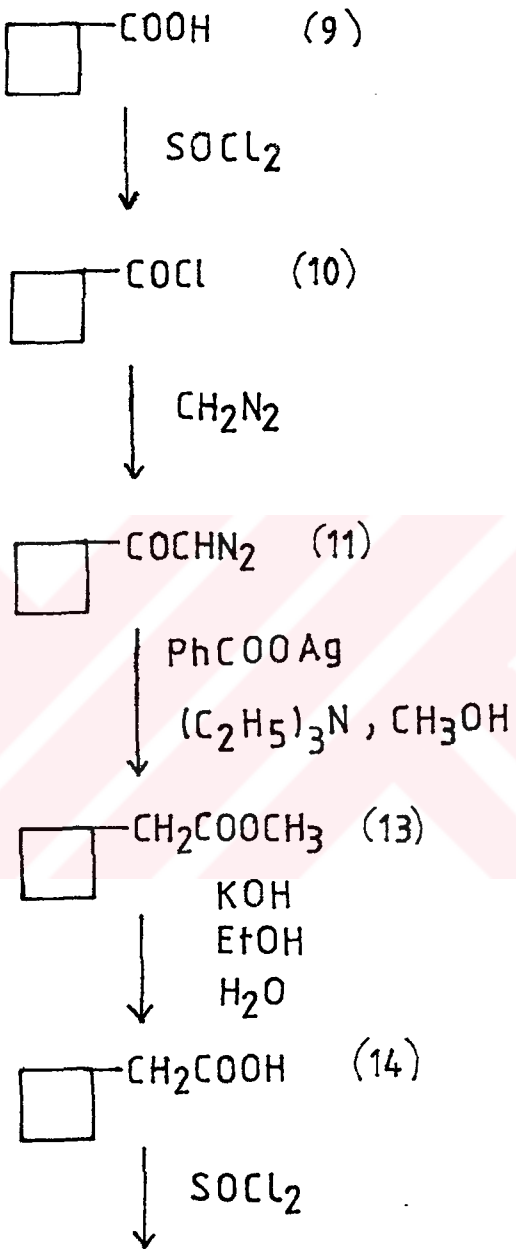
2.1.8. Butyrophenone (57)

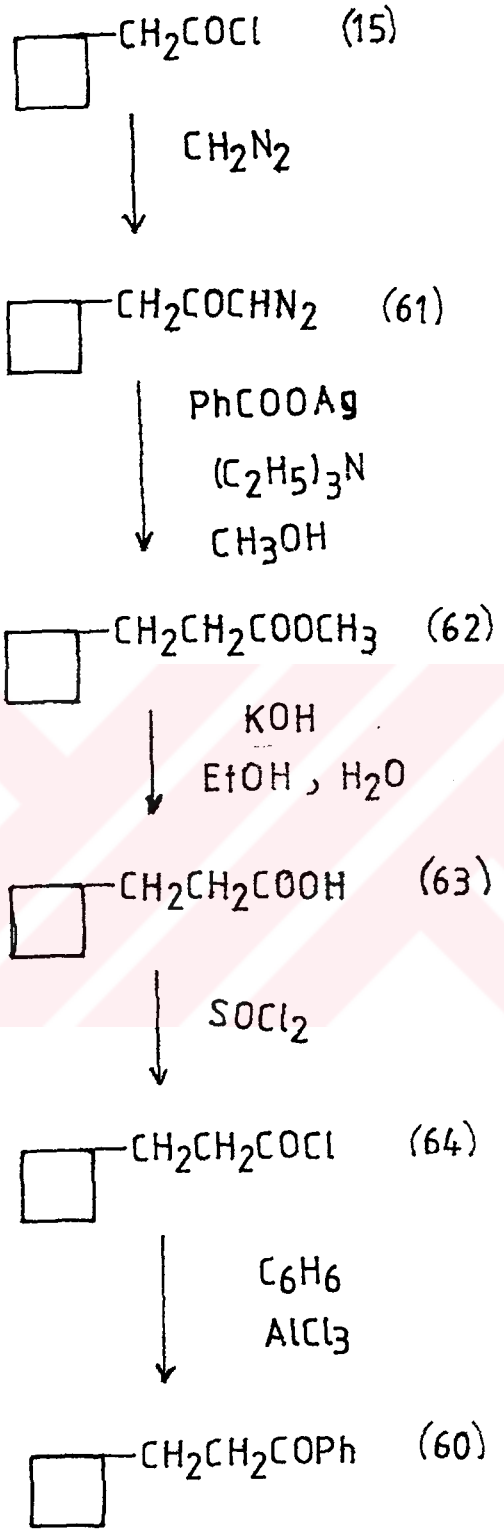


n-Butyric acid (58) was chlorinated with $SOCl_2$ to n-butyryl chloride (59) which was reacted with benzene and $AlCl_3$ to yield butyrophenone (57).

To search for the homoconjugative effect of the four-membered ring on a carbanion center β- to the ring 3-cyclobutyl-1-phenyl-1-propanone (60) has been synthesized together with the 1-phenylpent-4-ene-1-one (65) and 4-methyl-1-phenyl-1-pentanone (68) as model compounds.

2.1.9. 3-Cyclobutyl-1-phenyl-1-propanone (60):




CH2COCl (15)
CH2N2
CH2COCHN2 (61)
PhCOOAg
(C2H5)3N
CH3OH
CH2CH2COOCH3 (62)
KOH
EtOH , H2O
CH2CH2COOH (63)
SOCl2
CH2CH2COCl (64)
C6H6
AlCl3
CH2CH2COPh (60)

Beginning from cyclobutanecarboxylic acid (9), two Arndt-Eistert homologations were made. The homologated acid (63) was converted to acid chloride (64), which was treated with Ph_2Cd to obtain the 3-cyclobutyl-1-phenyl-1-propanone (60).

Compound (60) is in the literature, but no data about the physical and spectral properties are available.

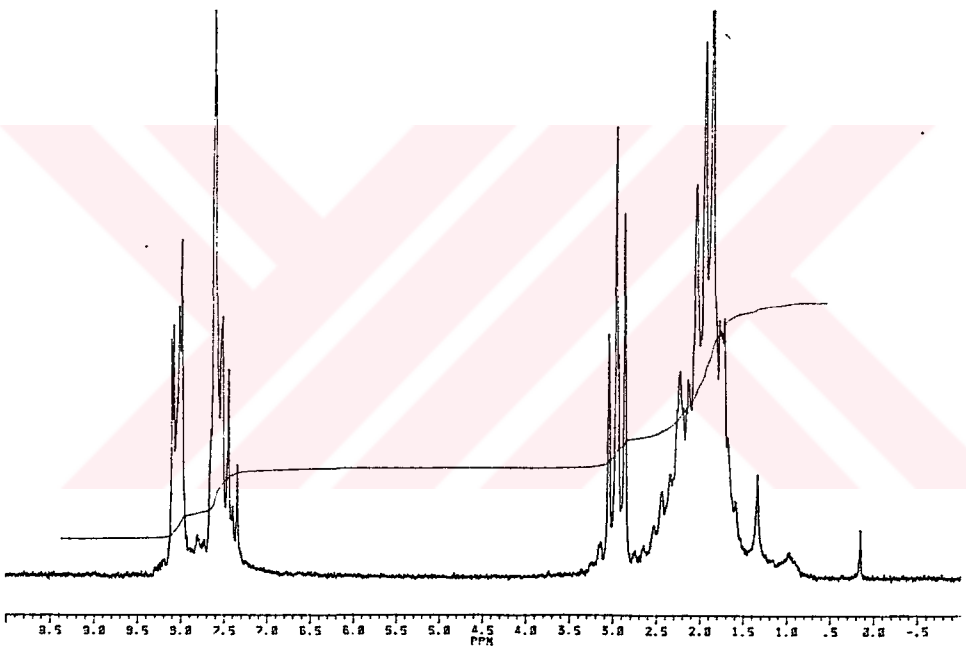


Figure 43. ^{1}H-NMR Spectrum of 3-Cyclobutyl-1-phenyl-1-propanone (60) in $CDCl_3$.

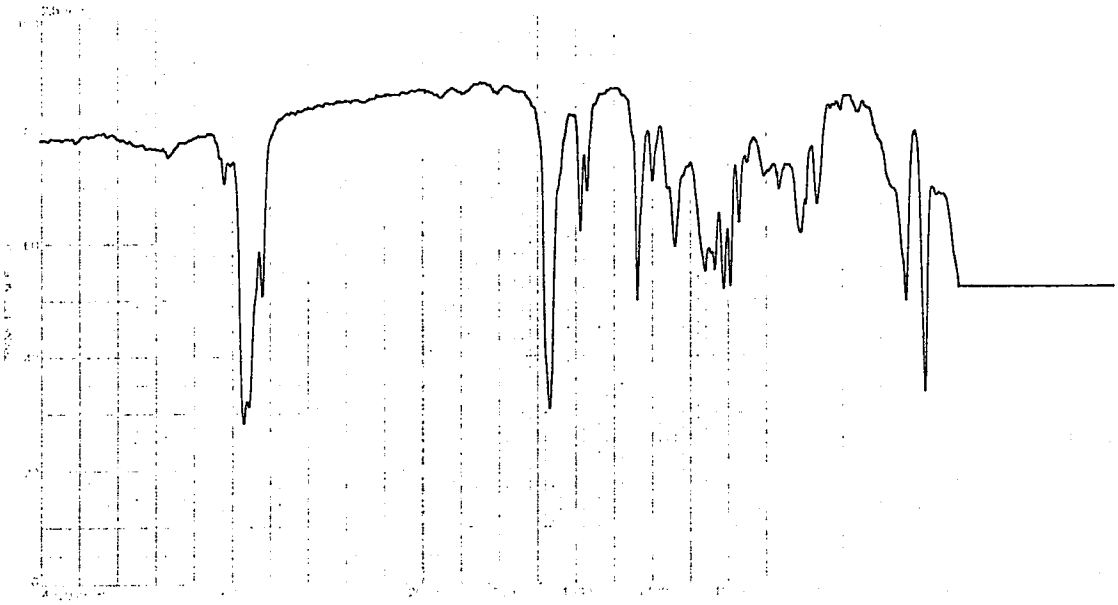


Figure 44. IR Spectrum of 3-Cyclobutyl-1-phenyl-1-propanone (60) as neat.

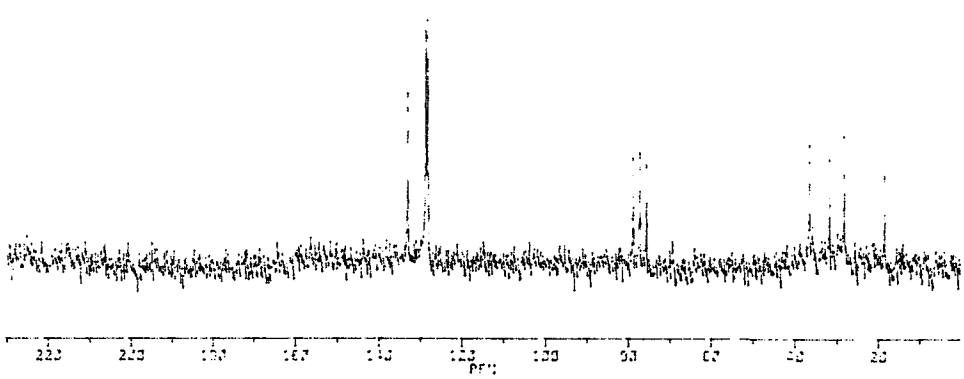
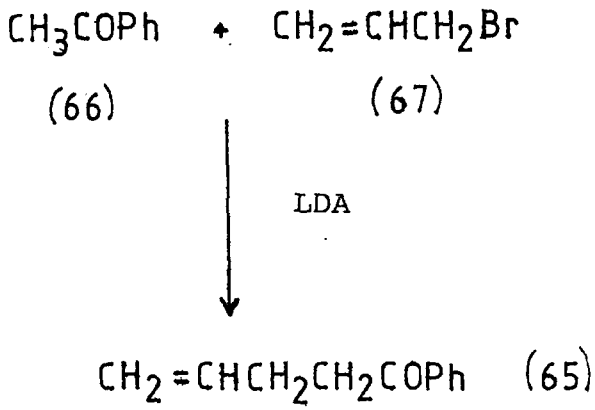


Figure 45. ^{13}C-NMR Spectrum of 3-Cyclobutyl-1-phenyl-1-propanone (60) in $CDCl_3$.

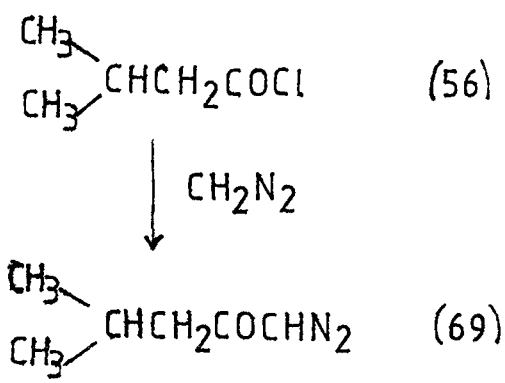
2.1.10. 1-Phenylpent-4-ene-1-one (65):

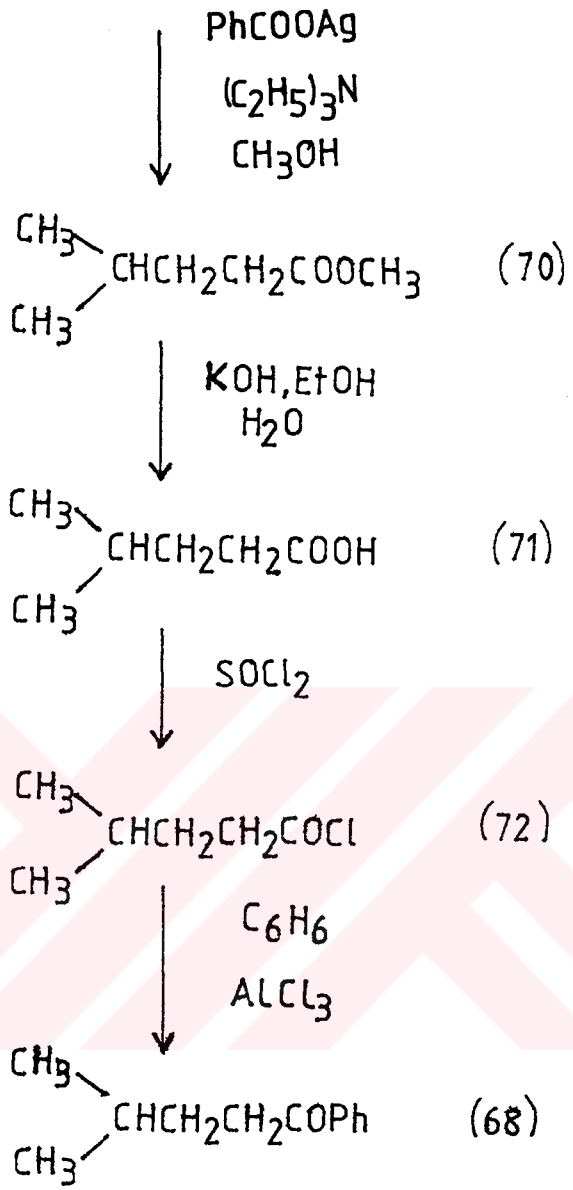


LDA was prepared from BuLi and diisopropylamine and was reacted with acetophenone (66) and allyl bromide (67). 1-Phenylpent-4-ene-1-one (65) was isolated from tlc.

2.1.11. 4-Methyl-1-phenyl-1-pentanone (68):

The synthesis of compound (56) has been described on page 117.

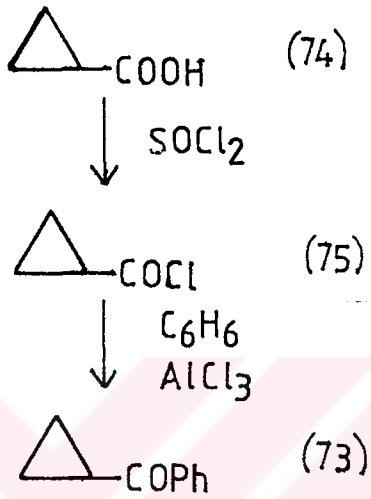




Isovaleryl chloride (56) was reacted with $SOCl_2$. The Arndt-Eistert homologated acid (71) was reacted with $SOCl_2$ to obtain acid chloride (72). According to Friedel-Crafts reaction, using benzene and $AlCl_3$, 4-methyl-1-phenyl-1-pentanone (68) was finally synthesized.

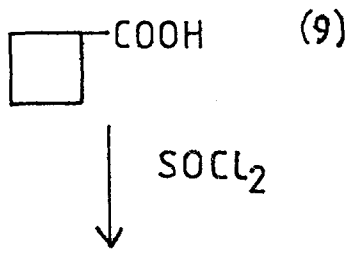
To determine the relative kinetic acidities of the methine hydrojens, cyclopropyl, cyclobutyl and isopropyl phenyl ketones were synthesized.

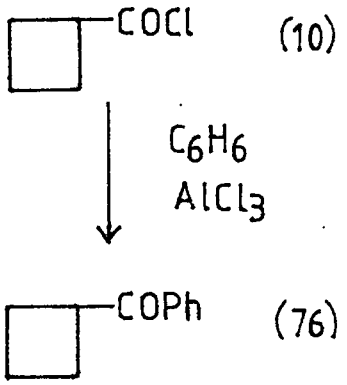
2.1.12. Cyclopropyl Phenyl Ketone (73)



Cyclopropanecarboxylic acid (74) was reacted with $SOCl_2$ to obtain cyclopropanecarbonyl chloride (75) which yielded cyclopropyl phenyl ketone (73) with benzene and $AlCl_3$ according to Friedel-Crafts reaction.

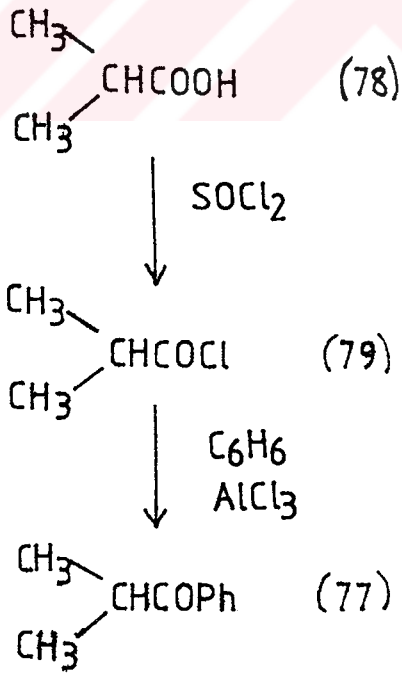
2.1.13. Cyclobutyl Phenyl Ketone (76):





Cyclobutanecarboxylic acid (9) was reacted with $SOCl_2$ to give cyclobutanecarbonyl chloride (10) which yielded cyclobutyl phenyl ketone (76) with benzene and $AlCl_3$ according to Friedel-Crafts reaction.

2.1.14. Isobutyrophenone (77):



Isobutyric acid (78) was chlorinated with $SOCl_2$ to give isobutyryl chloride (79) which gave isobutyrophenone (77) with benzene and $AlCl_3$ according to Friedel-Crafts reaction.

The other synthesized compounds for kinetic studies were propiophenone (80) and 3,3-dimethylbutyrophenone (81).

2.1.15. Propiophenone (80):

CH_3CH_2COOH (82)

$\downarrow SOCl_2$

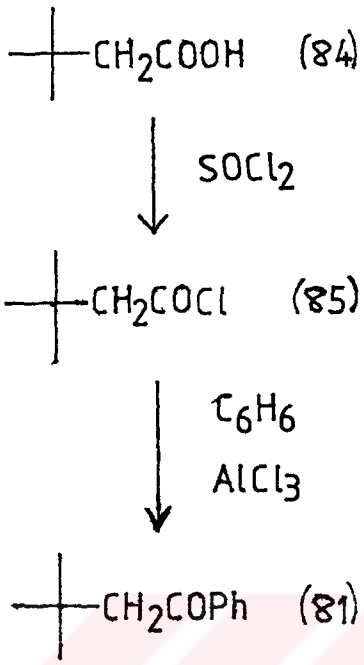
CH_3CH_2COCl (83)

$\downarrow C_6H_6, AlCl_3$

CH_3CH_2COPh (80)

Propionic acid (82) was reacted with $SOCl_2$ to give propionyl chloride (83) which yielded propiophenone (80) with benzene and $AlCl_3$ according to Friedel-Crafts reaction.

2.1.16. 3,3-Dimethylbutyrophenone (81):



3,3-Dimethylbutyric acid (84) was chlorinated with $SOCl_2$ to 3,3-dimethylbutryl chloride (85) which yielded to 3,3-dimethylbutyrophenone (81) with benzene and $AlCl_3$ according to Friedel-Crafts reaction.

2.2. Kinetic Measurements:

The hydroxide catalyzed H-D exchange rates were measured by nmr spectroscopy. The rate of disappearance of the signals due to the exchanging protons with respect to time was studied at the probe temperature of the nmr spectrometer, following the procedure in the study of Peynircioglu[2] (Figure.46, p.73). Exchange was treated as irreversible and pseudo-first order kinetic behavior was assumed. Ketones were allowed to undergo exchange competitively, in pairs, thus assuring identical conditions for each component of the pair. The relative rates were independent of the amounts of the ketones in the pair and also the amount and composition of the base system. The ketone pairs were selected in such a way as to ensure sufficient chemical shift differences between the exchanging protons of each ketone in their combined nmr spectrum to make measurements on both ketones possible. Another point was to permit the observation of the disappearance of the exchanging protons of both ketones and to obtain reproducible results.

In this work, the kinetic study of 2-phenylcyclobutylcarbinyl phenyl ketone (29) could not be carried out because the exchanging acidic hydrogens

could not be seen seperately in the nmr spectrum, they were masked by the cyclobutyl protons.

o-Nitro-1-phenylcyclobutylcarbinyl phenyl ketone (27) was used only as a reference ketone; in the determination of the relative rate of exchange of 3-phenylcyclobutylcarbinyl phenyl ketone (41) .

Isovalerophenone (53) was assigned a relative rate of unity. The rates of exchange of all other ketones were then related, by appropriate pairwise comparisons to that of (53).

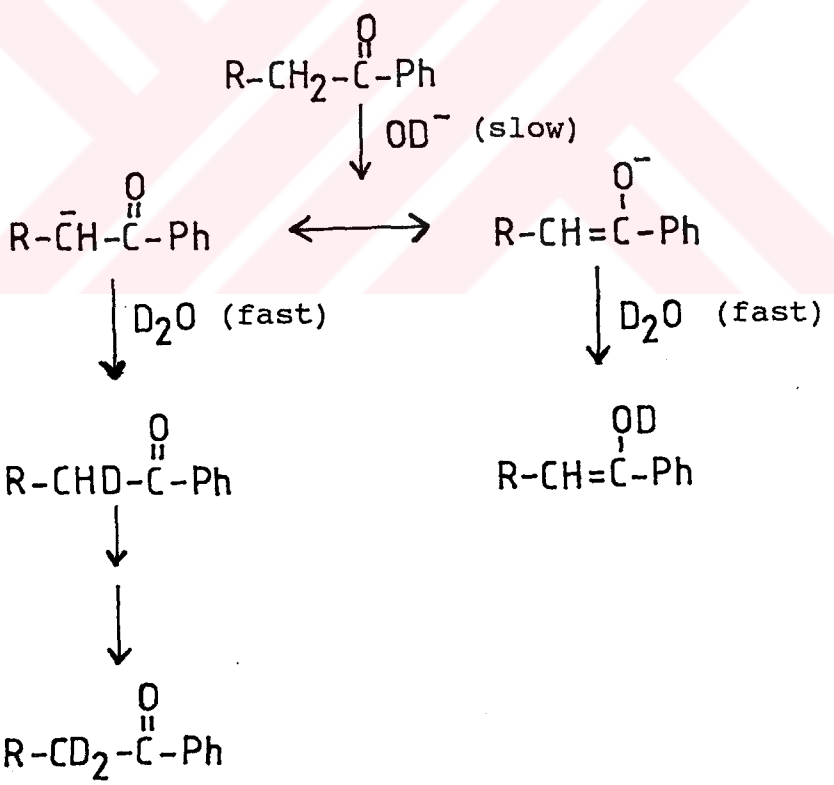


Figure 46. General Example to H-D Exchange Reaction

2.2.1. Results and Discussion of the Kinetic Studies

The hydroxide-catalyzed H-D exchange rates of the α-protons of the series of ketones, the synthesis of which were described in the previous sections are listed in table 1 (p.75).

It is already known that[43] the allylic ketone (86) exchanges too fast for its rate to be compared with those of the reference (53), cyclopropylcarbinyl- (87), and cyclobutylcarbinyl- (8) phenyl ketones by the method employed in this work. Comparison of the rates of exchanges of (53), (87), and (8) reveals a distinct rate enhancement of the four-membered ring (compared to isopropyl group) in addition to the already known[43] similar rate increase by the three-membered ring. This rate enhancement due to the cyclobutyl group is 2.5 times smaller than that observed[43] for the three-membered ring although it is not easy to estimate the steric retardation imposed by the larger four-membered ring. This steric (and inductive) retardation can clearly be seen when one compares the rates of exchange of acetophenone (66), propiophenone (80), butyrophenone[43] (57), and the reference ketone (53). The rates are nearly the same for (80) and (57), where

there is only one β-methyl substitution.

Table 1. Relative Rates (k) of Exchange of the Open-Chain and Cyclic Ketones.

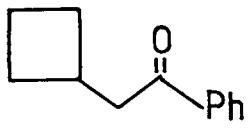
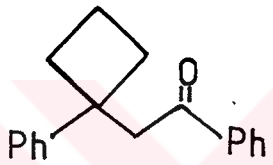
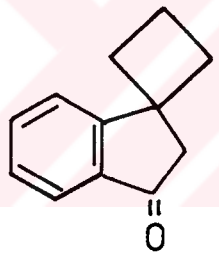
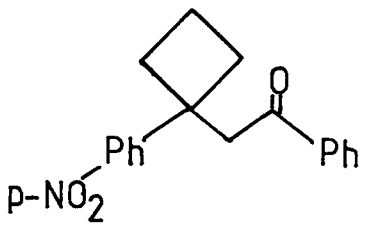
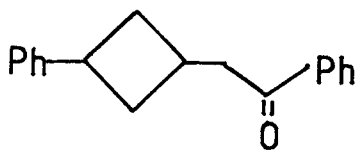
Compound	k_{rel}
(8) 	2.0
(16) 	0.96
(26) 	11.0
(28) 	4.3
(41) 	3.2

Table 1.(cont'd)

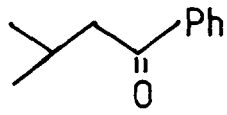
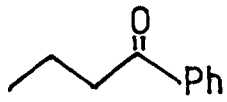
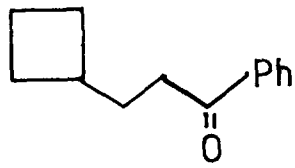
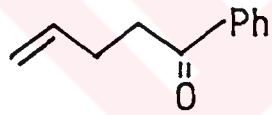
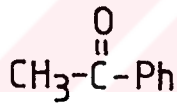
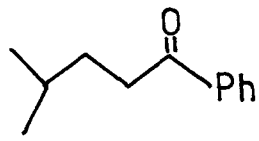
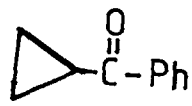
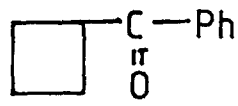
*(53)		1.0
*(57)		2.9
(60)		1.2
(65)		2.8
(66)		3.2
(68)		1.2
(73)		----
(76)		1.6

Table 1.(cont'd)

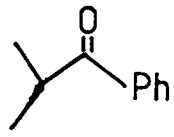
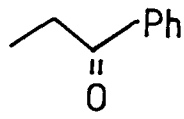
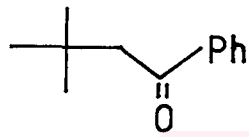
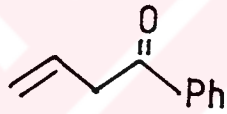
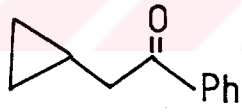
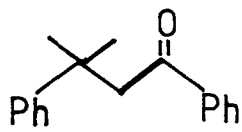
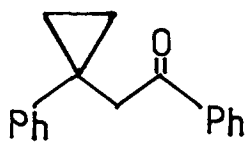
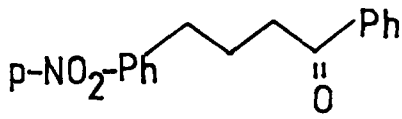
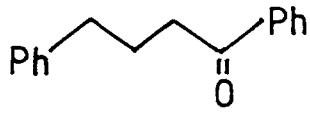
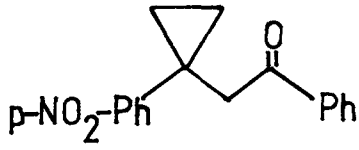
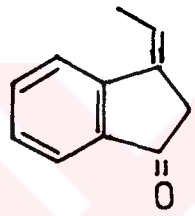
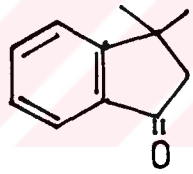
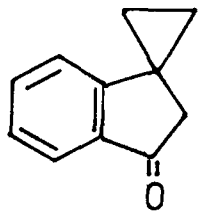
(77)		0.49
(80)		2.9
(81)		0.49
*(86)		fast
*(87)		4.8
*(88)		1.0
*(89)		7.9

Table 1.(cont'd)

*(90)		20.0
*(91)		4.2
*(92)		36.0
*(93)		fast
*(94)		11.0
*(95)		33.0

(* See ref.[43])

However, the rate decreases by a factor of 2.9 times upon second β-methyl substitution (see (53)) and by a factor of 5.9 times upon third β-methyl substitution (see (81)) on (80), have been observed.

An α-methyl substitution on (80) (isobutyrophenone, (77)) decreases its rate 5.9 times, equivalent to a tri-β-methyl substitution on (80). (cf. compound (81)). Isovalerophenone (53) is thought to be a better reference ketone compared to (57) and (80) for (87) and (8) because of the steric-inductive retardation due to β-methyl substituents. This kind of retardation in compound 8 can be approximated to be at least as much as that present in the reference ketone (53).

Comparison of the rates of exchange of 3-phenyl-3-methylbutyrophenone[43] (88), 1-phenylcyclopropylcarbinyl phenyl ketone (89), and 1-phenylcyclobutylcarbinyl phenyl ketone (16) reveals, on the other hand, no detectable increase in the rate of exchange due to 1-phenyl- substituted cyclobutyl group! In contrast,an 8-fold increase due to 1-phenylcyclopropyl group had been observed[43] when the relative rates of (88) and (89) was compared. A nitro group substituted at the para- position of the 1-phenyl group in (16) (to form compound (28)) increases the rate of

exchange of (16) by 4.4 fold. Relative rate increases of 4.6 and 4.8 had also been observed[43] upon comparisons of the rates of exchange of (92) with that of (89) and 4-(p-nitrophenyl)butyrophenone (90) , with 4-phenylbutyrophenone (91) , where the effect of the p-nitro substitution had been diagnosed only to be inductive. Since the same is also observed when the effect of 1-phenylcyclobutyl (in compound (16)) and 1-(p-nitrophenylcyclobutyl) (in compound (28)) groups are compared, any possibility of the transmission of the resonance effect of the nitro group by the four-membered ring is excluded.

When the rates of exchange of compounds (57) and (91) are compared a 1.4 fold increase[43] is detected upon a 4-phenyl substitution on (57). When this 1.4 fold increase is compared with the 1.6 fold increase, when the rates of 3-phenylcyclobutylcarbinyl phenyl ketone (41) and of (8) is compared, the existence of perhaps a very weak conjugative effect of the four-membered ring can be conceived.

The rates of exchange of 1-phenylpent-4-ene-1-one (65), 4-methyl-1-phenyl-1-pentanone (68), and 3-cyclobutyl-1- phenyl-1-propanone (60) have also been compared in order to see if any homoconjugative

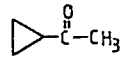
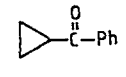
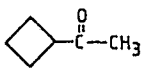
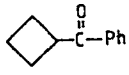
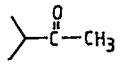
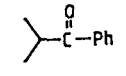
stabilizing effect of the four-membered ring is in operation. Although an effect could be detected for the vinyl group no rate enhancement could be seen for the cyclobutyl group.

In the examination of the relative rates of exchange in isobutyrophenone (77), cyclobutyl phenyl ketone (76) and cyclopropyl phenyl ketone (73) one may expect to see the increasing acid character of the α-H. In these, however, it is known that the formation of enolate of (73) would be rather difficult[44,45]. Deprotonation at α- position would lead to additional strain when an exocyclic double bond is formed! The low acidity of monofunctional COR- substituted cyclopropanes has been confirmed many times[45], although controversies on this are not non-existent[46].

One noteworthy example[44] supporting the low acidity of COR- substituted cyclopropanes investigates the reaction of cyclopropanecarboxaldehyde in basic medium. Although only Cannizaro products were observed in that case, cyclobutanecarboxaldehyde yields normal aldol condensation products. In an earlier work[45], however, the rate of exchange of the α-H in compound (73) has been found to be 14 times more than that of compound (77) in a base system of $OD^-/DMF/D_2O$. This observation of

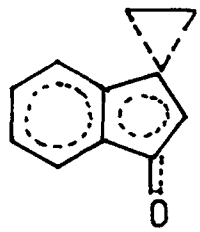
the importance of acidity of the α-H due to the increased s character in the exocyclic bond of the three-membered ring, overriding the I-strain in the enolate formed could not be repeated in later work[45d]. Van Wijnen and coworkers[45a] in their study with sodium methoxide in methanol found the rate of exchange of (73) relative to (77) to be 0.0067, and Ruppe and Sachs[45b] found the rate of cyclopropyl methyl ketone relative to isopropyl methyl ketone to be 0.02 in their base system of OD^-/dioxane/D_2O. In this same study the rate of exchange of cyclobutyl methyl ketone relative to isopropyl methyl ketone is found to be 2.1. In this work the rate of exchange of (76) relative to (77) is 3.3. In line with most of the previous work[45] no detectable exchange of the α-H's of (73) has been observed. The results of this work and ref.[45a] have been tabulated in table 2.

Table 2. Comparison of Rate of Exchange of Methyl and Phenyl Substituted Ketones.

	k_{rel} [45a]		k_{rel}
	0.02		---
	2.1		3.3
	1.0		1.0

These results indicate that it is highly improbable that the different solvent systems could change the transition states of compound (73) leading to its enolate to such extent that the kinetic acidity of (73) is raised much more than the acidity of (77). The fact that the base-catalyzed deuteration of the methine hydrogen in the cyclopropyl ketones is resisted in spite of the increased s character of the exocyclic carbon atomic orbitals is confirmed once more in this work.

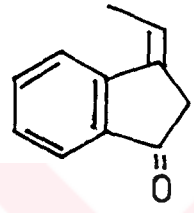
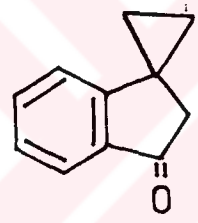
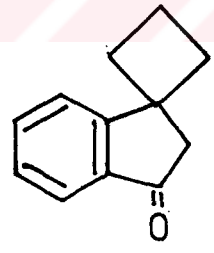
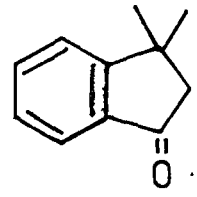
3,3-Trimethylene-1-indanone (26) has also been synthesized in this work to compare its base-catalyzed rate of enolization with those of E-3-ethylideneindanone (93) , 3,3-dimethylindanone (94) and 3,3-dimethyleneindanone (95),the relative rates of which had been determined previously[43],where,in addition to the immeasurably fast exchange of (93) a 3 fold increase in the rate of exchange of (95) with respect to (94) had been found. Although a rationalization had been intended to be put forward in terms of possible spirocyclic conjugation in the enolate of (95), (95a), in view of the relatively small (3-fold) rate



(95a)

enhancement (compared to the 5-fold rate enhancement three-membered ring in (87) relative to (53)) this argument had not been pursued too far[43].The relative rates of exchange (with respect to (94)) in compounds (93),(94),(95), and (26) have been tabulated in table 3.

Table 3. Rate of Exchange Values of Some Cyclic Ketones.

		k_{rel}
(93)		fast[43]
(95)		3.0[43]
(26)		1.0
(94)		1.0

There is no detectable rate enhancement of compound (26) relative to (94). This observation is similar to what is found when the exchange rates of (88) and (16) are compared, while an 8-fold increase of the rate of compound (89) relative to (88) had previously been observed[43].

In the cyclic ketones (93,94,95, and 26) there are complex electronic, steric, and conformational effects and a through discussion is perhaps not justified[43].

A net increase in the rate of exchange due to the cyclobutyl group is clearly seen only in compound (8), when its rate is compared to that of (53). Indeed, a recent study[1], part of which stems from this thesis, which uses semi-empirical MNDO calculations claims that the cyclobutyl group has the ability to stabilize an adjacent carbanion center, similar to vinyl and cyclopropyl groups, although to a lesser extent. In this study, the acidities of isobutane (96), propene (97), methylcyclopropane (98), and methylcyclobutane (99) were determined in the formation of isobutyl, allyl, cyclopropylcarbinyl, and cyclobutylcarbinyl carbanions. When sp^2 hybridization is assumed at the carbanion centers and bisected conformations of the rings are

chosen, the acidities calculated for the compounds (96-99) correlate quite well (table 4) with the relative rates of exchange in compounds (53),(86),(87)and (8), which are the benzoylated derivatives of (96-99). The enolates of these ketones are planar carbanions.

Table 4[1]. Acidities of the compounds (96-99), and relative rate of exchange of ketones (86),(87), (8), and (53).

Compound ($R-CH_3$)	R	ΔH° (kJ/mole)	Compound $R-CH_2COPh$	k_{rel}
(97)	vinyl	1618.4	(86)	fast
(98)	cyclopropyl	1694.7	(87)	4.8
(99)	cyclobutyl	1718.2	(8)	2.0
(96)	isopropyl	1725.0	(53)	1.0

The reasons for the cyclobutyl group's ineffectiveness in the rate enhancement (compared to compound (8)) upon 1-phenyl substitution in compound (16) and also in compound (26) is not well understood.

CHAPTER III

EXPERIMENTAL

Melting points were determined using Reichert melting point apparatus. Varian T-60A NMR spectrometer was used for kinetic measurements and most of the routine NMR has been taken by Bruker-80 spectrometer. For IR spectra, PU 9700 Infrared spectrometer and Nicolet 510 FT-IR spectrometer were used. A Hewlett-Packard 185 C, H, N Micro-Analyzer instrument was used for elemental analysis. Mass spectra were taken by VG-TRIO2 mass spectrometer. Kieselguhr GF_{254} Silicagel was used for preparative tlc.

3.1. Synthesis

3.1.1. Synthesis of Cyclobutylcarbinyl Phenyl Ketone (8) .

3.1.1.1. Cyclobutanecarbonyl Chloride (10) .

Cyclobutanecarboxylic acid (9) (26.5g , 0.26mole) was added to redistilled thionyl chloride (23.87ml , 0.33mole) at 30-40°C. When all the acid was added, it was heated for 30 min. and distilled. [24g, 80%, bp.133°(685mm), lit bp[47] 137°(750mm)]

3.1.1.2. Cyclobutyl Diazomethyl Ketone (11) and N,N-Dimethylcyclobutylacetamide (12).

Cyclobutanecarbonyl chloride (10) (8.89g , 0.08mole) was added to diazomethane (10g , 0.24mole) in ether (500ml) at 0°C with stirring. After stirring for 2 h. at 5°C , ether was removed under reduced pressure. To the residue were added dioxane (28.16ml) , dimethylamine (22.35ml) , 10% aqueous $AgNO_3$ solution (3.35ml) and freshly prepared Ag_2O (0.45g). A brisk evolution of gas occurred, and it was necessary to cool the flask in an ice-bath. Ag_2O was added from time to time to maintain

the brisk evolution of nitrogen. After stirring for 1h. at 25°C in the presence of excess Ag_2O, the mixture was filtered and the solvent removed under reduced pressure. The crude product was distilled yielding N,N-dimethylcyclobutylacetamide (12) . [6g, 56%, bp.110°(20mm), lit[47]bp.92-93°(4.9mm)]

3.1.1.3. Cyclobutylacetic Acid (14) .

N,N-Dimethylcyclobutylacetamide (12) (6g, 0.04mole) was refluxed with 15% HCl (140ml) for 48h. After cooling the reaction mixture, it was extracted with ether and dried over $MgSO_4$. Removal of the solvent followed by distillation of the crude acid, yielded cyclobutylacetic acid (14). [3g, 62%, bp.86°(15mm), lit[47]bp.78°(2mm)]

3.1.1.4. Cyclobutylacetyl Chloride (15) .

Prepared as in the case of cyclobutanecarbonyl chloride (10) from cyclobutylacetic acid (14) (3g, 0.03mole) and thionyl chloride (2.4ml, 0.03mole). [2.9g, 84%, bp.140°(685mm), lit[47]bp.153°(747.4mm)]

3.1.1.5. Cyclobutylcarbinyl Phenyl Ketone (8) .

Cyclobutylacetyl chloride (15) (2.9g, 0.02mole) was added to dry benzene (6ml, 0.07mole) containing anhydrous $AlCl_3$ (3.2g, 0.02mole) during a period of 2h. The considerably darkened reaction mixture was refluxed for 30 min. to complete the reaction. It was then cooled and hydrolized with cold water. The upper oily layer was separated, washed with 10% NaOH solution, water and dried over anhydrous $MgSO_4$. Benzene was removed and the residue was distilled to yield (8) [1.8g, 47%, bp.142°C(15mm)].

NMR ($CDCl_3$) : δ 1.5-2.5 complex m (6H, cyclobutyl-)
2.7-3.1 complex m (1H, cyclobutyl-)
7.2-8.1 complex (5H, Ar-)
3.1 doublet (CH_2-)

IR (neat) : 1690 cm^{-1} (C=O)

$C_{12}H_{14}O$ calc. C: 82.75 found. C: 83.75

H: 8.05 H: 8.06

M^+ : 174

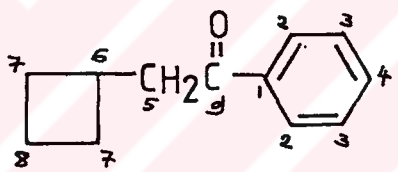
^{13}C-NMR: C1 132.720 C5 45.497

C2 128.400 C6 31.941

C3 127.950 C7 28.546

C4 130.936 C8 18.805

C9 199.542



3.1.2. Synthesis of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

3.1.2.1. 1-Phenylcyclobutane Carbonitrile (18) .

Under nitrogen, dimethyl sulfoxide (600ml) and NaH (63.4g, 1.32mole) mixture was cooled to 30°C. A solution of benzyl cyanide (17) (70.2g, 0.6mole) and 1,3-dibromopropane (133.2g, 0.66mole) in 400ml of dry ether was added at a rate to maintain a 25-30°C reaction temperature. The resultant thick slurry was stirred overnight and cooled in ice-water. 2-Propanol (30ml) was then added dropwise to the reaction mixture followed by addition of 500ml of water. The mixture was then filtered through Filter-Aid, the layers were separated, and the aqueous layer was extracted four times with 300ml portions of ether. The combined ether layers were dried over $MgSO_4$, concentrated, and the product (18) was distilled [23.7g, 25%, bp.90-100°(0.3mm), lit[35] bp.80°(0.1mm)].

3.1.2.2. 1-Phenylcyclobutanecarboxylic Acid (19) .

1-Phenylcyclobutane carbonitrile (18) (23.7g,

0.15mole) and KOH (16.97g, 0.3mole) were heated in β,β′-dihydroxyether for 3h. It was then poured into H_2O (228ml) , washed with ether to remove any unreacted nitrile or amide. The aqueous phase was acidified and extracted with ether. The ether layer was dried with Na_2SO_4. Removal of the solvent yielded the acid (19) [23g, 90%, mp.105-108°, lit[48] mp.105-108°].

3.1.2.3. 1-Phenylcyclobutanecarbonyl Chloride (20) .

A solution of $SOCl_2$ (22ml, 0.3mole) in sodium dried benzene (40.44ml) was added dropwise, with stirring, to a slurry of 1-phenylcyclobutanecarboxylic acid (19) (19g, 0.11mole) in sodium-dried benzene (107.8ml). The reaction mixture was heated under reflux, with stirring for 4h. Benzene and $SOCl_2$ were removed by distillation and the residue was fractionated, yielding 1-phenylcyclobutanecarbonyl chloride (20) [19.5g, 93%, bp.88°(0.5mm), lit[49] bp.66°(0.15mm)].

3.1.2.4. 1-Phenylcyclobutyl Diazomethyl Ketone (21) .

1-Phenylcyclobutanecarbonyl chloride (20) (19.5g, 0.1mole) was added to 3M excess ethereal diazomethane at

0°C. The reaction was stirred overnight, the ether and excess diazomethane were then removed to yield the diazoketone (21) [20g, 100%].

3.1.2.5. Methyl (1-phenylcyclobutyl)acetate (23) .

The diazoketone (21) (20g, 0.1mole) was dissolved in absolute methanol (156ml) and to it was added silver benzoate (20.2g) in triethylamine (238.5ml) catalyst with stirring at room temperature. After stirring overnight, the reaction mixture was filtered, volatile material was removed and the remaining oil was taken in ether. It was then neutralized with 2N HCl, washed with 10% Na_2CO_3 and water and then distilled to yield (23) [10.45g, 51.2%, bp.98-110°(1.5-1.7mm), lit[50] bp.112-114°(3.5mm)].

3.1.2.6. 1-Phenylcyclobutylacetic Acid (24) .

Methyl (1-phenylcyclobutyl)acetate (23) (10.4g, 0.05mole) was saponified by refluxing with KOH (4.3g, 0.08mole) in water (50.05ml) and ethanol (61.6ml, 95%) for 15-20h. The alcohol was removed and the alkaline residue was extracted with ether. The aqueous phase was acidified and the liberated oil solidified.

Recrystallization from ethanol yields (24) [8.7g, 90%, mp.75-76°, lit[50]mp.75-76°].

3.1.2.7. 1-Phenylcyclobutylacetyl Chloride (25) .

Same procedure as in the preparation of 1-phenylcyclobutanecarbonyl chloride (20) was followed, $SOCl_2$ (7.2ml) in dry benzene (13.5ml) and 1-phenylcyclobutylacetic acid 24 (6.9g, 0.04mole) in dry benzene (36ml) were used to yield (25) [6g, 80%, bp.90-100°(1mm), lit[50]bp.95-96°(1.5mm)]

3.1.2.8. 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Phenylmagnesium bromide was prepared from bromobenzene (4.4g, 0.03mole) in anhydrous ether (33ml) and Mg (0.68g, 0.03mole) in anhydrous ether (33ml). Anhydrous $CdCl_2$ (3.8g, 0.02mole) was added to the cooled (ice-bath) Grignard solution, which was stirred for 5 min at room temperature and refluxed for 75 min. until the Gilman test[51] for the Grignard reagent gave a negative result. Ether was distilled until it left a viscous black residue and replaced by dry benzene (39ml). The mixture was vigorously stirred and refluxed for 10 min.

and then cooled in ice to 5°C. 1-Phenylcyclobutylacetyl chloride (25) (3g, 0.02mole) in dry benzene (39ml) was introduced portionwise to the vigorously stirred suspension of Ph_2Cd in dry benzene (39ml). The mixture was stirred at room temperature for 15 min., then at reflux for 12h., hydrolized with HCl, the organic layer was washed with Na_2CO_3 solution then with H_2O and dried over $CaCl_2$. Removal of the solvent left an oily residue. The impure product was crystallized several times from hexane to give the ketone (16) as a colorless solid [1.8g, 51.4%, mp.57-58°].

NMR ($CDCl_3$) : δ 2-3 complex m (6H, cyclobutyl-)
7-8 complex (10H, Ar-)
3.4 singlet (2H, CH_2-)

IR (KBr pellet) : 1697 cm^{-1} (C=O)

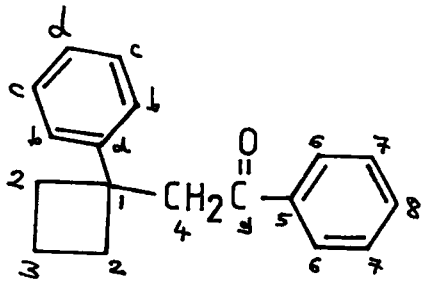
$C_{18}H_{18}O$ calc. C: 86.4 found. C: 86.16
H: 7.20 H: 7.32

M^+: 250

^{13}C-NMR : Ca 148.999 C1 45.374 C5 137.8
Cb 125.300 C2 33.238 C6 128.001
Cc 125.832 C3 16.051 C7 127.742

Cd 125.832 C4 49.332 C8 132.288

C9 198.859



3.1.3. Synthesis of 3,3-Trimethylene-1-indanone (26) .

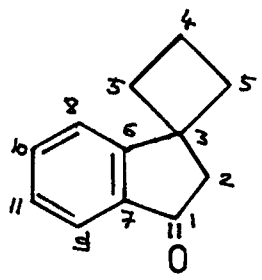
1-Phenylcyclobutylacetyl chloride (25) (2.5g, 0.01mole) in dry benzene (50.56ml) was treated with anhydrous aluminium chloride (2g, 0.01mole) and refluxed with stirring for 3h. The solution was poured on ice with vigorous stirring and the benzene phase was separated, neutralized, dried over Na_2SO_4 and evaporated. The remaining oil was distilled to yield (26) [0.7g, 33.9%, bp.116°(1.5mm), lit[50] purification by glpc.].

NMR ($CDCl_3$) : δ 1.9-2.7 complex m (6H, cyclobutyl-)
2.9 singlet (2H, CH_2-)
7.2-7.8 complex (4H, Ar-)

IR (neat) : 1720 cm^{-1} (C=O)

M^+: 172

^{13}C-NMR : C1 204.967 C6 135.486 C11 127.291
C2 52.148 C7 161.311
C3 44.200 C8 122.583
C4 16.316 C9 135.021
C5 35.634 C10 123.764



3.1.4. Synthesis of o- and p-Nitro-1-Phenylcyclobutylcarbinyl Phenyl Ketone (27 and 28[2]) .

1-Phenylcyclobutylcarbinyl phenyl ketone (16) (0.41g, 0.002mole) in acetic anhydride (2.5ml) was added portionwise to a nitrating mixture made up of fuming HNO_3 (0.82ml) in acetic anhydride (2.5ml) (the temperature of the nitrating mixture was not allowed to exceed 20° during its preparation), cooled to -20°, under magnetic stirring, over a period of 25 min. The temperature of the reaction mixture was kept between -40° and -20° during the addition. The mixture was allowed to stir for 5 min. and poured into boiling water, cooled and extracted with ether, the ether extracts were washed with aqueous Na_2CO_3 solution and dried over Na_2SO_4. Removal of solvent under reduced pressure gave an oily residue. The desired o- and p- isomers were isolated by preparative tlc. (Kieselguhr GF_{254}). Hexane-EtOAc (16:1) mixture was used. Upper layer was found to be the o-isomer (27) [0.11g, 19%, mp.95-97°] and the lower layer to be the p- isomer (28) [0.3g, 51%, mp.76°].

For o- isomer:

NMR ($CDCl_3$) : δ 1.6-2.7 complex m (6H, cyclobutyl-)
3.8 singlet (2H, CH_2-)
7-8 complex (4H, Ar-)

IR (KBr pellet) : 1690 cm^{-1} (C=O)

$C_{18}H_{17}NO_3$	calc.	C: 73.22	found.	C: 74.36
		H: 5.76		H: 6.26
		N: 4.74		N: 4.82

For p-isomer:

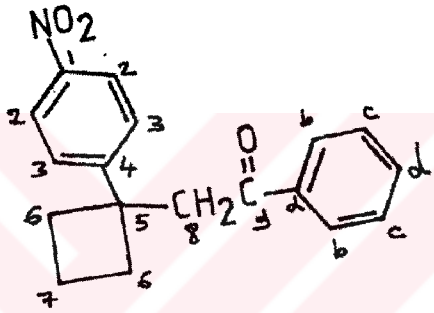
NMR ($CDCl_3$) : δ 1.6-2.6 complex m (6H,cyclobutyl-)
3.6 singlet (2H,CH_2-)
7.2-8.2 complex (9H,Ar-)

IR (KBr pellet) : 1690 cm^{-1} (C=O)

$C_{18}H_{17}NO_3$	calc.	C: 73.22	found	C: 73.13
		H: 5.76		H: 5.37
		N: 4.74		N: 4.31

M^+: 295

^{13}C-NMR : C1 148.586 C9 197.616 Ca 137.8
C2 123.106 C6 33.523 Cd 132.975
C4 156.000 C7 16.192
C5 45.202 C8 49.016
Cb,Cc,C3= 127.759, 127.149, 128.422


NO2
1
2
2
3
3
4
6
5
CH2
8
O
C
9
a
b
c
d
b
c
6
7

3.1.5. Synthesis of 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) .

3.1.5.1. Ethylcinnamyl Malonate (31) .

Redistilled ethyl malonate (Riedel) (8.2g, 0.05mole) was added during 30 min. to a hot solution of sodium (1.17g, 0.05mole) in anhydrous methanol (34.5ml). Cinnamyl chloride (30) (7.1g, 0.05mole) was then added with vigorous stirring at a rate sufficient to keep the solution gently refluxing. Heating was continued until the mixture was neutral to moist litmus (2h.) , whereafter most of the methanol was removed by distillation. The oil obtained by pouring the residue into water gave, on fractionation, much low-boiling material together with the desired product (31) [6.8g, 49%, bp.140-150°(0.6mm), lit[52]bp.137-140°(0.1mm)].

3.1.5.2. Diethyl (3-bromo-3-phenylpropyl) Malonate (32) .

Dry hydrogen bromide was passed through diethyl cinnamyl malonate (31) (6.8g, 0.02mole) over a period of 2h. The temperature rose to 50° and was kept between 40 and 45° when the exothermic reaction ceased. The product

was treated with ice-water, and extracted with a mixture of benzene and ether. After washing the benzene solution with water and ice-cold 2% $NaHCO_3$ solution, it was dried over Na_2SO_4 and the solvent removed under vacuum. The product so obtained was used without further purification in the next step, as distillation caused decomposition.

3.1.5.3. 2-Phenylcyclobutane-1,1-dicarboxylic Acid (34) .

To a suspension of NaH (1.18g, 0.02mole, 50% in oil) in THF (24.6ml) was added, slowly with stirring and cooling, under N_2, diethyl (3-bromo-3-phenylpropyl) malonate (32) (0.02mole) in THF (2.46ml), at 0-5° over a period of 50 min. The mixture was allowed to stand at 20° overnight and THF was distilled until the internal temperature reached 80°. Ice was added and the mixture was diluted with water. After separating the organic layer, the aqueous phase was extracted three times with ether and the combined organic layers were washed once with water. The solvent was removed and the residue saponified by treatment with refluxing KOH solution (4.1g, 0.07mole in 12.3 ml of 50% EtOH) over 3h. Most of the solvent was removed under vacuum on a water-bath and the residue was taken up in water. The aqueous solution was washed twice with ether to remove the oil from the

NaH, and acidified with 37% HCl. The organic acid which separated was isolated by ether extraction and crystallized from chloroform, yielding 2-phenylcyclobutane-1,1-dicarboxylic acid (34) [4g, 74%, mp.173°, lit[53] mp.173-174°].

3.1.5.4. Decarboxylation of 2-Phenylcyclobutane-1,1-dicarboxylic acid ; 2-Phenylcyclobutanecarboxlic Acid (35) .

2-Phenylcyclobutane-1,1-dicarboxylic acid (34) (4g 0.02 mole) was heated at 10mm pressure and an oil bath-temperature of 200-210°. After distillation, the distillate (1.4g) was dissolved in a mixture of ether (1.65ml) and hexane (9.35ml), decanted from some insoluble oil, and chromatographed through a 50x150 mm column of 70-230 mesh silicagel. Elution was carried out with a 15:85 mixture of ether-hexane. Fractions of 100ml were collected. A good separation of cis-trans isomers could not be obtained. The following reactions were made as a mixture of isomers.

3.1.5.5. 2-Phenylcyclobutanecarbonyl Chloride (36) .

A solution of $SOCl_2$ (6ml, 0.08mole) in dry benzene (12ml) was added dropwise, with stirring, to 2-phenylcyclobutanecarboxylic acid (35)(3g, 0.022mole) in dry benzene (18ml). The reaction mixture was heated under reflux for 4h. Benzene and $SOCl_2$ were removed and the residue was distilled to yield (36) [2.3g, 70%, 100-120°(0.9mm)].

3.1.5.6. 2-Phenylcyclobutyl Diazomethyl Ketone (37) .

2-Phenylcyclobutanecarbonyl chloride (36) (2.3g, 0.01mole) was added to 3M excess ethereal diazomethane at 0°. The reaction was stirred overnight, the ether and excess diazomethane were removed and diazoketone (37) was obtained [2.36g, 100%].

3.1.5.7. Methyl (2-phenylcyclobutyl)acetate (38) .

2-Phenylcyclobutyl diazomethyl ketone (37) (2.36g 0.01mole) was dissolved in CH_3OH (19.5ml) and to it, silver benzoate (2.52g) in triethylamine (30ml) was added with stirring at room temperature. After stirring

overnight, the reaction mixture was filtered, excess methanol was removed and the remaining oil was taken in ether. It was neutralized with 2N HCl, washed with 10% Na_2CO_3 solution and H_2O. Evaporation of ether yielded (38) [1.2g, 50%].

3.1.5.8. 2-Phenylcyclobutylacetic Acid (39) .

Methyl (2-phenylcyclobutyl)acetate (38) (1.2g, 0.01mole) was saponified by refluxing with KOH (0.5g) in water (5.8ml) and ethanol (7.1ml) for 15h. The alcohol was removed and the alkaline residue was extracted with ether. The aqueous phase was then acidified and the liberated oil was taken up in ether. Evaporation of ether yielded (39) [1g, 89.5%, bp.138-144°(0.7mm), lit[54] bp.162°(1mm)].

3.1.5.9. 2-Phenylcyclobutylacetyl Chloride (40) .

Preparation was made following the same procedure as in the preparation of 2-phenylcyclobutanecarbonyl chloride (36) . Thionyl chloride (1.06ml) in dry benzene (2ml) and 2-phenylcyclobutylacetic acid (39) (1g, 0.01mole) in benzene (5.3ml) were used to yield (40) [0.7g,

63%, bp.102-104°(0.4mm)].

3.1.5.10. 2-Phenylcyclobutylcarbinyl Phenyl Ketone (29) .

Phenylmagnesium bromide was prepared from bromobenzene (1.8g,0.01mole) in dry ether (13.5ml) and Mg (0.28g, 0.01mole) in dry ether (13.5ml). Anhydrous $CdCl_2$ (1.56g, 0.01mole) was added to the cooled (ice-bath) Grignard solution, which was stirred for 5 min. at room temperature and refluxed for 75 min. until the Gilman test[51] for the Grignard reagent gave a negative result. Ether was distilled until it left a viscous black residue and replaced by benzene (16ml). The mixture was vigorously stirred and refluxed for 10 min. and then cooled in ice to 5°. 2-Phenylcyclobutylacetyl chloride (40) (1.2g, 0.01mole) in dry benzene (16ml) was introduced portionwise to the vigorously stirred suspension of Ph_2Cd in dry benzene (16ml) . The mixture was stirred at room temperature for 15 min., then at reflux for 12h., hydrolized with HCl. The organic layer was washed with Na_2CO_3 solution, then with H_2O and dried over $CaCl_2$. Removal of the solvent left an oily residue. This residue was purified firstly by column chromatography using Hexane:EtOAc (9:1) mixture. Then, it was obtained as colorless crystals after purifying with column using Hexane:EtOAc (16:1)

mixture [0.7g, 49%, mp.36-37°).

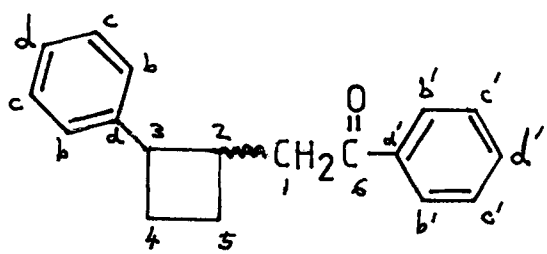
NMR ($CDCl_3$) : δ 1.6-2.6 complex m (4H, cyclobutyl-)
2.8-3.5 complex m (4H, cyclobutyl + CH_2)
7.2-8.2 complex (10H, Ar-)

IR (KBr pellet) : 1680 cm^{-1}

$C_{18}H_{18}O$ calc. C: 86.4 found C: 84.8
H: 7.2 H: 7.6

M^+: 250

^{13}C-NMR : C1,C3= 44.536, 46.847
C2 39.592 C5 25.399
C4 26.781 C6 199.004
Cb,Cc,Cd,Cb′,Cc′= 126.581,127.909,125.998,
128.351,128.171
Ca 143.956 Ca′ 137.8 Cd′ 132.690



Spectral Data for 3,4-Dimethylene-1-tetralone (40a).

NMR ($CDCl_3$) : δ 0.75-2.0 complex (6H, cyclobutyl-)

2.4-3.2 complex (2H, CH_2-)

7.0-8.0 complex (4H, Ar-)

Elemental Analysis of 40a:

$C_{12}H_{12}O$: calc. C : 83.72 found. C : 81.7

H : 6.976 H : 7.21

3.1.6. Synthesis of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) .

3.1.6.1. 2-Phenylpropane-1,3-diol (43).

Diethyl phenylmalonate (Aldrich) (130.7g, 0.55mole) was added, under N_2, to a stirred solution of $LiAlH_4$ (25g, 0.66mole) in ether (663ml) at a rate to maintain refluxing; refluxing and stirring were continued for all night. The cooled mixture was decomposed with 44.4ml of water and 880.3ml of 15% H_2SO_4; the ether layer was then washed and dried over Na_2SO_4. Fractionation gave an oil. The diol [42.4g, 51%, bp.120-130°(0.5mm), lit[55] bp.134-139°(0.7mm)] solidified on cooling and was used directly in the next step.

3.1.6.2. 2-Phenylpropane-1,3-diol-di-p-toluenesulfonate (44) .

To a solution of 2-phenylpropane-1,3-diol (43) (20.7g, 0.14mole) in 106.7ml of dry pyridine was added, below 10°, p-toluenesulfonyl chloride (54.2g, 0.28mole). After 12h. at 20° the mixture was treated with cold HCl , and the resulting solid filtered off. Recrystallization

from ethanol gave colorless crystals [51.7g, 80%, mp.127-128°, lit[55]mp.127.5-128°].

3.1.6.3. 3-Phenylcyclobutane-1,1-dicarboxylic Acid (46) .

A solution of 2-phenylpropane-1,3-diol-di-p-toluenesulfonate (44) (20g, 0.04mole) and diethyl malonate (7.58g, 0.05mole) in 266.67ml of dry dioxane was warmed almost to reflux under N_2, and a suspension of NaH (5.23g, 0.21mole) was added in 80 min. at a rate to cause spontaneous refluxing. After stirring and refluxing for 1h., further NaH (5.23g, 0.21mole) was added in 3h. After a further 15h. of refluxing, the dioxane was removed under reduced pressure, the residue treated with water, extracted with ether and the combined ether extracts were dried over $MgSO_4$. Fractionation gave diethyl 3-phenylcyclobutane-1,1-dicarboxylate (45) . [7.5g, 68%, bp.132-140°(0.5mm), lit[55] bp.126.5-129.5° (0.32mm)]. The ester was saponified in a refluxing solution of KOH (5.13g) in 50% EtOH (14.88ml) for 15h., solvent was removed under reduced pressure and the residue taken up in water. The aqueous solution was washed twice with ether, cooled, acidified with conc.HCl and the precipitated solid filtered off. Recrystallization was made from water to yield (46)

[5.81g, 49%, mp.180°, lit[55]mp.181-182° dec.].

3.1.6.4. 3-Phenylcyclobutanecarboxylic Acid (47)* .

3-Phenylcyclobutane-1,1-dicarboxylic acid (46) (15g, 0.07mole) was decarboxylated by heating at 200-210° for 30 min. The resulting oil was chromatographed on a 70-230 mesh silica column (65x3.5), using 10% ether in hexane and collecting 100ml fractions. After obtaining some oil from fractions no.7 and first 50ml part of no.8, 1.2g. of sticky solid was collected from the second 50ml part of fraction no.8. The solid (trans) acid [0.7g, 6%, mp.60-66°, lit[55]mp.65-66°] was pressed on a porous plate and recrystallized from hexane.

3.1.6.5. 3-Phenylcyclobutanecarbonyl Chloride (48).

A solution of $SOCl_2$ (5.7ml, 0.07mole) in sodium-dried benzene (11.4ml) was added dropwise, with stirring, to the solution of 3-phenylcyclobutane-carboxylic acid (2.85g, 0.02mole) in sodium-dried benzene

(* See footnote on p.54)

(17.1ml). The reaction mixture was heated under reflux, with stirring 4h. Benzene and $SOCl_2$ were removed by distillation and the residue was distilled to yield (48) [2.7g, 87%, bp.93-103°(0.5mm), lit[56]bp.132°(0.15mm)].

3.1.6.6. 3-Phenylcyclobutyl Diazomethyl Ketone (49) .

3-Phenylcyclobutanecarbonyl chloride (48) (2.7g, 0.01mole) was added to 3M excess ethereal diazomethane at 0^0. The reaction was stirred overnight, the ether and excess diazomethane were then removed and the diazoketone (49) [2.5g, 90%] was obtained .

3.1.6.7. Methyl (3-phenylcyclobutyl)acetate (50)

3-Phenylcyclobutyl diazomethyl ketone (49) (2.5g, 0.01mole) was dissolved in methanol (19.5ml). Silver benzoate (2.52g) in triethylamine (30ml) was added to it with stirring at room temperature. After stirring overnight, the reaction mixture was filtered, volatile material was removed and the remaining oil was taken up in ether. It was neutralized with 2N HCl, washed with 10% Na_2CO_3 and water, and then distilled to yield (50) [1.9g, 74.5%].

3.1.6.8. 3-Phenylcyclobutylacetic Acid (51) .

Methyl (3-phenylcyclobutyl)acetate (50) (1.9g,0.01mole) was saponified by refluxing with KOH (0.79g) in water (9.14ml) and ethanol (11.2ml, 95%) for 15-20h. The alcohol was removed and the alkaline residue was extracted with ether, the aqueous phase was acidified and the liberated oil was solidified to yield (51) [1.6g, 94%, mp.33-37°, lit[56] mp.36-37°].

3.1.6.9. 3-Phenylcyclobutylacetyl Chloride (52) .

Preparation was performed as in the case of 3-phenylcyclobutanecarbonyl chloride (48) . $SOCl_2$ (1.7ml) in benzene (3.2ml) and 3-phenylcyclobutylacetic acid (1.6g,0.01mole) in benzene (8.4ml) were used to yield (52) [1.3g, 74%, bp.120-122°(1.3mm)].

3.1.6.10. 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) .

It was prepared similar to the 1-phenyl and 2-phenylcyclobutylcarbinyl phenyl ketones, (16) and (29) . To prepare phenylmagnesium bromide, bromobenzene (1.2g) in ether (9ml) and Mg (0.19g) in ether (9ml) were used.

Ph_2Cd was obtained using anhydrous $CdCl_2$(1.04g, 0.01mole) in benzene (10.56ml). 3-Phenylcyclobutylacetyl chloride (52) (0.8g, 0.004mole) in benzene (10.56ml) was added to the suspension of Ph_2Cd. After refluxing for 12h. ,the reaction mixture was hydrolized and extracted with ether. Removal of the solvent left an oily residue. It was purified with column and tlc. Hexane-EtOAc (16:1) mixture was used [0.7g, 73%, mp.30-31°].

NMR ($CDCl_3$) : δ 1.8-4.2 complex m (6H, cyclobutyl-)
3.3-3.5 doublet (2H, CH_2-)
7.2-8.3 complex m (10H, Ar-)

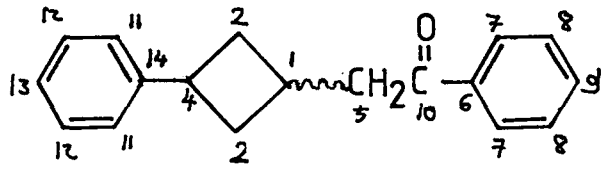
IR (KBr pellet) : 1685 cm^{-1} (C=O)

$C_{18}H_{18}O$ calc. C: 86.4 found. C: 85.56
H: 7.20 H: 7.19

M^+: 250

^{13}C-NMR : C1 36.169 C6 136.946
C2 34.069 C9 132.750
C3 27.362 C10 199.318
C4 45.367 C14 145.736
C5 44.437
C7,C8,C11,C12,C13= 128.374,128.098,126.192,

127.878,125.560



3.1.7. Synthesis of Isovalerophenone (53) .

3.1.7.1. Isovaleric Acid (55) .

Dilute H_2SO_4 (140ml conc.H_2SO_4+ 85ml H_2O) and redistilled iso-amyl alcohol (54) (80g, 0.91mole) mixture was added portionwise to the $Na_2Cr_2O_7$ (200g in 400ml H_2O) solution during a period of 2.5h. When all the alcohol was added, the mixture was refluxed for 30min., 350ml of the distillate was collected by distillation. KOH (30g) pellets were added to the distillate. Upper ester (isoamyl isovalerate) layer was removed and aqueous layer was treated with dilute H_2SO_4 (30ml) (1:1 by volume) and the liberated isovaleric acid was extracted with CCl_4. It was dried with anhydrous $MgSO_4$ and distilled to yield (55) [38g, 41%, bp.160-165°, lit[51]bp.172-176°].

3.1.7.2. Isovaleryl Chloride (56).

Isovaleric acid (55) (4.23g, 0.04mole) was added to redistilled $SOCl_2$ (3.7ml, 0.05mole) at 30-40°. When all the acid was added, it was heated for 30 min. and distilled to yield (56) [4.77g, 99%, bp.108-112°, lit[51]bp.114.5-115.5°(771mm)] .

3.1.7.3. Isovalerophenone (53) .

Isovaleryl chloride (56) (1.98g, 0.02mole) was added to dry benzene (4.25ml, 0.05mole) containing anhydrous $AlCl_3$ (2.26g, 0.02mole) during a period of 2h. The reaction mixture darkened considerably and was refluxed for additional 30min. to complete the reaction. It was then cooled and hydrolized with cold water. The upper oily layer was separated, washed with 10% NaOH solution, water, and dried over anhydrous $MgSO_4$. Benzene was removed and the residue was distilled to yield (53) [0.65g, 25%, bp.112-118°(25mm), lit[51]bp.128°(55mm)] .

3.1.8. Synthesis of Butyrophenone (57) .

3.1.8.1. n-Butyryl Chloride (59) .

n-Butyric acid (58) (22g, 0.25mole) was added to $SOCl_2$ (37.5g, 0.32mole). It was refluxed for half an hour and distilled to yield (59) [28g, 50%, bp.100-101°, lit[51]bp.100-101°] .

3.1.8.2. Butyrophenone (57) .

n-Butyryl chloride (59) (12.36g, 0.11mole) was added to dry benzene (31ml, 0.35mole) containing anhydrous $AlCl_3$ (16.5g, 0.12mole) during a period of 2h. The reaction mixture darkened considerably and was refluxed for 30min. to complete the reaction. Then, it was cooled and hydrolyzed with cold water. The upper oily layer was separated, washed with 10% NaOH solution, water, and dried over anhydrous $MgSO_4$. Benzene was removed and the residue was distilled to yield (57) [10g, 58%, bp.220-223°, lit[51] bp.227-230°] .

3.1.9. Synthesis of 3-Cyclobutyl-1-phenyl-1-propanone (60).

3.1.9.1. Cyclobutylcarbinyl Diazomethyl Ketone (61) and Methyl (3-cyclobutyl)Propionate (62) .

Cyclobutylacetyl chloride (15) (2g, 0.02mole) (see p.90) was treated with CH_2N_2 (1.89g,0.05mole) in dry ether. It was stirred overnight and then the diazoketone (61) (1.8g, 0.01mole) was obtained by evaporation of ether. Compound (61) (1.8g, 0.01mole) was dissolved in CH_3OH (20.3ml), and onto it, silver benzoate (2.6g) in

triethylamine (31ml) was dropped. It was stirred overnight, then the mixture was filtered, CH_3OH was evaporated, and the residue was taken in ether, neutralized with 2N HCl, washed with 10% Na_2CO_3 and water. Removal of solvent yielded (62) [1.2g, 56%, lit[57]] .

3.1.9.2. Cyclobutanepropionic Acid (63) .

Methyl (3-cyclobutyl)propionate (62) (1.2g, 0.01mole) was saponified with KOH (0.75g) in H_2O (8.6ml) and EtOH (10.7ml). After refluxing for 6h., EtOH was evaporated and the residue was dissolved in H_2O and extracted with ether. The aqueous phase was acidified with HCl and the liberated oil was taken up in ether, which was removed to yield (63) [0.8g, 74%, bp.140-150°(30mm), lit[58]bp.125°(30mm)] .

3.1.9.3. Cyclobutanepropionyl Chloride (64) .

Cyclobutanepropionic acid (63) (0.8g, 0.01mole) was added to $SOCl_2$ (0.56ml, 0.01mole). The mixture was refluxed for half an hour, and distilled to yield (64) [0.1g, 11%, bp.164°(685mm), lit[59]] .

3.1.9.4. 3-Cyclobutyl-1-phenyl-1-propanone (60) .

Cyclobutanepropionyl chloride (64) (0.1g, 0.001mole) was added to dry benzene (0.2ml, 0.002mole) containing anhydrous $AlCl_3$ (0.1g, 0.001mole). The remaining steps were made as in the case of isovalerophenone (53) (see p.118). The ketone (60) was purified by tlc (Hexane:EtOAc; 16:1). [0.05g, 36%, lit[60]].

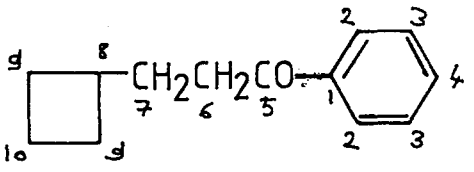
NMR ($CDCl_3$): δ 1.5-2.5 complex m (8H, cyclobutyl+ CH_2)
2.6-3.2 triplet (2H, CH_2)
7.2-8.2 complex (5H, Ar-)

IR (neat): 1680 cm^{-1}

$C_{13}H_{16}O$ calc. C: 82.978 found. C: 82.29
H: 8.51 H: 8.77

M^+: 188

^{13}C-NMR : C1 137.8 C4 132.856
C2 128.550 C5 202.000
C3 128.104 C6 36.348
C7,C8,C9,C10= 31.596,35.00,28.107,18.354



3.1.10. Synthesis of 1-Phenylpent-4-ene-1-one (65)

n-Butyl-lithium (Aldrich) (1.6M in hexane, 22.5ml, 0.012mole) was added to an ice-bath stirred solution of diisopropyl amine in dry THF under Argon atmosphere. After stirring at room temperature, a clear pale yellow solution was obtained. It was cooled to -78° in CH_3OH-liquid N_2 and acetophenone (Merck) (3.5ml, 0.01mole) in dry THF was added. It was left for 5h. It was cooled again to -78° in CH_3OH-liquid N_2 and allyl bromide (67) (3ml, 0.01mole) in THF was added. The mixture was left overnight, 1N HCl and saturated NH_4Cl solutions were successively added and extracted with ether. Ether phase was washed with saturated NaCl and dried over $MgSO_4$. Ether was then evaporated and the residue separated with tlc, (Hexane:EtOAc; 16:1) to yield (65) [0.14g, 8.75%, lit[61] bp.125-127°(16mm)] .

3.1.11. Synthesis of 4-Methyl-1-phenyl-1-pentanone (68) .

3.1.11.1. Isobutyl Diazomethyl Ketone (69) and Methyl (4-methyl)pentanoate (70) .

Isovaleryl chloride (56) (2.4g,0.02mole) (see.p.117) was treated with CH_2N_2 (2.5g, 0.06mole) to obtain

diazoketone (69) . Compound (69) (2.7g, 0.02mole) was dissolved in CH_3OH (33.4ml) and onto it, silver benzoate (4.3g) in triethyl amine (51.14ml) was added. After stirring overnight at room temperature, the reaction mixture was filtered, CH_3OH was evaporated and the remaining oil was taken in ether. It was neutralized with 2N HCl, washed with 10% Na_2CO_3 and H_2O. Ether was evaporated to yield (70) [0.6g, 25%, lit[62]].

3.1.11.2. 4-Methylpentanoic Acid (71) .

Methyl (4-methyl)pentanoate (70) (0.6g, 0.005mole) was saponified by refluxing with KOH (0.41g) in H_2O (4.7ml) and EtOH 95% (5.87ml) for 6h. The alcohol was removed, the residue was extracted with ether, the aqueous phase was acidified and the liberated oil was taken in ether. Ether was evaporated to obtain the acid (71) [0.5g, 94%, lit[62]].

3.1.11.3. 4-Methylpentanoyl Chloride (72) .

4-Methylpentanoic acid (71) (0.5g, 0.004mole) was added to $SOCl_2$ (0.39ml, 0.006mole). It was heated for half an hour and then distilled to yield (72) [0.3g,

0.52%, bp.112°(685mm), lit[63]].

3.1.11.4. 4-Methyl-1-phenyl-1-pentanone (68) .

4-Methylpentanoyl chloride (72) (0.3g, 0.002mole) was added to dry benzene (0.6ml, 0.007mole) containing anhydrous $AlCl_3$ (0.3mole, 0.002mole). The remaining steps were made as in the case of isovalerophenone (53) (see. p.11 8). The ketone (68) [0.2g, 52%, lit[64]bp.255-256°] was purified by tlc (Hexane:EtOAc; 16:1).

3.1.12. Synthesis of Cyclopropyl Phenyl Ketone (73) .

3.1.12.1. Cyclopropanecarbonyl Chloride (75) .

Cyclopropanecarboxylic acid (74) (5.45g, 0.06mole) was added to $SOCl_2$ (5.7ml, 0.08mole). The mixture was refluxed for half an hour and distilled to yield (75) [6.2g, 94%, bp.112-120°(685mm), lit[65]bp.119°] .

3.1.12.2. Cyclopropyl Phenyl Ketone (73) .

Cyclopropanecarbonyl chloride (75) (0.4g, 0.004mole) was added to dry benzene (1ml, 0.01mole) containing anhydrous $AlCl_3$ (0.54g, 0.004mole) during a period of 2h. The remaining steps were made as in the case of isovalerophenone (53) (see.p.118). [0.4g, 72%, bp.120-122°(14mm), lit[65]bp.121-123°(15mm)] .

3.1.13. Synthesis of Cyclobutyl Phenyl Ketone (76) .

Cyclobutanecarbonyl chloride (10) (see.p.88) (0.5g, 0.004mole) was added to dry benzene (1.15ml, 0.01mole) containing anhydrous $AlCl_3$ (0.61g, 0.005mole) during a period of 2h. The remaining steps were made as in the case of isovalerophenone (53) (see.p.118) [0.6g, 87%, bp.124-127°(9mm), lit[65]bp.114-118°(7mm)] .

3.1.14. Synthesis of Isobutyrophenone (77) .

3.1.14.1. Isobutyryl Chloride (79) .

Isobutyric acid (78) (3g, 0.04mole) was added dropwise to the $SOCl_2$ (1.82ml, 0.04mole). The mixture

was refluxed for half an hour and distilled to yield (79) [3g, 83%, bp.89°, lit[65]bp.91-93°] .

3.1.14.2. Isobutyrophenone (77) .

Isobutyrl chloride (79) (3g, 0.03mole) was added to dry benzene (8ml, 0.03mole) during a period of 2h. The remaining steps were made as in the case of isovalerophenone (53) (see.p.118) [2.6g, 63%, bp.214°, lit[65]bp.217°] .

3.1.15. Synthesis of Propiophenone (80) .

3.1.15.1. Propionyl Chloride (83) .

Propionic acid (82) (5g, 0.07mole) was added dropwise to $SOCl_2$ (6.07ml, 0.08mole). The mixture was refluxed for half an hour and distilled to yield (83) . [4g, 64.5%, bp.72°, lit[66]bp.77-79°] .

3.1.15.2. Propiophenone (80).

Propionyl chloride (83) (2.66g, 0.03mole) was

added to dry benzene (8.2ml, 0.09mole) containing anhydrous $AlCl_3$ (4.17g, 0.03mole) during a period of 2h. The remaining steps were made as in the case of isovalerophenone (53) (see.p.118) [2.31g, 60%, bp.214°, lit[65]bp.218°] .

3.1.16. Synthesis of 3,3-Dimethylbutyrophenone (81) .

3.1.16.1. 3,3-Dimethylbutanoyl Chloride (85) .

3,3-Dimethylbutanoic acid (84) (Merck) (4.55g, 0.04mole) was added dropwise to $SOCl_2$ (3.5ml, 0.05mole). The mixture was refluxed for half an hour and distilled to yield (85) [4.4g, 83%, bp.90-120°(685mm), lit[65]bp.127-129°] .

3.1.16.2. 3,3-Dimethylbutyrophenone (81) .

3,3-Dimethylbutanoyl chloride (85) (2g, 0.015mole) was added to dry benzene (3.95ml, 0.04mole) containing anhydrous $AlCl_3$ (2.1g, 0.02mole) during a period of 2h. The remaining steps were made as in the case of isovalerophenone (53) (see.p.118) [2g, 77%, bp.108-110°(10mm), lit[66]bp.110-111°(11mm)] .

3.2. Kinetic Measurements:

Varian T-60A NMR spectrometer (probe temperature 30°) was used throughout the rate measurements. Pyridine was dried over KOH pellets and molecular sieves. A stock solution of 0.2M NaOH in D_2O was prepared.

3.2.1. Procedure.

The ketone pair was dissolved in pyridine in the nmr tube. The stock solution was then added to the solution in the nmr tube, the contents were shaken rapidly and the tube was then placed into the probe of the spectrometer for integration of the peaks due to the exchanging protons. The stopwatch was started and continued to take integrals until the exchange of faster exchanging ketone was complete. Readings were taken at suitable intervals. Since the observed rate was first order, the first time reading was taken as initial zero time. The quantities of the ketones, pyridine, and the stock solution to be placed in the nmr tube were determined by trial and error until the sufficient signal for the nmr integration was obtained. A measurable speed of exchange was obtained; for the faster exchanging

ketone pairs, the amount of stock solution was reduced and the solution in the tube was diluted with D_2O before adding the stock solution. Exchanges were usually followed to more than one half-life.

3.2.2. Treatment of Experimental Results.

Exchange was assumed to be as effectively irreversible during its initial stages. Pseudo-first order kinetics was assumed and logI was plotted vs. time, where I is the integral amplitude at a given time corresponding to the reacting site in question.

The observed pseudo-first order rate constant, k_o, and the bimolecular rate constant, k, could have been obtained from the slopes of the plots mentioned above and from the base concentration, by means of the equations $k_o = 2.303 \times slope$ and $k = k_o/[OD^-]$. Since, in the present work, the interest was to measure the relative rates of each ketone pair, the ratio of the slopes of each corresponding line gave the ratio of the bimolecular rate constants; i.e., $k_1/k_2 = slope_1/slope_2$, where the subscripts refer to the components 1 and 2, according to the equation shown below.

$$k_1/k_2 = \frac{k_{o1}/[OD^-]}{k_{o2}/[OD^-]} = \frac{2.303 \times slope_1/[OD^-]}{2.303 \times slope_2/[OD^-]} = \frac{slope1}{slope2}$$

The assumption that the exchange was effectively irreversible especially during the initial stages, and the pseudo-first order kinetic behaviour was tested by observing the exchange of isovalerophenone (53) at different base concentrations, the relative strengths of which were varied from 4 to 1. The slopes of these straight lines (graph 1) were then plotted against the relative base concentration (graph 2) to give a further straight line which indicates first order dependence of reaction rate on base concentration, and hence pseudo-first order behaviour in individual kinetic runs. In the ketone pairs, where the number of exchanging hydrogens in one of the molecule is different from two (acetophenone, cyclopropyl phenyl ketone, cyclobutyl phenyl ketone, and isopropyl phenyl ketone) the relative rates have been corrected for two hydrogens.

Rate of Exchange of Isovalerophenone (53) at Different Base Concentrations (graph 1).

Run I : 50μl ketone (53), 350μl pyridine, 50μl stock solution of base.

Relative Base Concentration : 4

I(mm)	logI	time(sec)
15.0	1.176	0
15.0	1.176	120
14.5	1.162	180
14.5	1.162	240
14.0	1.146	300
14.0	1.146	360
13.0	1.114	420
13.0	1.114	480
12.5	1.097	540
12.0	1.079	600
12.0	1.079	660
11.0	1.042	720
11.0	1.042	780
10.5	1.022	840
10.0	1.000	900
10.0	1.000	960
9.5	0.978	1020
9.0	0.954	1080

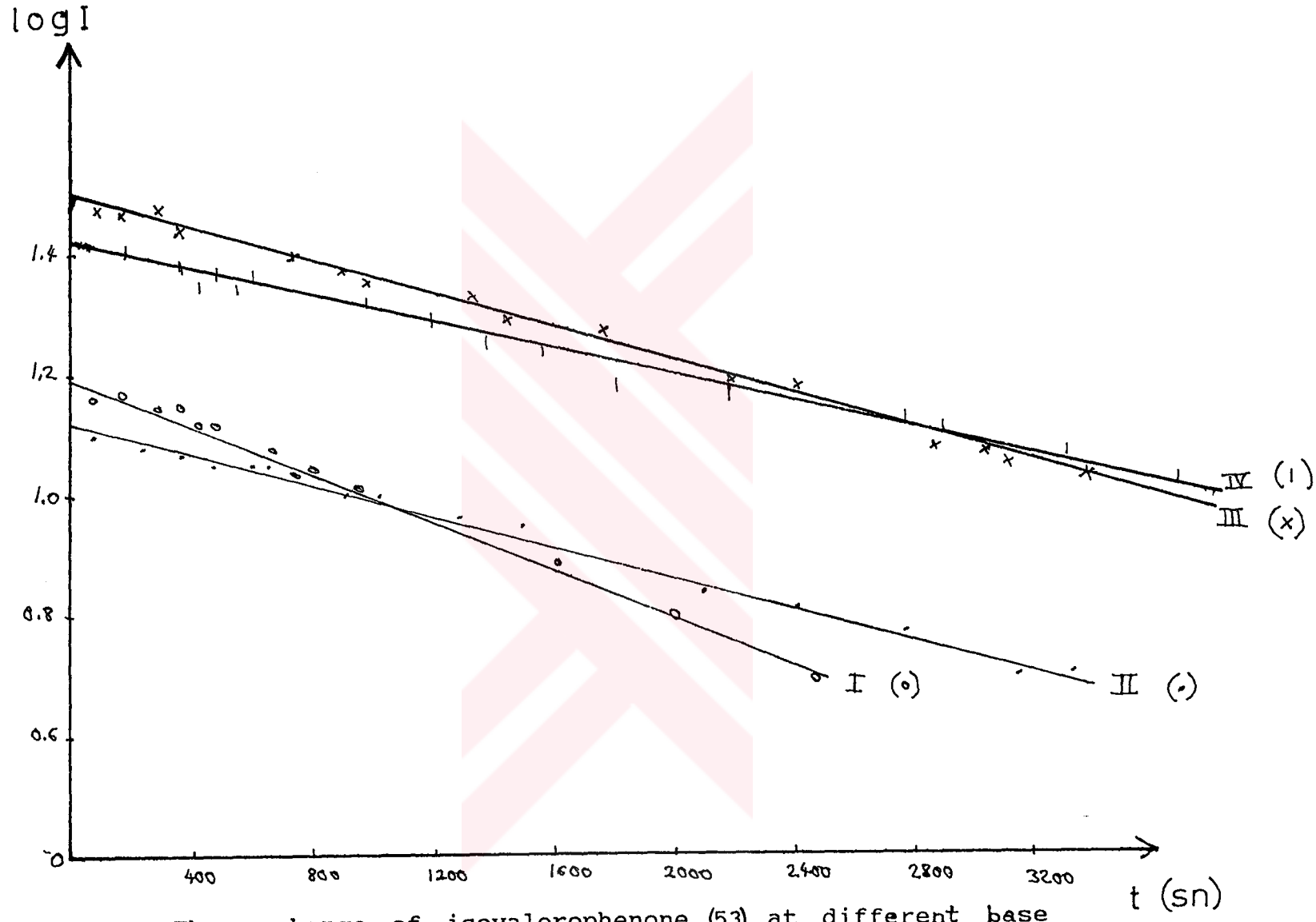
9.0	0.954	1140
9.0	0.954	1200
9.0	0.954	1260
9.0	0.954	1320
9.0	0.954	1380
9.0	0.954	1440
9.0	0.954	1500
9.0	0.954	1560
8.0	0.903	1620

Slope (graph 1): -19×10^{-5}

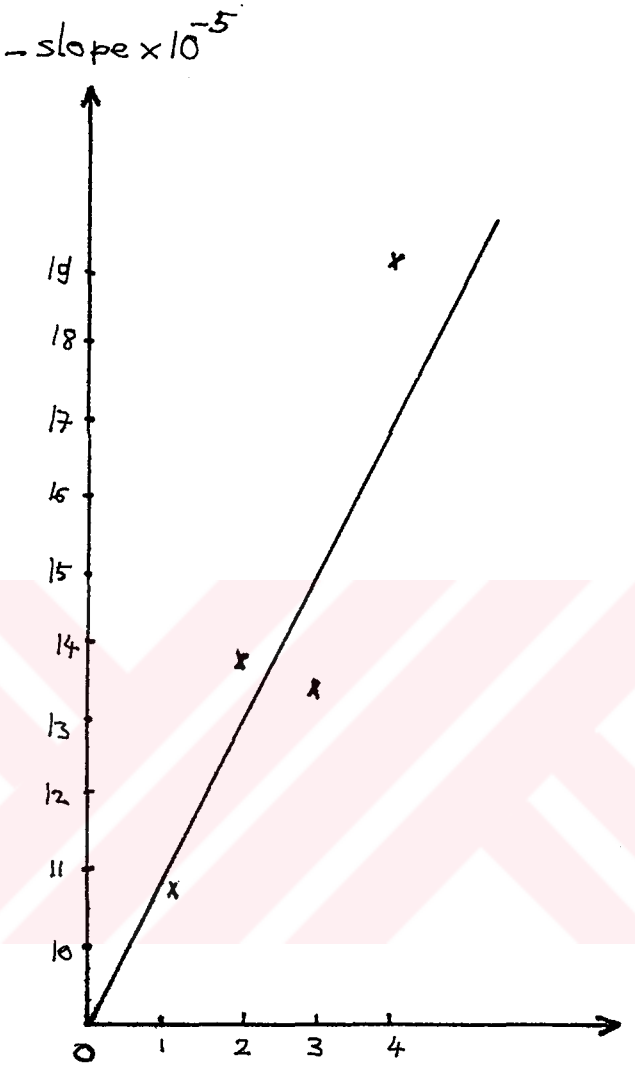
The conditions and results for runs II, III, IV are summarized below in the table 5 . In all runs 50μl of ketone (53) and 350μl of pyridine were used.

Table 5. Relative Base Concentrations and Slopes of (53).

Run	vol.stock soln.(μl)	vol.D_2O (μl)	relative base conc.	slope (graph 1)
II	37.5	12.5	3	-13.3×10^{-5}
III	25.0	25.0	2	-13.7×10^{-5}
IV	12.5	37.5	1	-10.7×10^{-5}



Graph 1. The exchange of isovalerophenone (53) at different base concentrations.



Graph 2. Relative base concentration.

3.2.3. Competition Experiments.

1. Relative Rate of Exchange of Cyclobutylcarbinyl Phenyl Ketone (8) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of Isovalerophenone (53) (integral amplitude I_2) and Cyclobutylcarbinyl Phenyl Ketone (8) (integral amplitude I_1).

Run I: Cyclobutylcarbinyl Phenyl Ketone (8) (0.02593g) and Isovalerophenone (53) (0.02402g) were dissolved in 350μl of pyridine and treated with 50μl of stock solution of base .

t(min.)	$\log I_1$	$\log I_2$
3	1.301	1.398
4	1.301	1.431
5	1.290	1.431
6	1.204	1.431
8	1.176	1.398
9	1.146	1.361
10	1.130	1.342
12	1.041	1.322

13	1.041	1.322
15	1.000	1.301
17	0.977	1.279
18	0.954	1.255
20	0.903	1.230

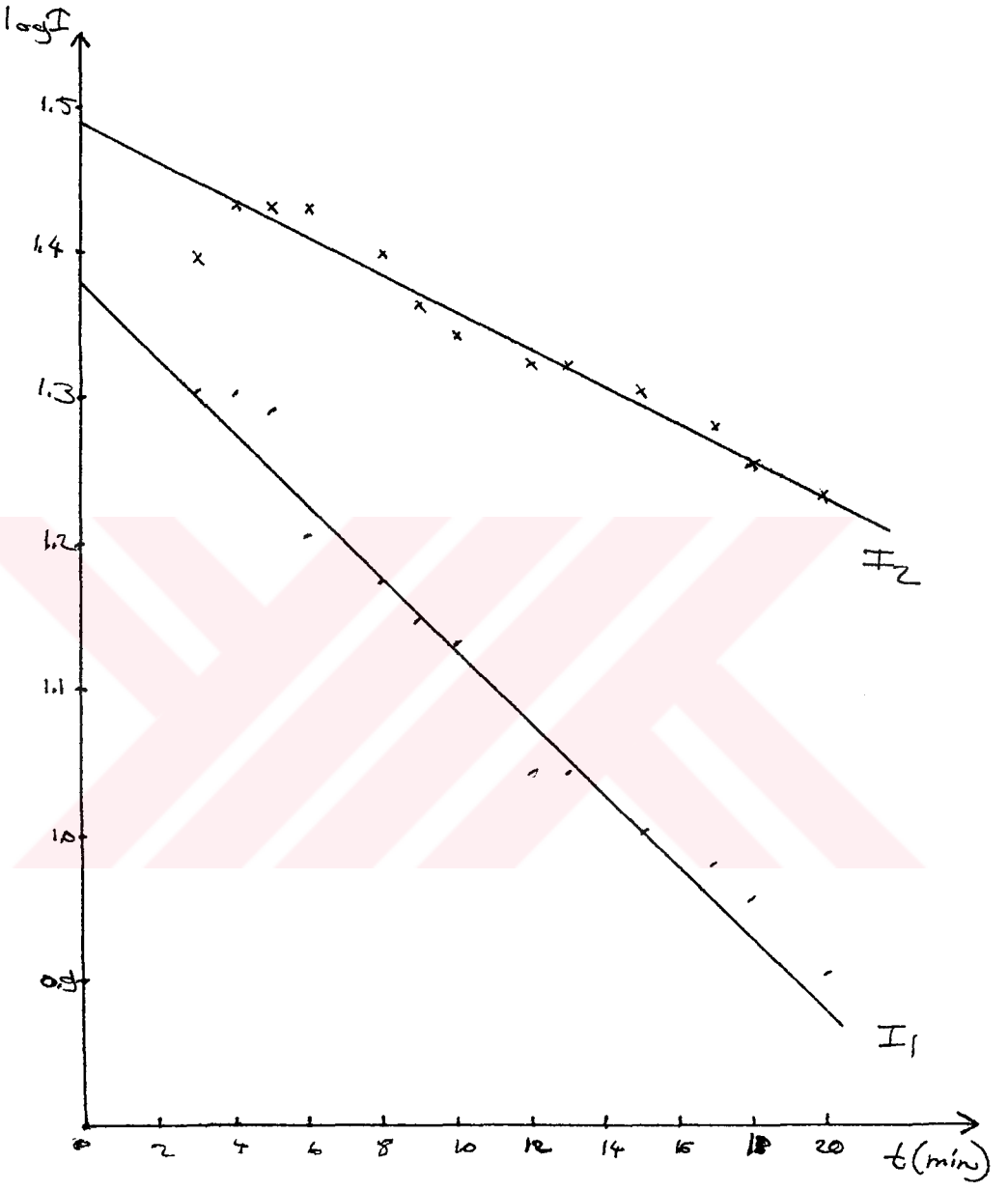
Run II: Cyclobutylcarbinyl Phenyl Ketone (8) (0.02415g) and Isovalerophenone (53) (0.02750g) were dissolved in 350μl of pyridine and treated with 50μl of stock solution of base.

t(min.)	$\log I_1$	$\log I_2$
2	1.061	1.415
3	1.041	1.398
6	0.845	1.361
7	0.845	1.371
11.5	0.845	1.322
13.0	0.778	1.301
22.0	0.699	1.176
25.0	0.477	1.176

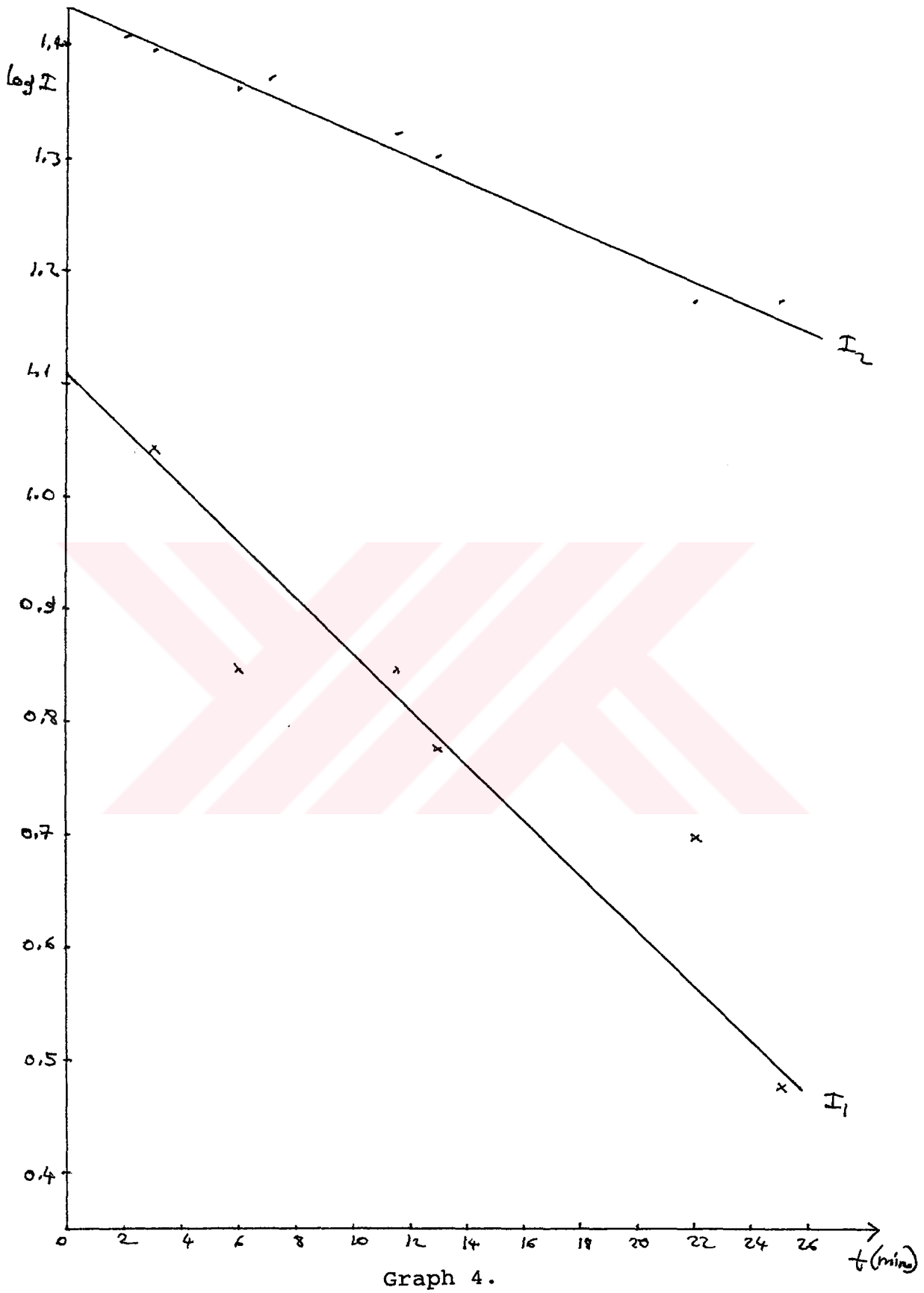
Run III: Cyclobutylcarbinyl Phenyl Ketone (8) (0.02318g) and Isovalerophenone (53) (0.02617g) were dissolved in 350μl pyridine and treated with 50μl of stock solution of base .

t(min.)	$\log I_1$	$\log I_2$
1.5	1.431	1.462
3.0	1.415	1.462
4.0	1.415	1.447
5.0	1.406	1.447
7.0	1.415	1.439
8.0	1.397	1.439
13.0	1.380	1.431
14.0	1.371	1.415
16.0	1.361	1.415
28.5	1.342	1.407
31.0	1.301	1.407

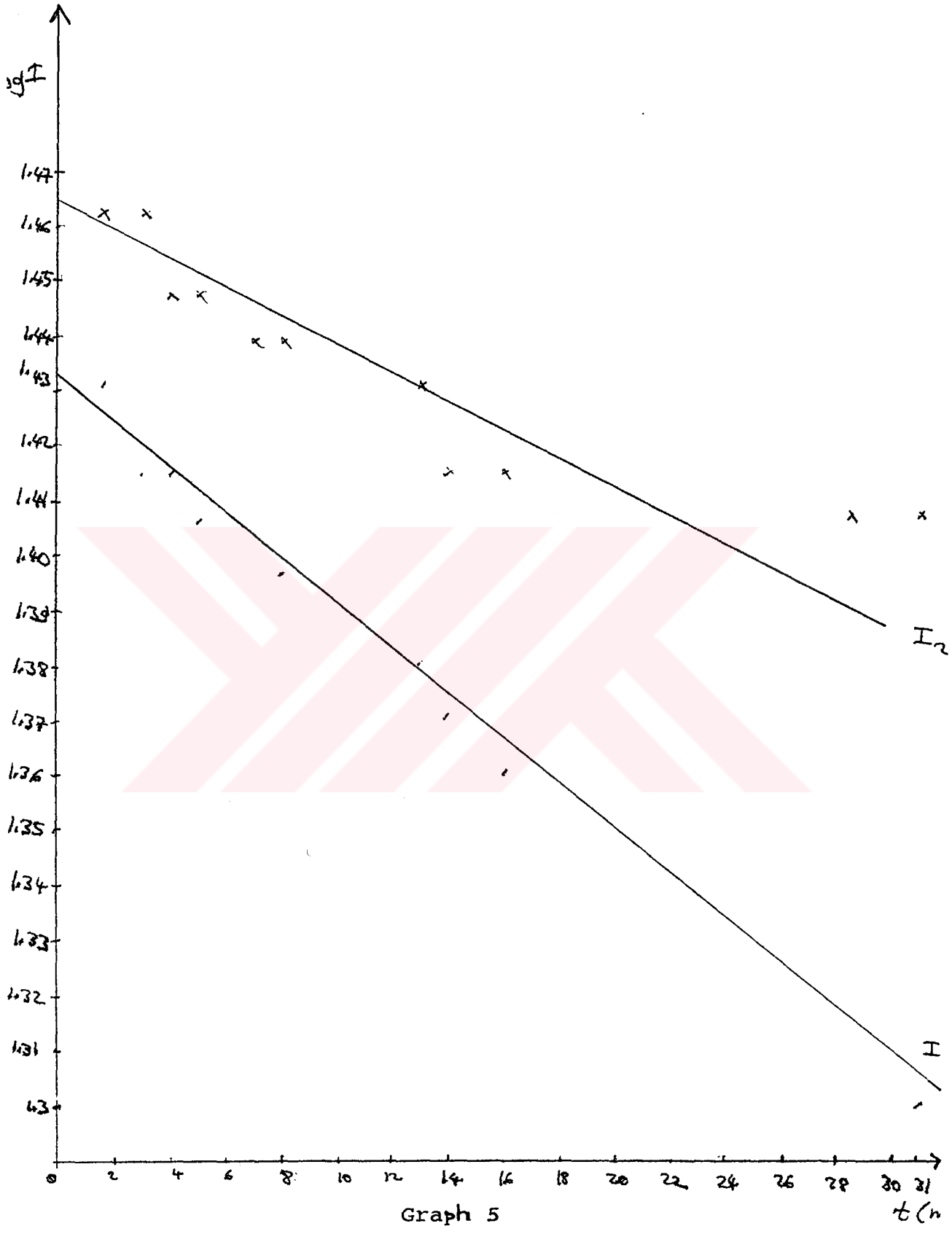
The data obtained in runs I, II, and III are plotted ($\log I_1$ and $\log I_2$ vs. time) in graphs III, IV, and V . The ratios of the slopes of the two straight lines (due to exchange of (8) and to that of (53)) in each graph are 2.2, 1.9, and 2.0 respectively. The average relative slope is taken as 2.0 .



Graph 3.


log I
1,4
1,3
1,2
1,1
1,0
0,9
0,8
0,7
0,6
0,5
0,4
0
2
4
6
8
10
12
14
16
18
20
22
24
26
t (min)
I2
I1

Graph 4.


lgI
1.47
1.46
1.45
1.44
1.43
1.42
1.41
1.40
1.39
1.38
1.37
1.36
1.35
1.34
1.33
1.32
1.31
1.3
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
31
I2
I
t (h

Graph 5

The data for most other relative rate measurements, where the signals due to the exchanging protons in each ketone did not overlap with those of other protons and thus made the direct measurements of the integral amplititudes in question possible, are obtained similarly. The experimental conditions and the results of those measurements will be given in the following sections.

2. Relative Rate of Exchange of Acetophenone (66) .

Measurement of the Relative Rates of Exchange of α-Methylene protons of Isovalerophenone (53) and Acetophenone (66) .

Run	vol.(53) (μl)	vol.(66) (μl)	vol.pyridine (μl)	vol.stock soln.(μl)	k(70)/k(51)
1	75	30	350	50	3.2
2	30	30	350	50	3.3

Average relative rate of exchange of (66) : 3.2

3. Relative Rate of Exchange of Propiophenone (80) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of Acetophenone (66) and Propiophenone (80) .

Run	vol.(80) (μl)	vol.(66) (μl)	vol.pyridine (μl)	vol.stock (μl)	k(80)/k(70)
1	50	25	350	50	0.87
2	50	20	350	50	0.94

k_{rel} to (53) : 2.8, 3.0 .

Average relative rate of exchange of (80) : 2.9

4. Relative Rate of Exchange of 3,3-Dimethylbutyrophenone (81) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 3,3-dimethylbutyrophenone (81) and 1-phenylcyclobutylcarbinyl phenyl ketone (16) .

Run	wt (81) (g)	vol.& wt. (16) (μl)&(g)	vol.pyr. (μl)	vol.stock (μl)	k(81)/k(16)
1	0.01107	30μl	350	50	0.55

2	0.03661	0.00766g	350	50	0.47

k_{rel} to (53) : 0.52, 0.45 .

Average relative rate of exchange of (81) : 0.49

5. Relative Rate of Exchange of Isobutyrophenone (77) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of Isobutyrophenone (77) and Isovalerophenone (53) .

Run	vol.(77) (μl)	vol.(53) (μl)	vol.pyr. (μl)	vol.stock soln.(μl)	k(77)/k(53)
1	30	20	350	50	0.54
2	25	25	350	50	0.44

Average relative rate of exchange of (77) : 0.49

6. Relative Rate of Exchange of 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 1-Phenylcyclobutylcarbinyl Phenyl

Ketone (16) and Isovalerophenone (53) .

Run	wt.(16) (g)	wt.(53) (g)	vol.pyr. (μl)	vol.stock (μl)	k(14)/k(53)
1	0.00684	0.00886	350	50	0.94
2	0.04093	0.04093	350	50	0.98

Average relative rate of exchange of (16) : 0.96

7. Relative Rate of Exchange of 1-p-Nitrophenylcyclobutylcarbinyl Phenyl Ketone (28) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 1-p-Nitrophenylcyclobutylcarbinyl Phenyl Ketone (28) and Isovalerophenone (53) .

Run	wt.(28) (g)	wt.(53) (g)	vol.pyr. (μl)	vol.stock soln.+D_2O(μl)	k(26)/k(53)
1	0.01654	0.02443	350	15+35	3.7
2	0.00649	0.02474	350	10+40	4.4
3	0.00706	0.02406	350	50+0	4.9

Average relative rate of exchange of (28) : 4.3

8. Relative Rate of Exchange of 3-Phenylcyclobutylcarbinyl Phenyl Ketone (41) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 3-phenylcyclobutylcarbinyl phenyl ketone (41) and 1-o-nitrophenylcyclobutylcarbinyl phenyl ketone (27) .

Run	wt.(41) (g)	wt.(27) (g)	vol.pyr. (μl)	vol.stock soln.(μl)	k(41)/k(27)
1	0.04144	0.00703	350	50	0.50
2	0.02472	0.00737	350	50	0.37

k_{rel} to (53) : 3.7, 2.7 .

Average relative rate of exchange of (41) : 3.2

9. Relative Rate of Exchange of 1-o-Nitrophenylcyclobutylcarbinyl Phenyl Ketone (27) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 1-o-Nitrophenylcyclobutylcarbinyl Phenyl Ketone (27) and Isovalerophenone (53) .

Run	wt.(27) (g)	vol.& wt.(53) (μl)&(g)	vol.pyr. (μl)	vol.stock soln.+D_2O(μl)	k(27)/k(53)
1	0.00879	20μl	350	50+0	6.5
2	0.00687	25μl	350	50+10	8.42
3	0.00687	0.02437g	350	40+10	7.40

Average relative rate of exchange of (27) : 7.4

10. Relative Rate of Exchange of 1-Phenylpent-4-ene-1-one (65) and 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 1-Phenylpent-4-ene-1-one (65) .

Run	wt.(65) (g)	wt.(16) (g)	vol.pyr. (μl)	vol.stock soln.(μl)	k(65)/k(16)
1	0.02035	0.00938	350	50	2.9
2	0.02549	0.00825	350	50	2.9

k_{rel} to (53) : 2.8, 2.8 .

Average relative rate of exchange of (65) : 2.8

11. Relative Rate of Exchange of 4-Methyl-1-phenyl-1-pentanone (68) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 4-Methyl-1-phenyl-1-pentanone (68) and 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Run	wt.(68) (g)	wt.(16) (g)	vol.pyr. (μl)	vol.stock (μl)	k(68)/k(16)
1	0.01973	0.01045	350	50	1.0
2	0.01923	0.01045	350	50	1.3
3	0.01937	0.00834	350	50	1.4

k_{rel} to (53) : 0.96, 1.25, 1.34 .

Average relative rate of exchange of (68) : 1.2

12. Relative Rate of Exchange of 3-Cyclobutyl-1-phenyl-1-propanone (60) .

Measurement of the Relative Rates of Excnange of α-Methylene Protons of 3-Cyclobutyl-1-phenyl-1-propanone (60) and 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Run	wt.(60) (g)	wt.(16) (g)	vol.pyr. (μl)	vol.stock (μl)	k(60)/k(16)
1	0.02112	0.00990	350	50	1.3
2	0.03046	0.00937	350	50	1.3

k_{rel} to (53) : 1.2, 1.2 .

Average relative rate of exchange of (60) : 1.2

13. Relative Rate of Exchange of Cyclobutyl Phenyl Ketone (76) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of Cyclobutyl Phenyl Ketone (76) and Isovalerophenone (53) .

Run	vol.(76) (μl)	vol.(53) (μl)	vol.pyr. (μl)	vol.stock soln.(μl)	k(76)/k(53)
1	25	25	350	50	1.8
2	20	30	350	50	1.5

Average relative rate of exchange of (76) : 1.6

14. Relative Rate of Exchange of 3,3-Trimethylene-1-indanone (26) .

Measurement of the Relative Rates of Exchange of α-Methylene Protons of 3,3-Trimethylene-1-indanone (26) and 1-Phenylcyclobutylcarbinyl Phenyl Ketone (16) .

Run	vol.& wt.(26) (μl)&(g)	wt.(16) (g)	vol.pyr. (μl)	vol.stock soln.+D_2O(μl)	k(26)/k(16)
1	10μl	0.02144	350	35+15	9.5
2	0.01199g	0.01208	350	35+15	11.3
3	0.01199g	0.01208	350	35+15	11.3

k_{rel} to (53) : 9.12, 10.85, 10.85 .

Average relative rate of exchange of (26) : 11

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