PHOTOCHEMICAL STUDIES OF α-SUBSTITUTED PROPIOPHENONES AND CONSTRUCTION OF BICYCLO[m.3.0] BRIDGED ALKENES: THERMAL REARRANGEMENT OF SPIROCYCLIC VINYLCYCLOPROPANES

A Thesis
Submitted to the
University of Poona
for the Degree of
Doctor of Philosophy
[in Chemistry]

By

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APRIL 1995

Dedicated to

my Wife

CERTIFICATE

CERTIFIED that the work incorporated in the thesis entitled "***Photochemical Studies of α-substituted propiophenones and construction of bicyclo [m.3.0] bridged alkenes: Thermal rearrangement of spirocyclic vinylcyclopropanes***" submitted by **Mr. Gulam Mohammed Nazeruddin**, was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr.H.R.Sonawane)
Research Guide

NCL, Pune 411 008.
April 1995

ACKNOWLEDGEMENTS

It is with a deep sense of gratitude that I record my sincere thanks to Dr.H.R.Sonawane, Scientist Emeritus, NCL, for his keen interest in my work, invaluable guidance, drive towards perfection and constructive criticism.

It is my pleasure to express my thanks to Dr.B.S.Nanjundiah, Scientist, NCL, for his immense help at all stages of this work, especially in the presentation of the thesis.

I wish to thank Dr.T.Ravindranathan and Dr.N.R.Ayyangar, the present and ex-Heads respectively of the Division of Organic Chemistry(Technology), NCL, for their constant support and interest in my work.

I am deeply indebted to the management "Anjuman Khairul Islam", Bombay, and the Principal, Dr.S.N.Kotwal, Poona College of Arts, Science & Commerce, Pune, for according permission to pursue my Ph.D. work, granting study leave, without which the execution of this work would not have been possible. It is my pleasure to acknowledge with thanks hearty cooperation extended by my colleagues, particularly Dr.Md.Qudrathullah, Head of the Department of Chemistry.

I would like to thank Prof.M.S.Wadia, Department of Chemistry, University of Pune, for his valuable suggestions and encouragement during the course of the work.

I am thankful to Dr.S.H.Iqbal, ex-Head, Division of Technical Services, NCL, and Dr. Islam Khan, Scientist, NCL, for their constant encouragement during the tenure of the work.

It is a pleasure for me to thank Dr.(Mrs.)Bhanu Chanda, Scientist, NCL, and Dr.D.G.Kulkarni, for their suggestions and help during the progress of the work. I am also thankful to my various associates at NCL, particularly Dr. Ravi Reddy, Dr.T.Ashok Rao, Dr.P.V.Dalvi, Mr.M.Jakkam, Mr.A.Ramani, Mrs.Y.Kulkarni, Mr. Sharavanan, Mr. Hegde, Mr. Dinesh and Mr. Godwin, for their cooperation during the execution of the work.

The services provided by the Library, Spectroscopy and Microanalysis Sections of NCL are gratefully acknowledged.

I am thankful to Mr.T.A.B.Mulla for drawing the figures and diagrams, and Mr.P.V.Iyer for typing the thesis in an elegant manner.

I am extremely thankful to the Director, NCL, for granting me a position of a Guest Worker at NCL and also for giving permission to submit my work in the form of a thesis.

Last but not the least, I must acknowledge the cooperation extended by my wife and children and for their patience and bearing my absence from home for a considerable time.

NCL, Pune 411 008. (G.M. Nazeruddin)

April 1995

C O N T E N T S

ABSTRACT

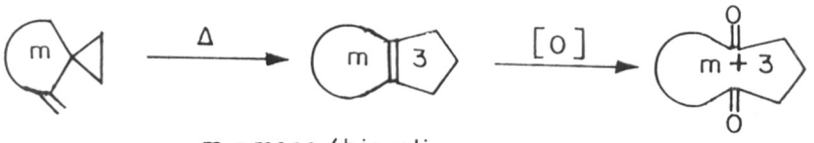
This thesis entitled "**Photochemical studies of α-substituted propiophenones and construction of bicyclo[m.3.0] bridged alkenes: Thermal rearrangement of spirocyclic vinylcyclopropanes**" is presented in four chapters.

Chapter I: Construction of bicyclo[m.3.0] bridged alkenes: Thermal rearrangement of spirocyclic vinylcyclopropanes to cyclopentenes

This chapter concerns with the construction of bicyclo[m.3.0] bridged alkenes by thermal rearrangement of spirocyclic vinylcyclopropanes to cyclopentenes.

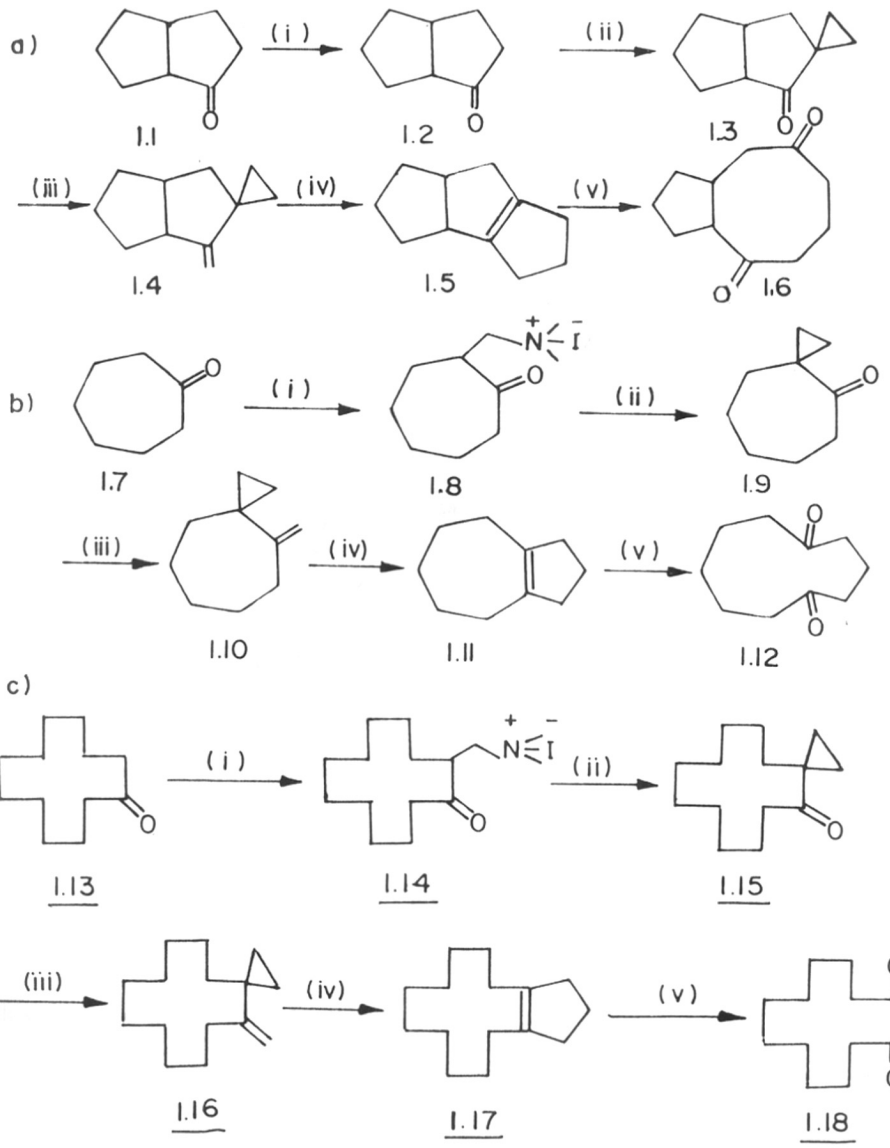
A large number of terpenoid natural products of carbon framework incorporating cyclopentene moiety fused onto medium-sized rings have come to focus recently as synthetic targets. This may be exemplified by precapnelladiene 5-8 and sesquiterpene ophiobolin 5-8-5. In this context, we conceived to develop a simple and efficient method to build a cyclopentane ring on to a given medium/large ring that would generate a class of bicyclo[m.3.0] bridged alkenes; such a method would be of immense synthetic value. Our approach towards this objective primarily rests upon the well-known vinylcyclopropane-cyclopentene rearrangement, a versatile and widely used strategy. Surprisingly, literature survey revealed that the thermal transformation of spirocyclic vinylcyclopropanes has remained practically unexplored. Such an explorative study described in this chapter led to the development of a convenient methodology to realize [m.3.0] bridged alkenes (Scheme-I). Oxidative scission of these alkenes furnished the corresponding medium and large-sized 1,5-diones, a class of potentially useful synthetic intermediates (Scheme-II). It is relevant to point out that a few 1,5-diones such as (**1.6** and **1.18**) constitute key synthetic intermediates in synthesis of precapnelladiene and muscone respectively.

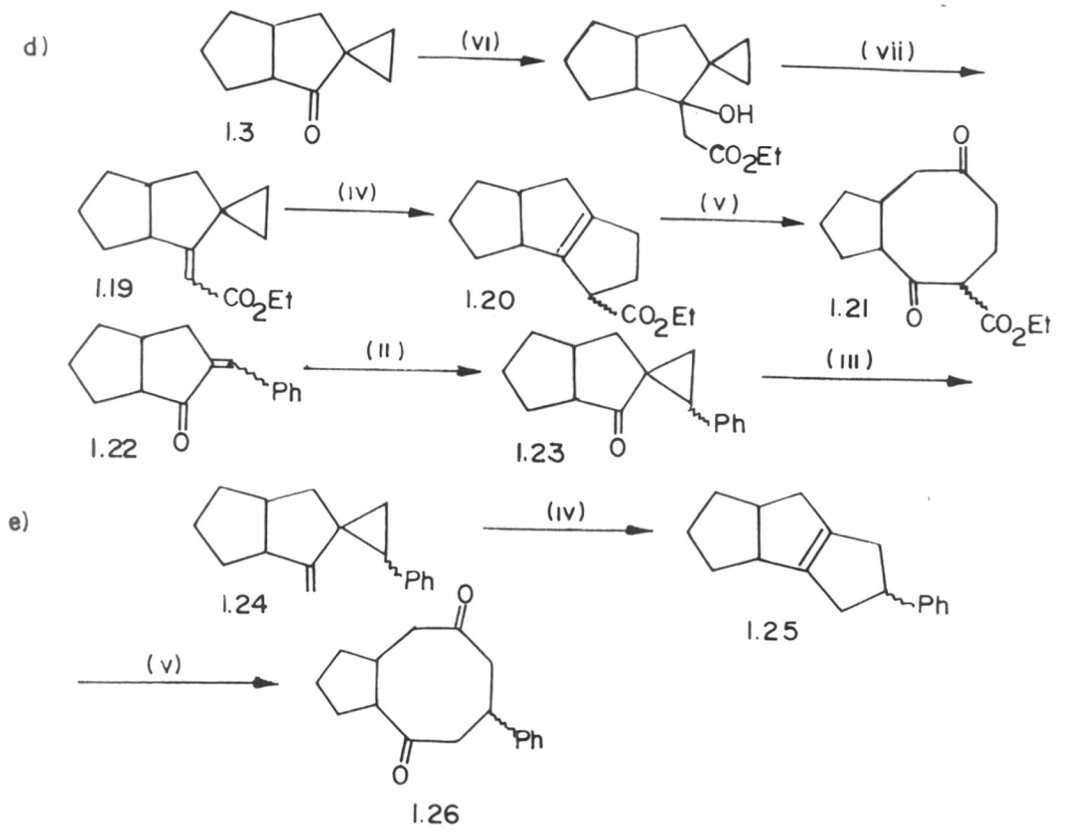
Scheme I



m = mono / bicyclic

Scheme II





(i) $(CH_3)_2\overset{+}{N}H_2\bar{C}l / CH_3I$; (ii) $-\overset{I+}{\underset{I}{S}}=O\bar{I} / NaH$; (iii) $Zn / TiCl_4 / CH_2Br_2$

(iv) Δ 500 °C; (v) $RuCl_3 - NaIO_4$, CCl_4 / MeCN / H_2O ;

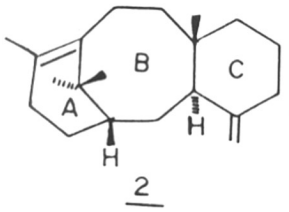
(vi) $Zn / BrCH_2COOEt$; (vii) dehydration

Chapter II: Application of vinylcyclopropane-cyclopentene rearrangement towards the construction of Taxane framework (A/B ring system) and synthesis of (±) β-cuparenone

This chapter consists of two Sections:

Section A: Synthetic efforts towards construction of A/B ring system of taxane skeleton

The taxane diterpenes are a group of substances isolated from various yew (Taxus) species that generally share carbon skeleton **2** indicated below:



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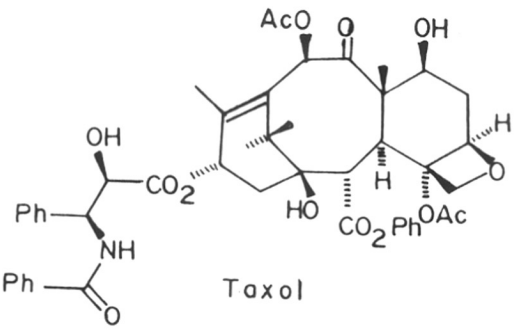


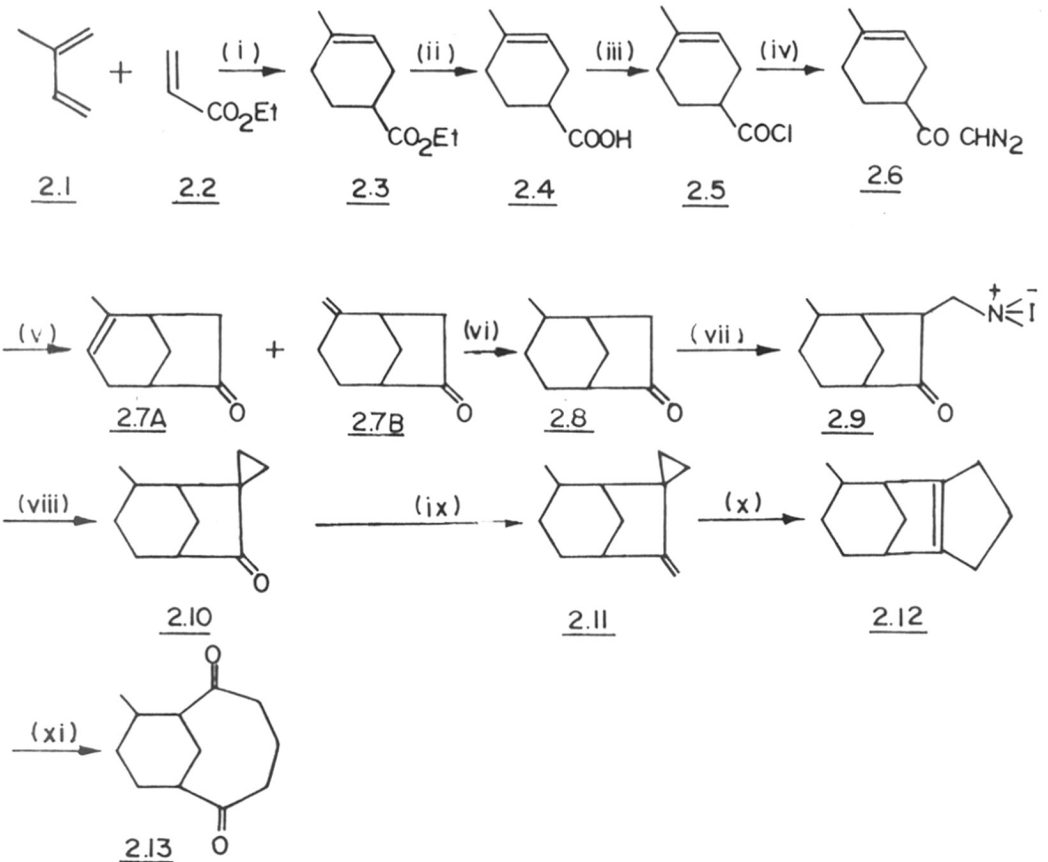
Taxol

Taxol is the most functionally and stereochemically complex of the taxanes and is currently the most promising anticancer drug. Construction of the congested eight-membered B ring is the most challenging facet of taxane synthesis.

The synthetic potential of the spirocyclic vinylcyclopropane rearrangement reaction that emerged from the work indicated in the previous Chapter prompted us to harness this reaction in constructing AB ring system of the taxane skeleton. The protocol that we adopted to build up A/B ring system is shown in Scheme-III.

Diels-Alder reaction of 2-methyl 1,3-butadiene with methyl acrylate gave a very good yield of the required product **2.3**. The latter was transformed to the corresponding α-diazoketone **2.6** and treated with BF_3-etherate. The expected isomeric mixture of bicyclic ketones **2.7** ensued. The corresponding saturated ketone **2.8**, was subjected to the previously employed protocol to generate α-spiro cyclopropyl ketone **2.10**. However, the reaction did not proceed and thus the further sequenceof reactions was arrested. The occurrence of Mannich reaction in bicyclo[m.3.0] octanone system (Scheme-IIa) and its non-occurrence in the present system was thought to be due to steric

Scheme III



(i) Δ140 °C ; (ii) Hydrolysis; (iii) Oxalyl Chloride, (iv) CH_2N_2 ;

(v) BF_3 – etherate ; (vi) $H_2/Pd-C$, (vii) $(CH_3)_2\overset{+}{N}H_2\bar{C}l/CH_3I$;

(viii) $-\overset{|}{\underset{|}{S}}=O\ \bar{I}$ / NaH ; (ix) Zn / $TiCl_4/CH_2Br_2$; (x) Δ 500°C ;

(xi) $RuCl_3 - NaIO_4$, CCl_4 / MeCN / H_2O .

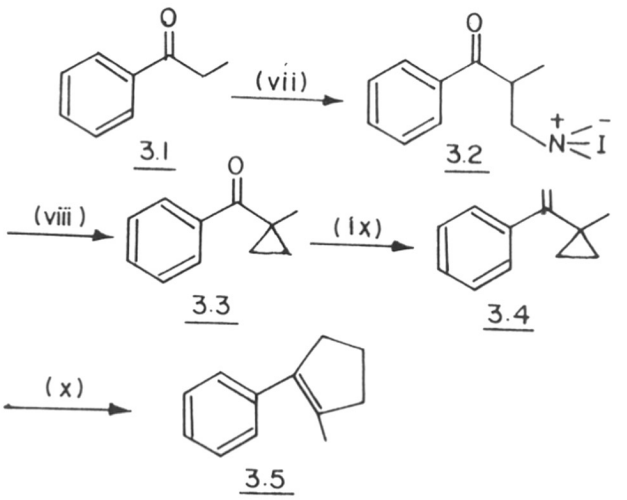
hindrance in the bicyclo[3.2.1] octanone system **2.8**.

Section B: Efforts towards the synthesis of (±) β-cuparenone

The sesquiterpenic ketone, β-cuparenone **3** first isolated from the essential oil of Mayur Pankhi, by virtue of possessing two contiguous quaternary centres in the cyclopentanone ring has served a testing ground for many different synthetic strategies.

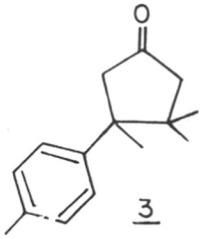
An examination of various methods employed to realize this molecule revealed that vinylcyclopropane-cyclopentene rearrangement was conspicuously untried and thus we planned to explore its potential. Before we embarked on the synthesis of **3**, we thought it necessary to check the efficacy of vinylcyclopropane-cyclopentene rearrangement on a model system (Scheme-IV). From the success realised, the protocol was extended to synthesize β-cuparenone. The required starting material **3.6** was prepared and subjected to thermal and photochemical rearrangement conditions. However, the desired rearrangement did not occur in either case. This was attributed to the steric congestion present in the substrate **3.6**.

Scheme IV

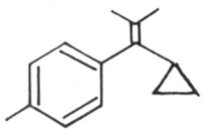


(vii) $(CH_3)_2\overset{+}{N}H_2\overset{-}{Cl}$ / CH_3I ; (viii) $-\overset{I+}{\underset{I}{S}}=O\ \overset{-}{I}$ / NaH; (ix) Zn / $TiCl_4$ / CH_2Br_2 ;

(x) Δ 500°C.



3



3.6

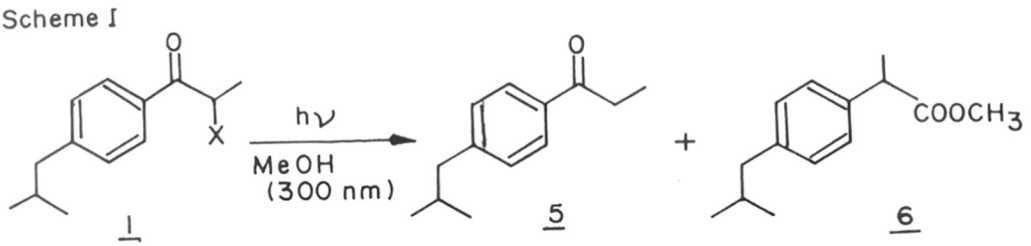
Chapter III: Photochemical investigation of α-substituted propiophenones

We have recently developed a photochemical method for the synthesis of α-aryl propionic acids. The key step in the methodology involved a photochemically induced 1,2-aryl migration in α-chloro *p*-substituted propiophenones. It was also observed that the nature of substituents in the *para* position influenced the rearrangement to a great extent. However, the study was restricted to α-chloro *p*-substituted propiophenones. In this context, we envisaged that a systematic study of the photochemistry of various α-substituted propiophenones and also that of α-chloro *m*-substituted propiophenones would generate valuable information, besides providing a methodology for the synthesis of many α-aryl propionic acids. The results that emanated from such a study is described in the following four sections.

Section A: Photochemistry of *p*-isobutyl-α-substituted propiophenones

Three differently α-substituted *p*-isobutylpropiophenones 1b-d were prepared by reported procedures and well characterized. Generally, a 3% degassed solution of 1b-d in methanol containing propylene oxide as an acid scavenger was irradiated at 300 nm light Rayonet photoreactor. The products from the photolysis were isolated by standard chromatographic techniques and characterized on the basis of spectral data. In many instances, the structural assignment was further confirmed by a direct comparison with authentic samples. The results from this study is depicted in Scheme-I and Table-1.

Scheme I



1 5 6

Table-1: Product distribution from the photolysis of α-substituted *p*-isobutylpropiophenones

Substrate	X	Conversion	Composition	
		%	**5**	**6**
1a	Cl	100	25	75
1b	Tosyl	50	99	--
#1c	OAC	15	99	--
1d	$N(Me)_2$	30	99	--

#Irradiated at 254 nm.

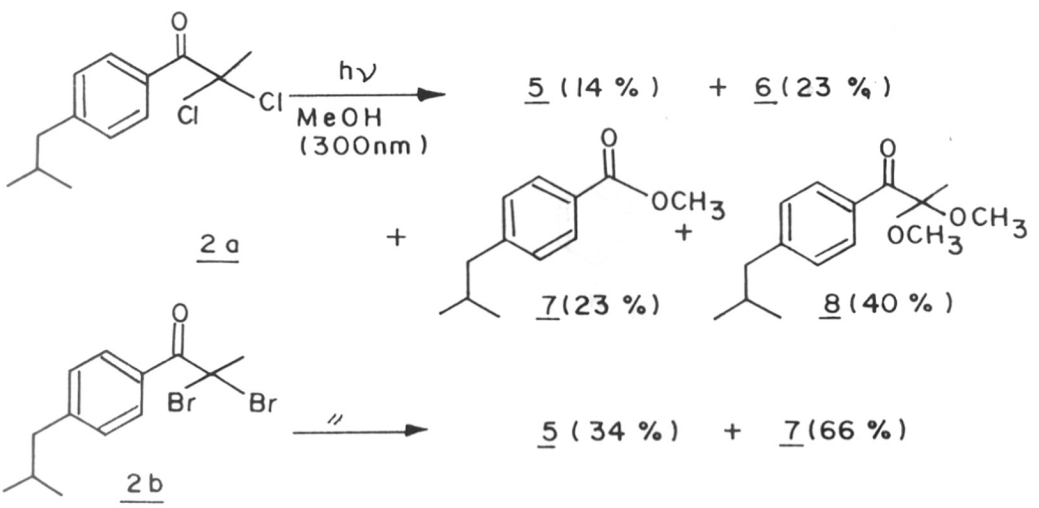
The salient feature of the results obtained from these substrates is their total proclivity for the formation of reduction products. Such a result is contrasting with those obtained from α-chloro substituted propiophenones which underwent essentially 1,2-aryl migration. Such a divergent photobehaviour has been rationalized in terms of conformational factors of the excited carbonyl in relation with the leaving group.

Section B: Photolysis of *p*-isobutyl-α,α-dihalopropiophenones

In the context of *p*-isobutyl-α-chloropropiophenone leading to 1,2-aryl migration on photolysis, it was prompting to check the photobehaviour of α,α-dichloro and dibromo *p*-isobutyl propiophenones. The results from such a study have been interesting (Scheme-II).It is striking to note that there has been a remarkably different type of photobehaviour from these α,α-dihalo ketones from that of mono α-chloro-substrates. A substantial reduction in the rearrangement product with a concomitant enhancement in solvolytic products is a unique feature. This facet has been understood in terms of the involvement of stabilized carbocations in the two successive photosolvolysis reactions. An additional interesting aspect of the result is the formation of substituted methyl

benzoate in both the cases.

Scheme II



Section C: Photochemistry of *m*-substituted-α-chloropropiophenones

With our interest in developing methods for various α-aryl propionic acids, we thought it worthwhile to study the representative photobehaviour of some *m*-substituted-α-chloro-propiophenones. Scheme-III and Table-2 depict the results from such a study.

A gross perusal of the results reveals that there has been change in the trend in the extent of radical and ionic products from these *m*-substituted compared to those that arose from the *para* compounds. An additional feature of the results is the incorporation of chlorine into the aromatic nucleus in the products. Various aspects of the results have been discussed drawing parallels from literature. Among the various substrates, the *m*-methyl substituted α-chloropropiophenones gave considerable 1,2-aryl migrated products.

Scheme III

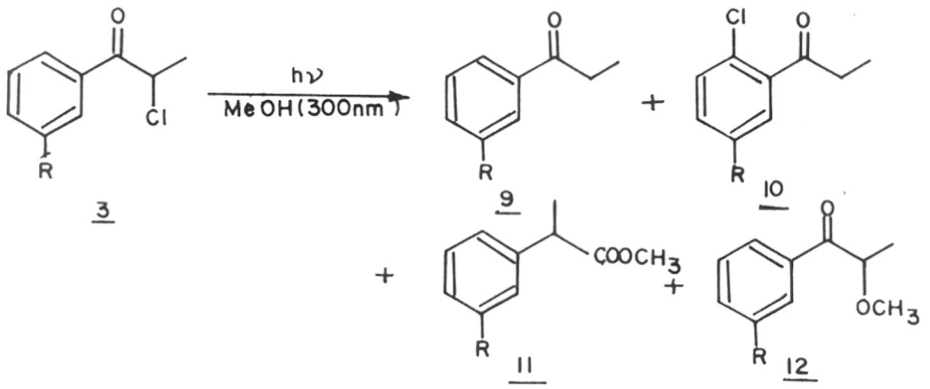


Table-2: Product distribution from the photolysis of 3a-d

Substrate	R	Conversion %	Composition 9	10	11	12
3a	*m*-OCH_3	100	13	68	--	19
	p-OCH_3	100	12	--	08	70
3b	*m*-Oph	100	70	21	08	--
3c	*m*-CH_3	70	33	--	66	--
	p-CH_3	100	8	--	76	--
#**3d**	*m*-NO_2	20	100	--	--	--

#Irradiated at 254 nm.

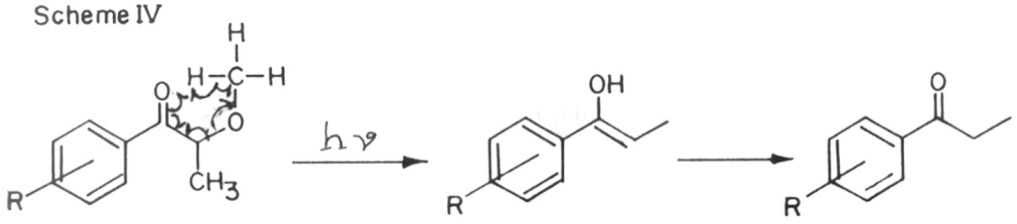
Section D: Photochemical studies of α-methoxy phenyl substituted propiophenones

Among the previously described substrates, phenyl substituted propiophenones were the commonly observed photoreduction products. An obvious genesis of this could be the photoreduction of C-X bond; alternatively, in the context of photochemical reaction being carried out in methanol, the solvolytic product (Scheme-IV) may also undergo a Norrish type II

fragmentation reaction leading to the same reduction product. Thus, in order to check this possibility and also to investigate the effect of different phenyl substituents on the photochemistry of [O=C - C -OCH_3] grouping, various such substrates were prepared and their photochemistry investigated (Scheme-IV, Table-3).

A remarkable feature of the results is the ubiquitous formation of the reduction products and oxetanols. These results indicate that the presence of a γ-hydrogen atom in the substrate essentially favours typical Norrish type II processes of β-cleavage and cyclization; however, no substantial substituent effect was observed.

Scheme IV



Scheme V

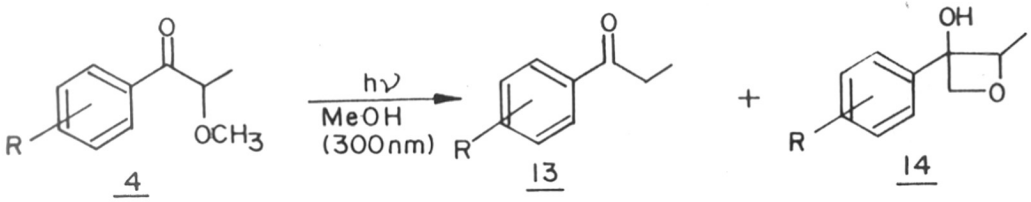


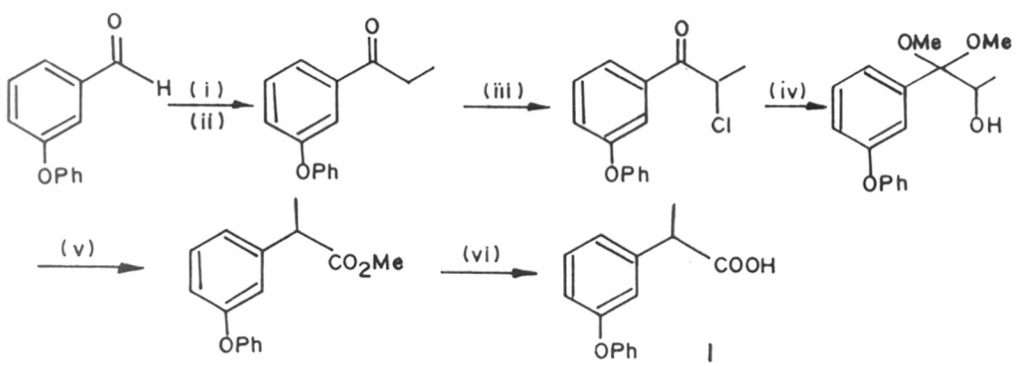
Table-3: Product distribution from the photolysis of 4a-e

Substrate	R	Conversion %	Composition **13**	**14**
4a	H	95	35	65
4b	*p*-CH_3	100	44	56
4c	*m*-CH_3	100	32	68
4d	*p*-OCH_3	65	50	50
4e	*p*-isobutyl	100	33	66

Chapter-IV: Synthesis of (±) fenoprofen, an important antiinflammatory agent

Fenoprofen constitutes an effective and widely used antiinflammatory agent. Surprisingly, while numerous approaches have been developed for the synthesis of Ibuprofen, neproxen, ketoprofen, etc., there has not been any reported convenient synthesis of fenoprofen. This situation warranted development of a synthetic route to the drug. It may be recalled (Chapter III, Table-2) that photolysis of *m*-phenoxy-α-chloropropiophenone resulted essentially in the reduction product along with a minor amount of the required fenoprofen ester; this made the photochemical approach unsuitable. Therefore, we contemplated to extend an available method (used for other drug of this class) to synthesise fenoprofen **1** in a convenient manner. The sequence of reactions employed is indicated in Scheme-VI. It may be mentioned that the strategy described here involves a limited number of steps leading to a high yield of the required drug molecule from the commercially available *m*-phenoxybenzaldehyde.

Scheme VI



(i) CH_3CH_2Br/Mg ; (ii) $Na_2Cr_2O_7/H_2SO_4$; (iii) $CuCl_2$-LiCl / DMF; (iv) Na/CH_3OH;
(v) $(Et)_3N$, CH_2Cl_2/SO_2Cl_2; (vi) Hydrolysis .

CHAPTER I

Construction of bicyclo[m.3.0] bridged alkenes: Thermal rearrangement of spirocyclic vinylcyclopropanes to cyclopentenes

***Objective**:The work described in this chapter aims at development of a convenient methodology for the construction of 5-8 fused carbocyclic systems utilizing spirocyclic vinylcyclopropane-cyclopentene rearrangement as the key reaction. The realization of this objective results as well in a facile method for the building up of [m.3.0] bridged alkenes.*

INTRODUCTION

Although eight membered rings are not as abundant as some of the smaller rings, they occur widely in nature especially in higher plants and marine organisms.[1] Many cyclopentanoid natural products, particularly terpenoids and lignans exhibit interesting biological profile and thus have served as target molecules in numerous synthetic studies.[2] Quite a few sesquiterpenoids isolated from marine sources have characteristic feature of a five membered ring fused to a eight membered one. A few examples of this class[3,4] are shown in Scheme-1.

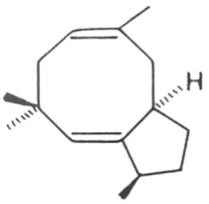
A further extension of this type of fusion may be found in several phytotoxic sesterterpenoids of the ophiobolin[5,6]/ceropastol[7] family having structures with a 5-8-5 ring system. A few examples of this class are included in the Scheme-1.

Among cyclooctanoid diterpenoids, taxanes occupy a prominent place. These uniquely bridged tricyclic ring skeletons are found in many species of the yew tree.[8] The most common substitution pattern of taxanes are exemplified by tauxisin,[9,10] taxinine,[11] baccatin[12] and taxol.[13,14a,b] The lastly mentioned compound taxol has been the topic of great synthetic interest currently, owing to its anticancer properties.

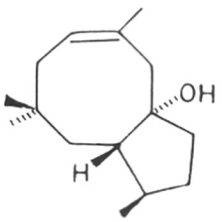
Construction of eight membered rings:

The synthesis of this class of ring systems has been a long standing problem owing to difficulties arising from a high degree of ring strain and transannular interaction.[15] Nevertheless, the presence of heteroatoms or SP^2 carbon in the ring have a dramatic effect in reducing the steric

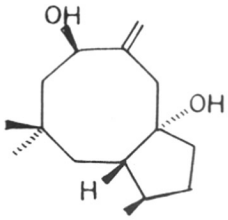
Scheme I



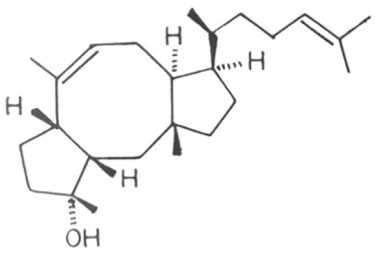
Precapnelladiene



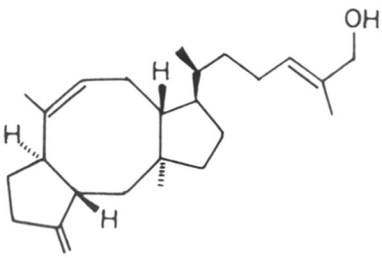
Dactylol



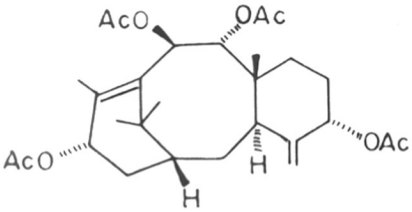
Poitediol



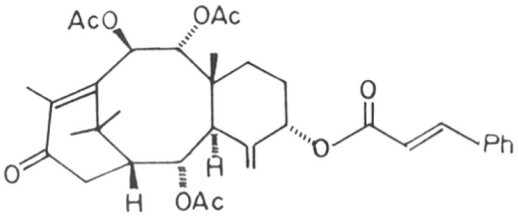
Ophiobolin F



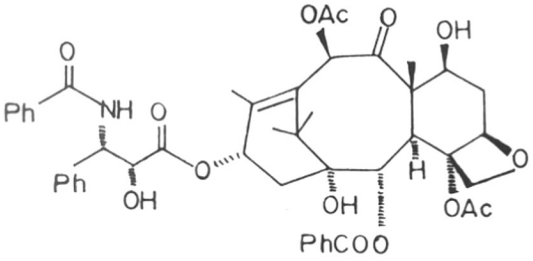
Ceroplastol I



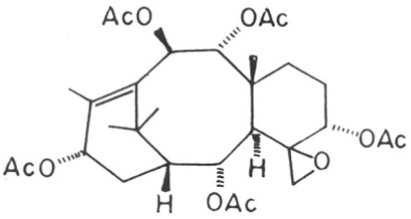
Taxusin



Taxinene



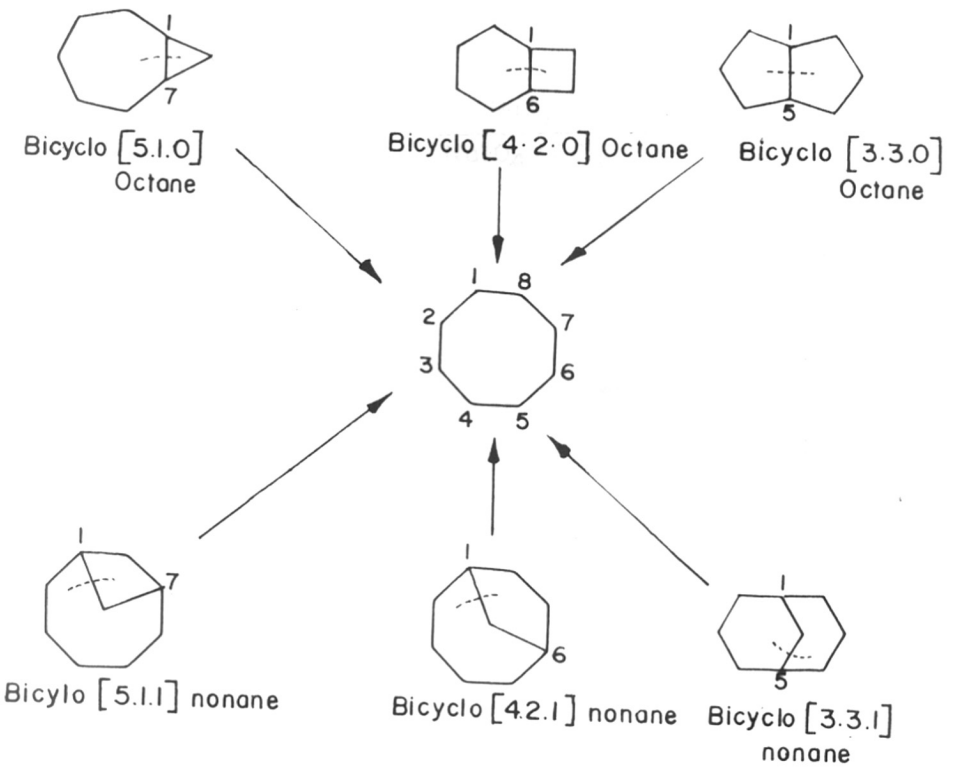
Taxol



Baccatin I

repulsions and thus make the system amenable to synthesis. Among the different types of strategies for cyclooctanoid system, an important route employed is the fragmentation reaction, as shown in Scheme-2.

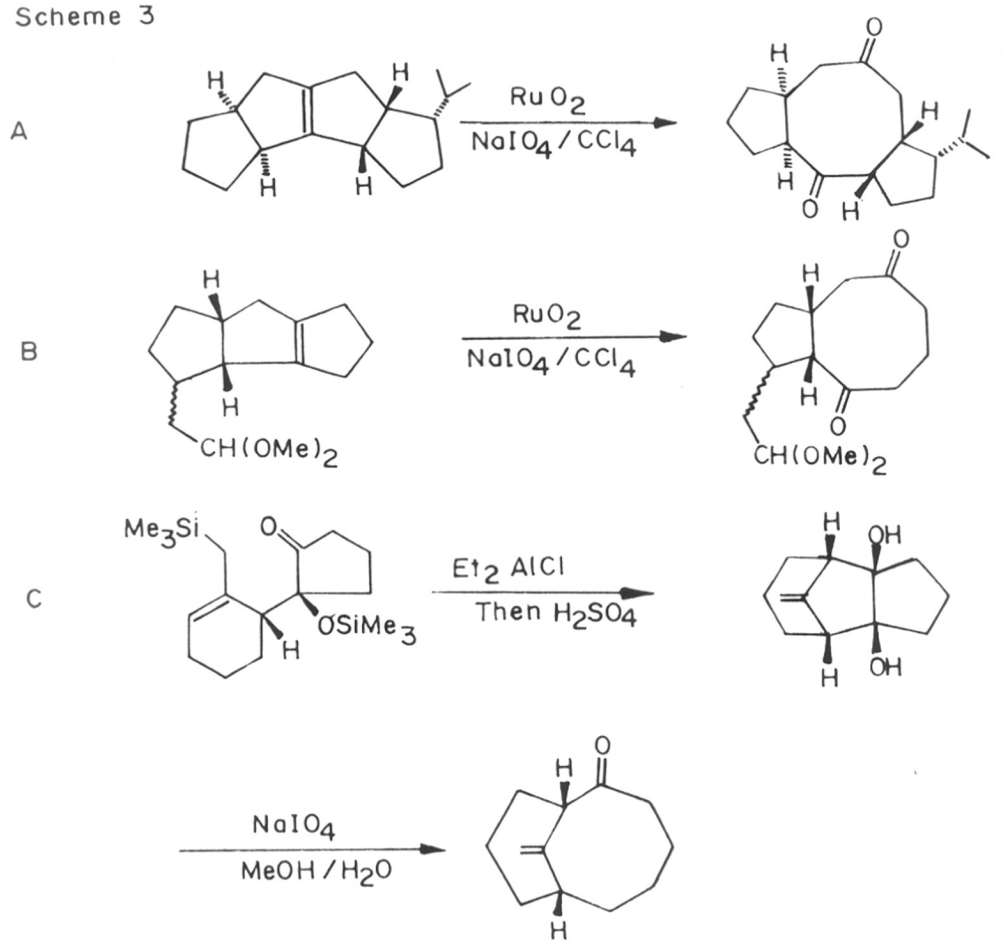
Scheme 2



Despite the availability of numerous synthetic strategies for this class of compounds, a few examples from the literature that involve fragmentation of a 1,5 bond in bicyclo[3.3.0]octane systems are highlighted below.

Mehta[16] has utilized the oxidative cleavage of a bridging olefinic bond leading to 1,5 cyclooctadiones and synthesized several linear di and triquinane systems in good yields (Scheme-3A,B).

Scheme 3

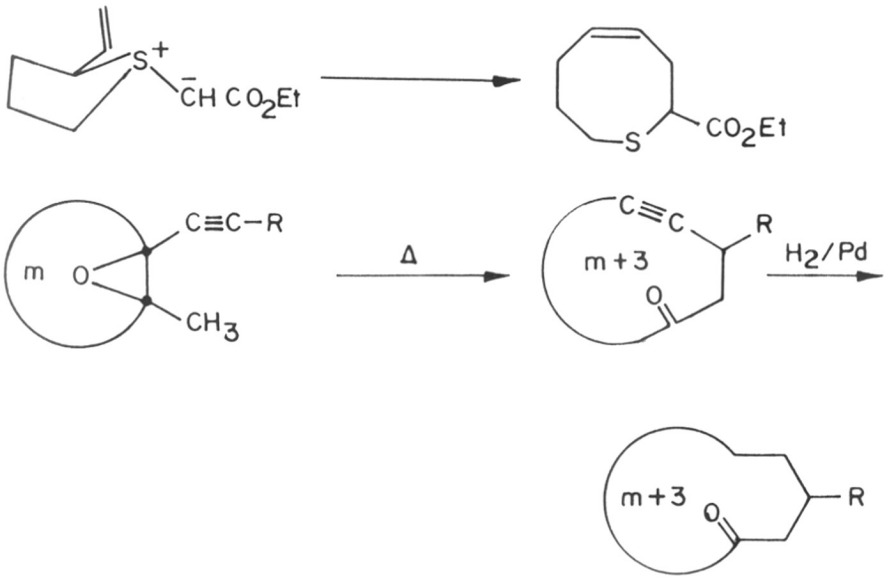


Similarly, the oxidative scission of a bridged 1,2 diol has been advantageously utilized by Trost[17] in the construction of taxane ring system (Scheme-3C).

As the present work involves a strategy for three carbon intercalation into existing ring system, it is pertinent to make a reference to a couple of such three carbon annulations.

A [3.2] sigmatropic rearrangement of S-alkylated, 2-vinyl thiocycloalkanes leads to a three carbon annulated ring.[18] This strategy utilizes an intramolecular nucleophilic attack promoted by an electron deficient heteroatom. Another strategy towards this end involves the thermolysis of 1-alkenyl-2-methyl 1,2 epoxy cycloalkanes[19] (Scheme-4).

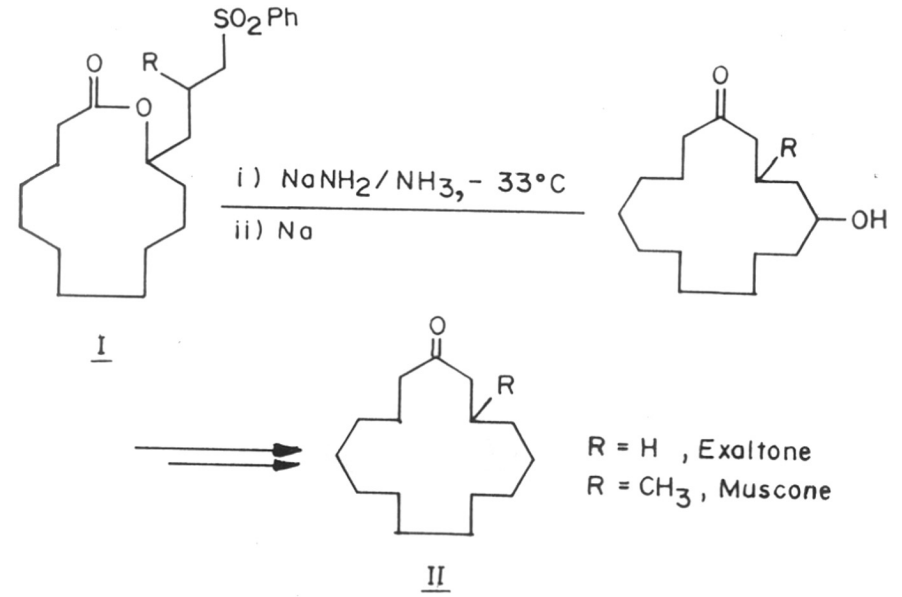
Scheme 4



Transformation of lactones into macrocarbocycles have been elegantly utilized in the synthesis of exaltone and muscone[20] (Scheme-5).

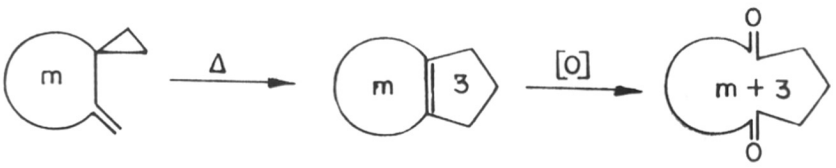
The intramolecular attack of a carbanion on the lactone carbonyl carbon of I gives rise to ring enlarged carbocycle with the incorporation of three carbon atoms. The phenyl sulfonyl lactones I upon treatment with $NaNH_2/NH_3$ in THF, followed by reductive removal of the phenyl sulfonyl residue were converted into exaltone and muscone II.

Scheme 5



The foregoing brief account of different methods leading to cyclooctane systems reveals that the vinylcyclopropane-cyclopentane rearrangement especially involving a spirocyclic vinylcyclopropane system has been totally left unexplored.[21] This situation promoted us to conceive a strategy, as depicted in the following Scheme-6.

Scheme 6

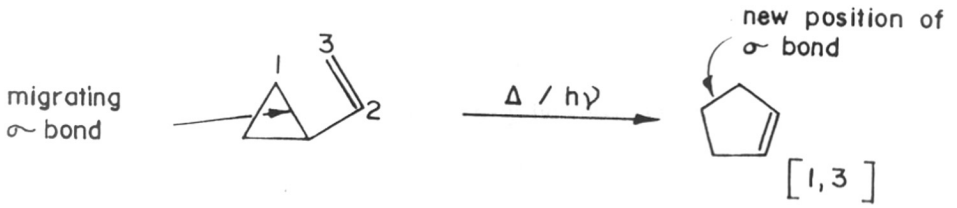


This strategy, in the first place, requires the preparation of spirocyclic vinylcyclopropane which has to be built up on an existing ring. With such substrates on hand, one has to investigate the feasibility of a vinylcyclopropane rearrangement which should lead to a bicyclo[m.3.0]alkene systems. The oxidative scission of the central olefinic linkage should result in intercatation of three

carbon atoms, furnishing an eight membered or a larger ring if m is equal or greater than five. In this context, it is necessary to provide a concise introduction to this rearrangement, particularly in the light of our work in this area for a decade.[22]

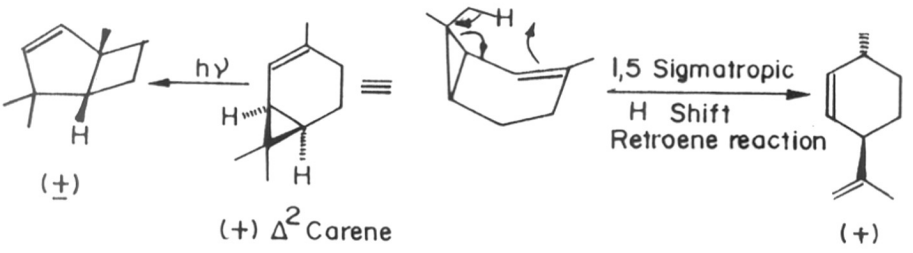
Vinylcyclopropane-cyclopentene rearrangement (VCR) is a thermal/photolytic transformation of vinylcyclopropane to a cyclopentene and is considered a special case of 1,3 sigmatropic migration of carbon (Scheme-7).

Scheme 7



The extensive work carried out by us on Δ^2-carene, an abundantly available monoterpenic hydrocarbon from Indian terpentine oil, and on its derivatives yielded many synthetic methodologies besides throwing light on the mechanistic aspects of this rearrangement.[22] A special feature known in the case of a *cis*-alkyl vinylcyclopropane such as Δ^2-carene is its total proclivity to undergo a competing retro-ene reaction[23] (1,5-sigmatropic hydrogen shift) (Scheme-8).

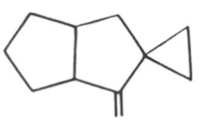
Scheme 8



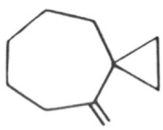
This problem of occurrence of retro-ene reaction was circumvented by a photoreaction which led to the desired VCR furnishing bicyclo[3.2.0]heptene system.[24] The formation of racemic products from chiral starting material indicated an involvement of a non-concerted radical mechanism. On the other hand, photochemical investigation of 4-α substituted chiral Δ^2-carene derivatives led to a diastereomeric mixture of chiral products and this investigation resulted in a convenient methodology for the construction of chiral bicyclo [3.2.0] heptenes.[25] The synthetic potential of this photorearrangement has been demonstrated by the synthesis of grandisol and both the enantiomers of marine natural product Δ^{9-12} capnellene.[26]

With this background of work in the area of VCP-CP rearrangement, we were surprised not to find a report of such a rearrangement from spirocyclic vinylcyclopropane. As conceptualized earlier (Scheme-6), the occurrence of this type of rearrangement could lead to 5-8 fused carbocycles. From this point of view, it was planned to investigate the thermal rearrangement of the following five substrates (Scheme-9).

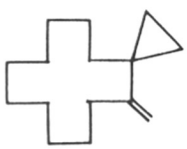
Scheme 9



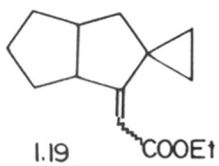
1.4



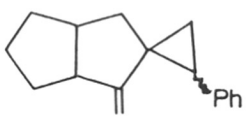
1.10



1.16



1.19

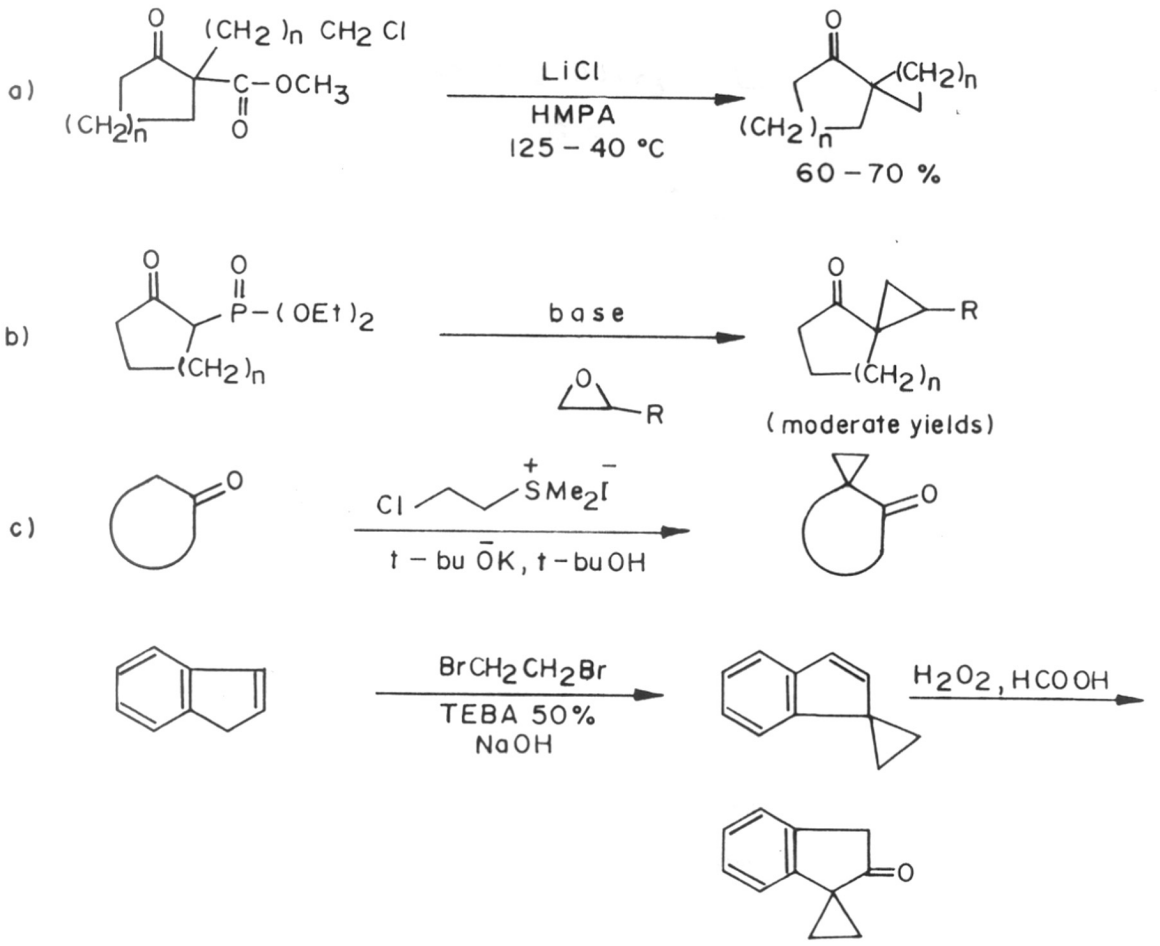


1.24

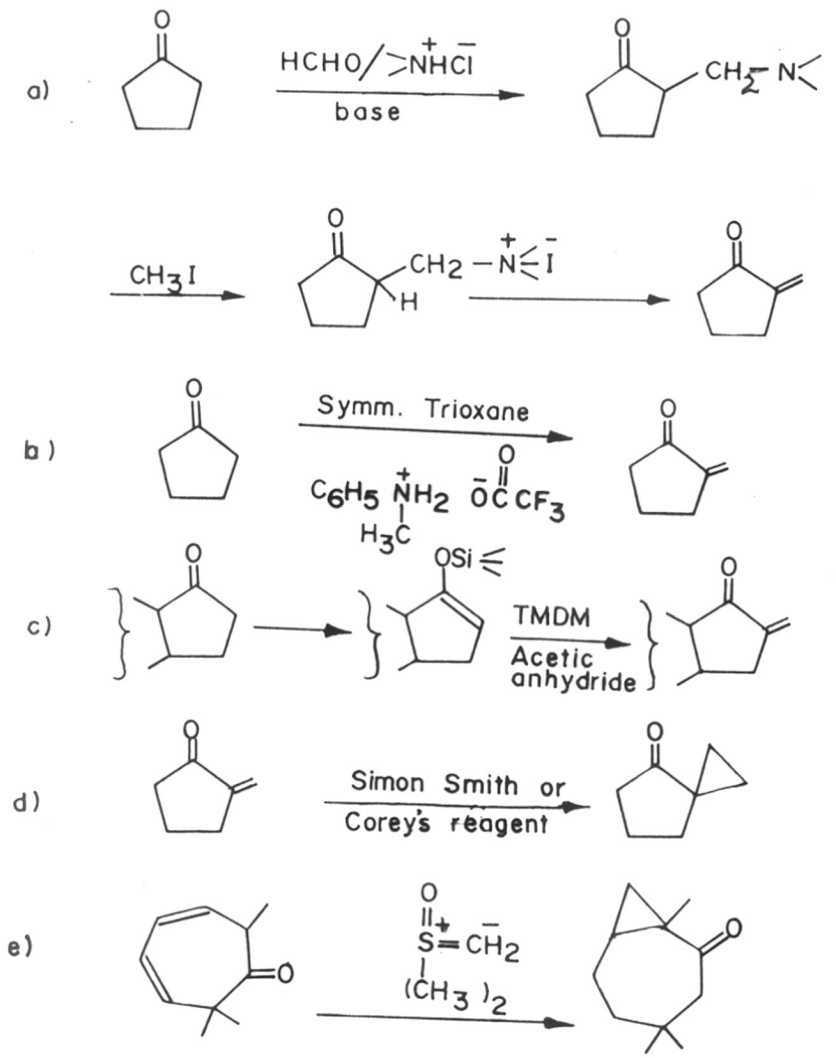
Preparation of spirocyclic vinyl cyclopropanes:

In order to prepare the required spiro substrates referred to above, a systematic survey of literature methods was undertaken, which showed two broad categories of reactions employed for this purpose. Obviously, both the methods utilize the activation provided by the carbonyl function to its α position in cyclic ketones. A brief collection of important methods in this regard are shown in Schemes 10 and 11.

Scheme 10



Scheme II



1. **Intramolecular alkylation** (Scheme-10a)

The reaction involves direct spiro annulation by intramolecular alkylation. Willis and Eilerman[27] reported an intramolecular decarboxylative alkylation route to spirocyclic ketones and used this strategy in the synthesis of (±)β-vetivone. This method comprised chloride-ion induced non-hydrolytic decarboxylation of ω-halogeno-β-keto esters which led to the desired spiro ketones

in 60-70% yield. Although the method appears to be attractive, the preparation of α, α-haloalkyl, carboxylate itself does not appear to be simple. In addition, the use of HMPA as a solvent in routine preparation is not preferred owing to its suspected carcinogenecity.

2. **Condensation of β-ketophosphate with epoxides** (Scheme-10b)

Recently, Wiemer *et al.*[28] reported a method for spirocyclic cyclopropyl ketones which involved the condensation of an epoxide with a β-ketophosphonate. Although the mechanistic aspects of this reaction are not delineated, it appears to involve enolate-initiated opening of the epoxide, followed by an intramolecular alkylation utilizing the leaving group efficacy of -PO-$(OEt)_2$. However, the yields from these reactions appear just moderate. In addition, synthesis of β-ketophosphonate derivatives need the use of electrophilic phosphorus reagents and involve quite a few synthetic steps.

3. **Sequential alkylation** (Scheme-10c)

An alternate method for direct spiro annulation of ketones was reported by Ronald and Ruder,[29] who realized spirocyclopropanation of different sized cyclic ketones. As can be seen from the Scheme, the reaction involves the alkylation of an enolate by 2-chloroethyldimethylsulfonium iodide in the presence of tertiary butoxide in tertiary butanol. The authors obtained yields in the range of 43-85% and surprisingly, have not reported this reaction on cyclopentanone. The spiroannulation appears to occur initially by a halide displacement alkylation, followed by intramolecular displacement of dimethyl sulphide. This reaction appears to be extremely sensitive to the reaction solvent and the results are attainable only in tertiary butanol as a solvent.

4. **Alkylation by phase-transfer catalysis** (Scheme-10d)

Mention may be made here of a report by Beak and Remieus[30] of spirocyclopropanation of indene by 1,2 dibromo ethane in the presence of aq. NaOH and TEBA (as a phase transfer catalyst).

The extreme reactivity of the benzylic and the allylic site was utilised in effecting spirocyclopropanation and the olefinic linkage was further oxidised by hydrogen peroxide/formic acid. This reaction appears to be suitable for reacting benzylic sites.

5. α-Methylenation-Cyclopropanation (Scheme-11)

The other strategy to realize these types of spirocyclopropyl ketones involves the initial preparation of α-methylene ketones, followed by their cyclopropanation. An interesting report in this direction appeared from Gras.[31] The ubiquitous presence of α-methylene ketone moiety in many naturally occurring sesquiterpenes and in antibiotics triggered synthetic efforts towards this class of compounds. In addition, the potential utility of α-methylene ketones in organic synthesis as Michael acceptors is an additional stimulus to generate the synthetic methods.[32,33] Methylenation at the carbon α to a carbonyl moiety can generally be achieved in the following manner: Base-catalysed condensation of formaldehyde[34] leading to Mannich α-aminoalkylation of C-H acidic compounds. This reaction is followed by quaternization and β-elimination of the dialkyl amino group (Scheme-11a). An analogous method was reported by Gras,[31] who introduced the use of N-methyl anilinium trifluoroacetate (TAMA) as a reagent for effective α-methylenation.

The procedure involved refluxing of a keto compound with trioxane and TAMA in tetrahydrofuran. Although different types of cyclic ketones are α-methylenated in very good yields, the crude products appear to dimerize or polymerize before isolation.[35] The postulated mechanism of this reaction involves the formation of the Mannich base by TAMA-induced condensation of the ketone and formaldehyde. Spontaneous β-deamination leads to the observed products. However, this reagent was not found to be suitable in the case of 17-keto steroids. A modification effected by Bakos and Vincze[36] involved the use of trimethyl silyl enol ether of the ketone with N,N,N',N'-tetramethyl diaminomethane (TMDM) and acetic anhydride (Scheme-11c). This modification resulted in good yield of the required α-methylene ketone in the steroidal series.

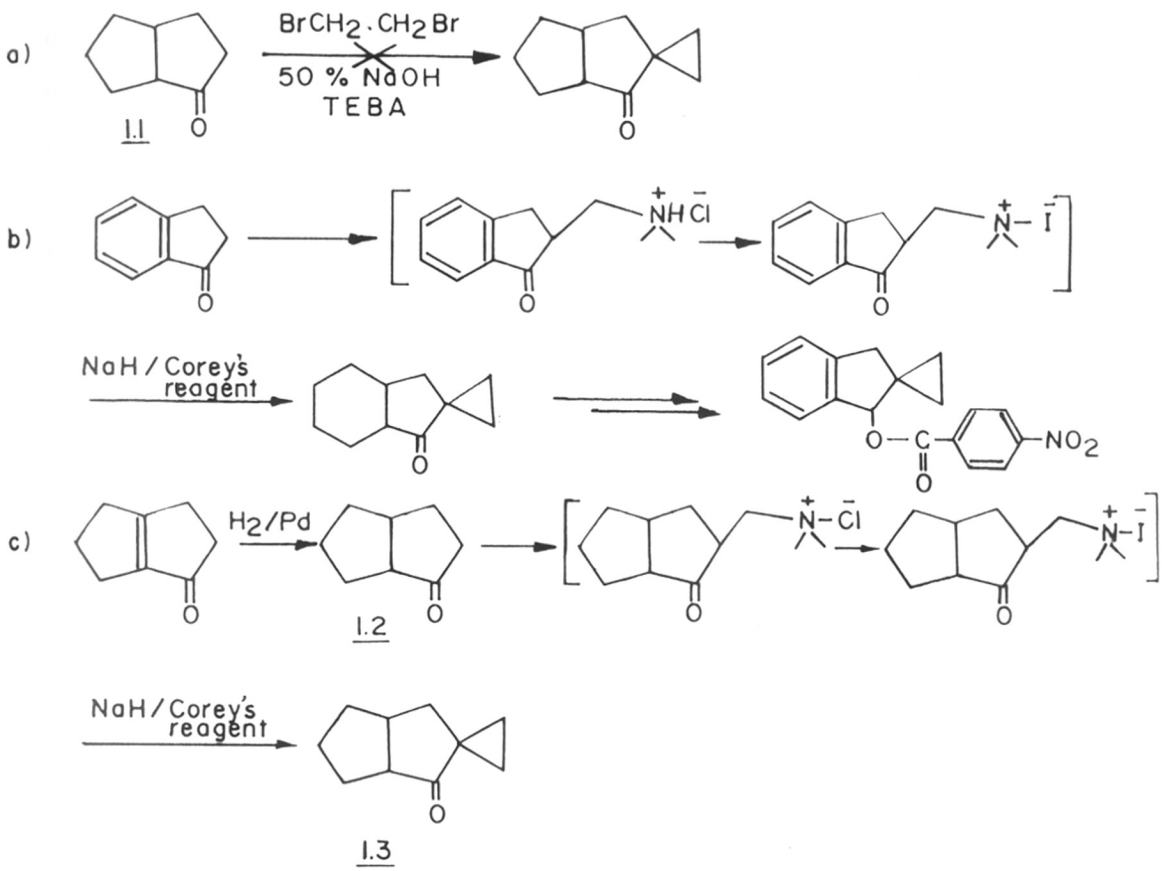
After realizing the exomethylene ketone, the subsequent step is the cyclopropanation which can be done by the classical Simon-Smith[37] reaction utilizing methylene iodide, zinc copper couple. An alternate and more suitable method, especially for the α,β unsaturated ketone is the use of dimethyl oxosulfonium methylide reported by Corey and Chaykovsky.[38] These authors reported the generation of this reactive intermediate and its synthetic applications. This ylide acting as a nucleophile serves to transfer methylene group to certain unsaturated linkages including -O=C-C=C. Thus, the reaction of this reagent with eucarvone resulted in a selective cyclopropanation of α,β unsaturated double bond (Scheme-11e).

An examination of foregoing discussions on different methods of spiroannulation reveals that in most of the direct methods, substrate for intramolecular alkylation are difficult to be prepared. While one of the methods was too sensitive to solvent, the other was suitable for a highly reactive site (Scheme-10). Nevertheless, the direct method involving phase transfer catalyzed-dialkylation by ethylene dibromide appeared attractive. Therefore, we thought of utilizing this strategy to prepare one of our substrates, **1.3** (Scheme-12a). The ketone **1.1** in CH_2Cl_2 was treated with 1,2-dibromoethane in the presence of aq. 50% NaOH and catalytic amount of TEBA. Surprisingly, the reaction did not occur in the desired manner and most of the starting material was recovered.

Alternatively, to realize α-methylenation, use of TAMA appeared extremely attractive. Therefore, this reagent was prepared and treated with the ketone **1.1** under the conditions described above. Surprisingly, we were not successful in realizing α-methylenation.

In this context, a report by Okata et al.[39] on the preparation of spiro [cyclopropane-1,2'-indan]1'yl *p*-nitrobenzoate for a solvolysis study was extremely useful. These authors prepared the α-cyclopropylketone by the Mannich reaction of the corresponding indenone. The trimethylammonium iodide obtained by the condensation of the ketone with the Mannich base was directly treated with dimethyl oxosulfonium methylide to lead to the desired spiroketone (Scheme-12b).

Scheme 12



This methodology was extended to our substrate **1.1**.

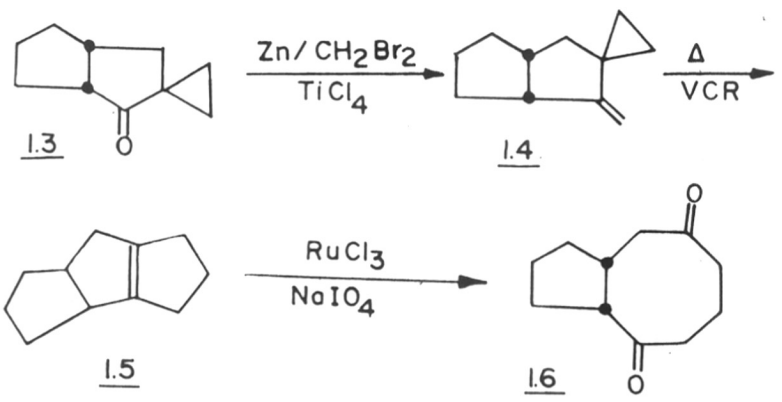
Preparation of α-spirocyclopropylbicyclo[3.3.0]octanone-2 **1.3** is shown in Scheme-12c. The required bicyclo[3.3.0]octan-2-one[40] **1.2** could be easily prepared by the catalytic hydrogenation of the corresponding 1-ene 2-one. The saturated ketone **1.2** was identified by its PMR spectral data. Treatment of this ketone with paraformaldehyde, dimethylammonium chloride, under Mannich condition[39] afforded a product which was further N-methylated with CH_3I in acetonitrile. Subjecting the product of this reaction to trimethyl sulfoxonium iodide in presence of NaH[39] furnished a product

in about 50% yield. The IR spectrum (Fig.1) showed a typical intense band at 1735 cm^{-1} for the cyclopentanone moiety along with a low intensity band at 3090 cm^{-1} indicative of the occurrence of spirocyclopropanation. The ^{1}H-NMR spectrum (Fig.2) was significant in displaying two groups of multiplets in the range 0.70-1.00 and 1.10-1.20 for the cyclopropyl protons. The observed downfield shift of the cyclopropyl protons could be ascribed to the anisotropy of the adjacent carbonyl group. The compound analysed satisfactorily for (C&H) for $C_{10}H_{14}O$. The ^{13}C NMR (Fig.3) provided ample evidence to characterize the product as **1.3**. The spectrum featured all the ten carbon atoms giving the following data:

^{13}C Data: 16.91(t), 20.38(t), 26.01(t), 28.59(s), 29.95(t), 35.83(t), 35.99(t), 38.85(d), 53.54(d), 223.01(s).

The reaction of cyclopropyl ketone **1.3** with $Zn/TiCl_4/CH_2Br_2$ under Lambardo conditions[41] yielded a clean product which could be readily identified as spirocyclic vinylcyclopropane **1.4** (Scheme-13).

Scheme 13



The PMR spectrum (Fig.4) displayed a 4H singlet at 0.70δ for the cyclopropane protons as against the well separated multiplets in the case of spiro ketone **1.3**; the spectrum besides showing two broad multiplets centered at 2.30 and 2.65 for the bridgehead methine protons showed a typical

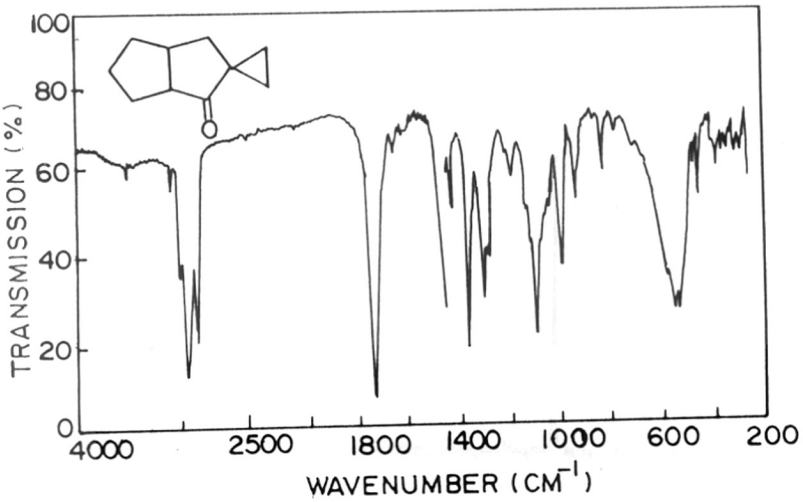


FIG. 1 IR SPECTRUM OF 1.3

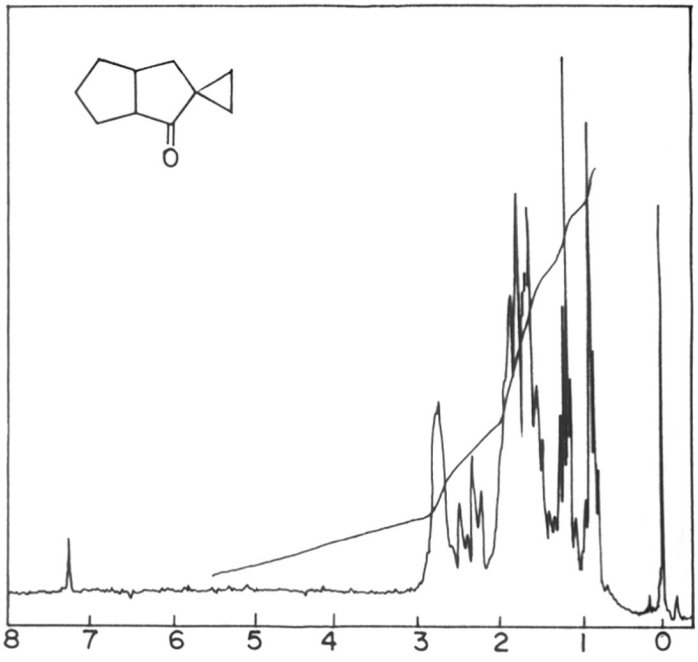


FIG.2 ^{1}H NMR (80 MHz) SPECTRUM OF 1.3

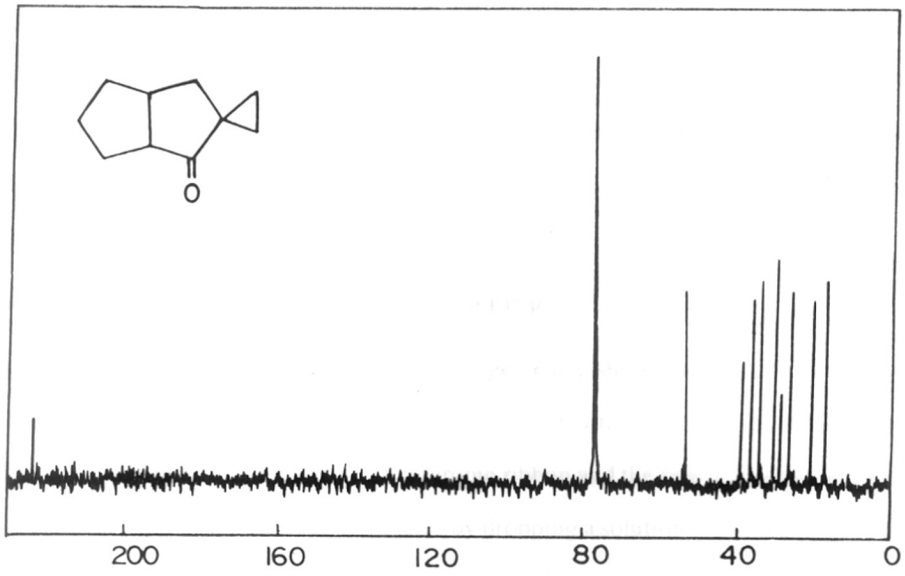


FIG. 3 ^{13}CNMR (300 MHz) SPECTRUM OF 1.3

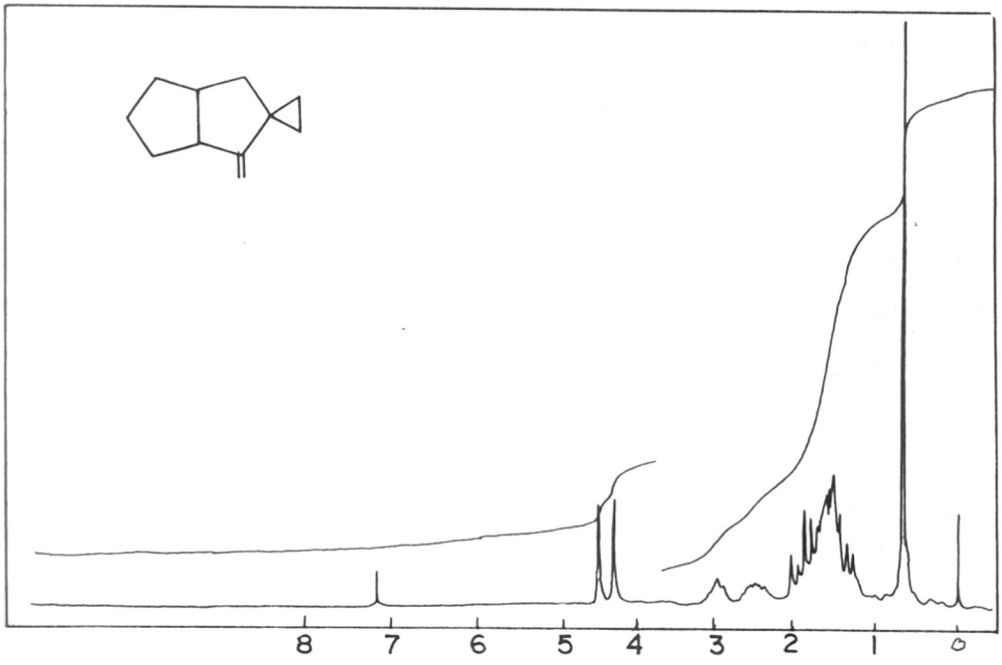


FIG. 4 ^{1}HNMR (80 MHz) SPECTRUM OF 1.4

pair of doublets for the exomethylene group. The IR spectrum was conspicuous by its absence of carbonyl absorption and by the presence of a moderately intense band at 1660 cm^{-1} for the exomethylene group. Further, structural support was derived from the ^{13}C NMR (Fig.5) spectral data: 15.15(t), 17.38(t), 25.77(s), 25.95(t), 33.22(t), 34.80(t), 41.63(d), 41.82(t), 50.15(d), 97.26(t), 163.11(s).

Thermal rearrangement of spirocyclic vinylcyclopropane (1.4)

The thermolysis unit employed for the rearrangement is shown in (Fig.6). The unit consisted of a quartz tube (16" x 0.5") uniformly packed with small quartz helices. Regulated heating of the reactor was realized by uniform winding of nichrome ribbon and the rate of heating was controlled by a dimmerstat. The thermolysis was conducted by dropping a solution of the substrate in pet.ether into the unit in an atmosphere of nitrogen. The products of the reaction after efficient condensation were collected in a flask kept in an ice bath. Thermolysis of 1.4 carried out as described above, furnished a clean product in almost quantitative yield and was found to be homogeneous by GLC. The IR spectrum of the product was typical of a hydrocarbon, being devoid of any functionality, but for the tetrasubstituted double bond. The PMR spectrum (Fig.7) displayed an ill-resolved multiplet in the region 1.20 to 2.40 accounting for 14 protons. The other 2H multiplet being in the region 2.6-3.20, ^{13}C-NMR spectrum (Fig.8) clearly showed resonances for eleven carbon atoms comprising two quaternary centres and two tertiary centres, as seen by the data: 25.84(t), 27.79(t), 28.04(t), 29.28(t), 30.13(t), 35.59(t), 37.27(t), 46.67(d), 47.52(d), 144.24(s), 148.03(s).

The above spectral data with the expectation of the occurrence of spirocyclic vinylcyclopropane-cyclopentene rearrangement enabled the characterization of the product as **1.5**. This structural assignment was further supported by a direct comparison of proton and ^{13}C-NMR spectral data with those reported for **1.5**.[42]

It can be seen that the transformation of **1.1** into **1.5** by the spirocyclic vinylcyclopropane rearrangement constitutes a net three carbon annulation furnishing a [m.3.0] bridged alkene system.

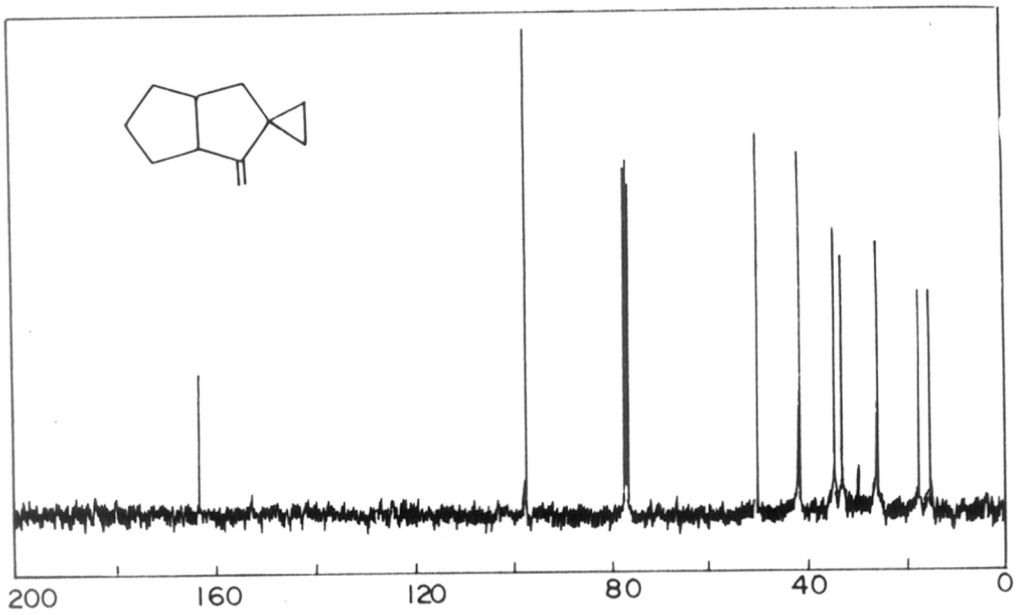


FIG. 5 ^{13}CNMR (300 MHz.) SPECTRUM OF 1.4

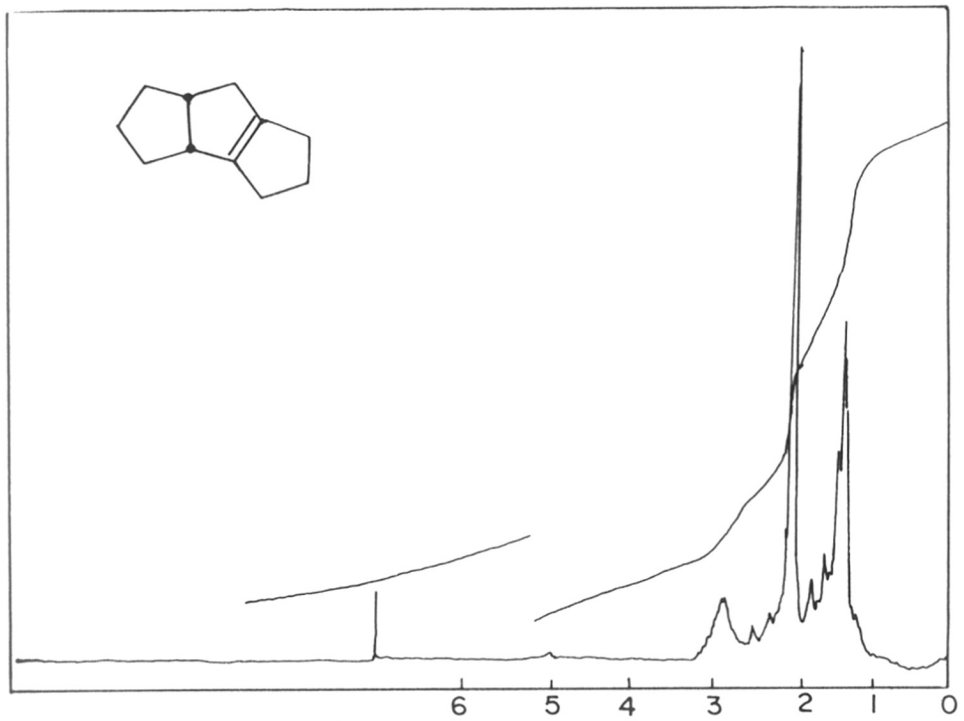


FIG. 7 ^{1}H NMR (80 MHz) SPECTRUM OF 1.5

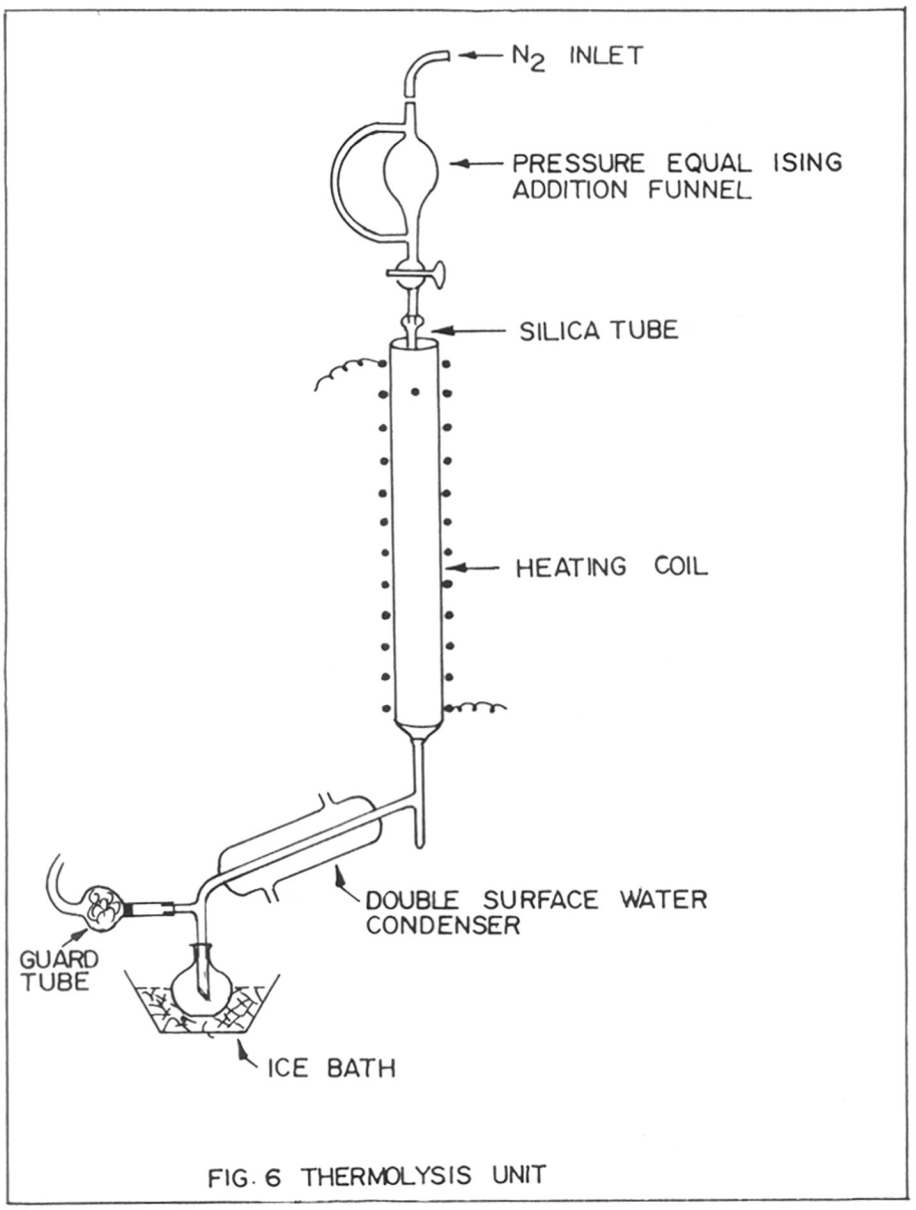


FIG. 6 THERMOLYSIS UNIT

Oxidative cleavage of 1.5[43]

A solution of tricyclic olefin **1.5** in CCl_4, acetonitrile and water was treated with **4.1** Eq. of $NaIO_4$ (sodium metaperiodate). Addition of 2.2 mole % of Ruthenium trichloride hydrate into this biphasic solution and a vigorous stirring of the reaction mixture for about 30 minutes at room temperature, followed by standard work up, furnished a product in about 65% yield. Passage of this product through a short column of silica gel yielded a material which was found to be homogeneous by TLC. The IR spectrum (Fig.9) displayed an intense and broad band at 1695 cm^{-1} indicating the presence of carbonyl function. The PMR spectrum (Fig.10) showed a range of multiplet in the region 1.10-2.70 integrating for 15H besides indicating a 1H double doublet centered at 3.10. The ^{13}C-NMR spectrum (Fig.11) clearly accounted for 11 carbon atoms including two signals at 213 and 214 for the SP^2 carbonyl carbon. The complete data is given below:

23.08(t), 25.95(t), 32.99(t), 40.81(d), 42.94(t), 44.64(t), 53.57(d), 212.97(s), 214.79(s). The mass spectrum showed a molecular ion peak at m/z, 180 and significant peaks at m/z, 152 and 124 probably arising by two sequential loss of carbon monoxide. These spectral data sufficed to identify the product as **1.6**. A direct matching of these data to those of **1.6** reported by Mehta *et al.*[15] provided additional structural support.

The transformation of bicyclo[3.3.0]octanone **1.1** to bicyclo [6.3.0]undeca-2,6-dione **1.6** constituted a ring expansion reaction by three carbon atoms, via the intermediacy of a [m.3.0] bridged alkene. Encouraged by these results, we wanted to explore the generality of this protocol in the synthesis of medium and large membered carbocycles.

Two spirocyclic vinylcyclopropanes **1.10** and **1.14** were prepared from cycloheptanone and cyclododecanone respectively, following the previously described Mannich reaction and Coreys cyclopropanation procedures. These substrates on thermolysis afforded the corresponding bicyclo bridged alkenes **1.11** and **1.17** in satisfactory yields. Finally, Ruthenium chloride/$NaIO_4$ oxidation

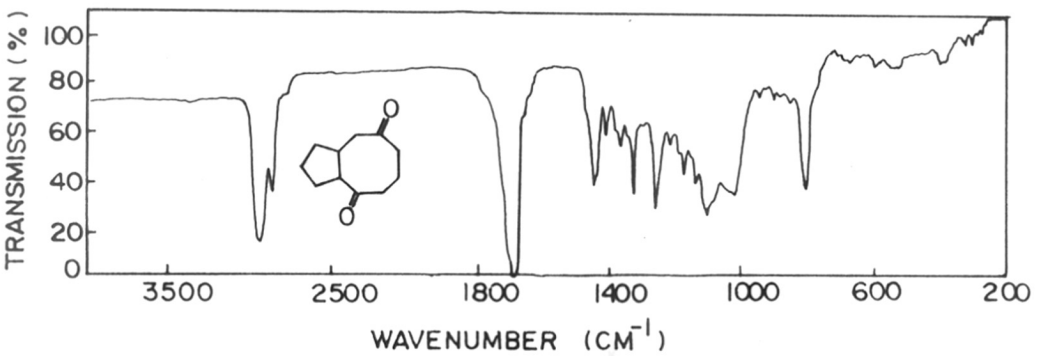


FIG. 9 IR SPECTRUM OF 1.6

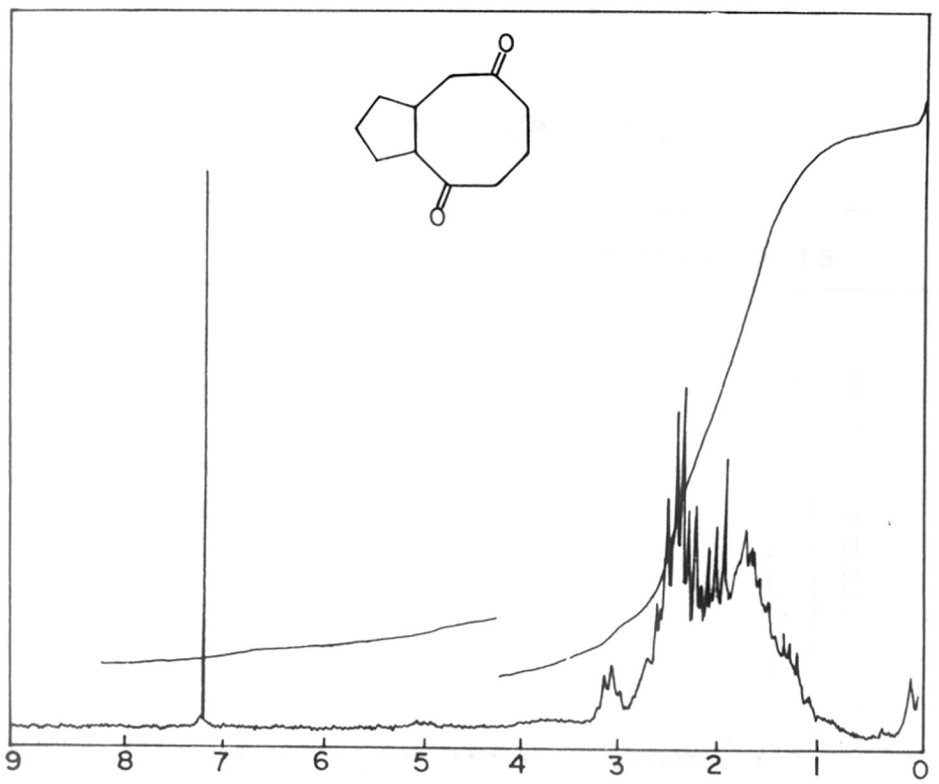


FIG.10 ^{1}H NMR (80 MHz) SPECTRUM OF 1.6

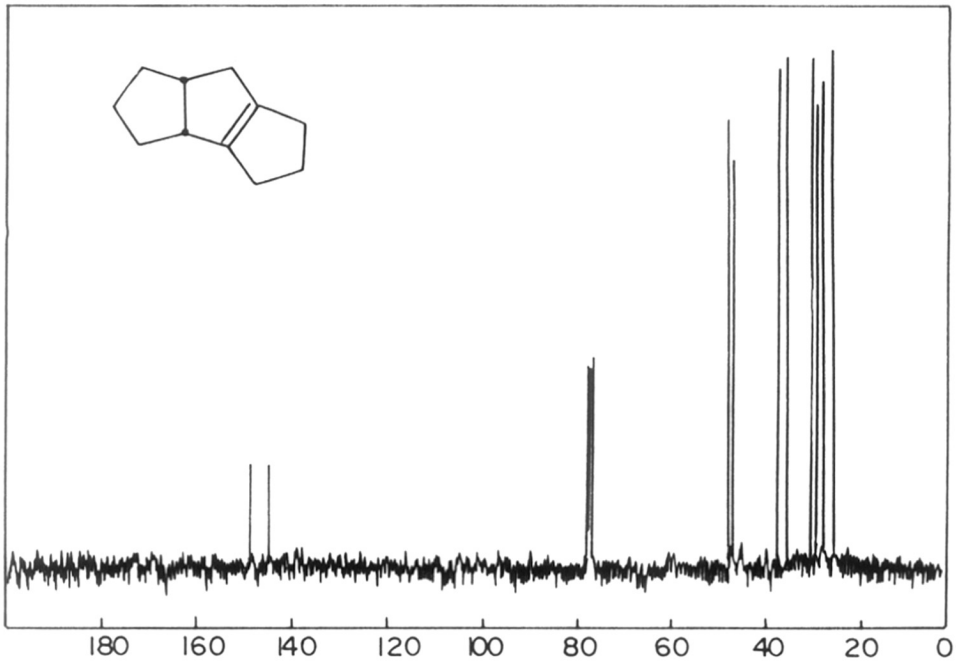


FIG. 8 ^{13}C NMR (300 MHz) SPECTRUM OF 1.5

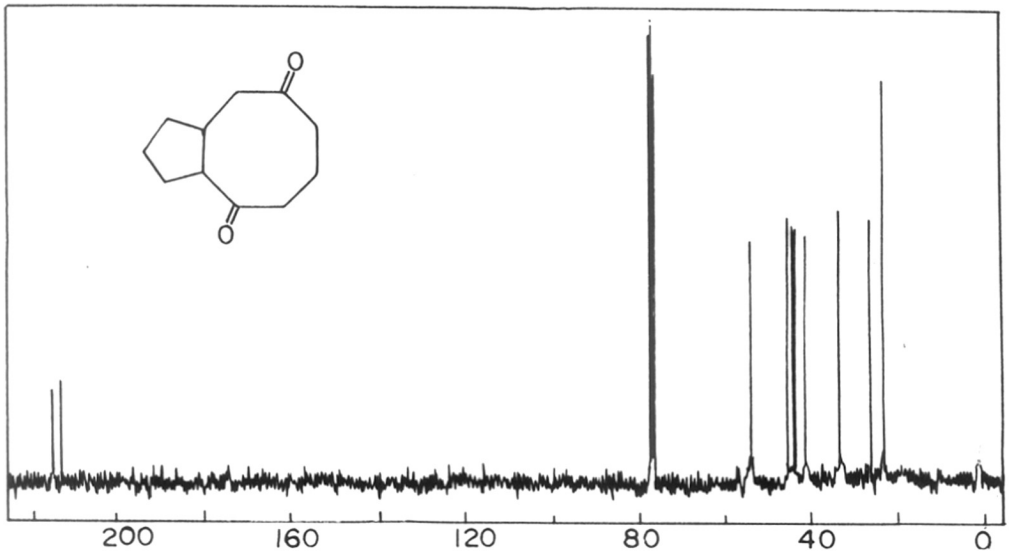
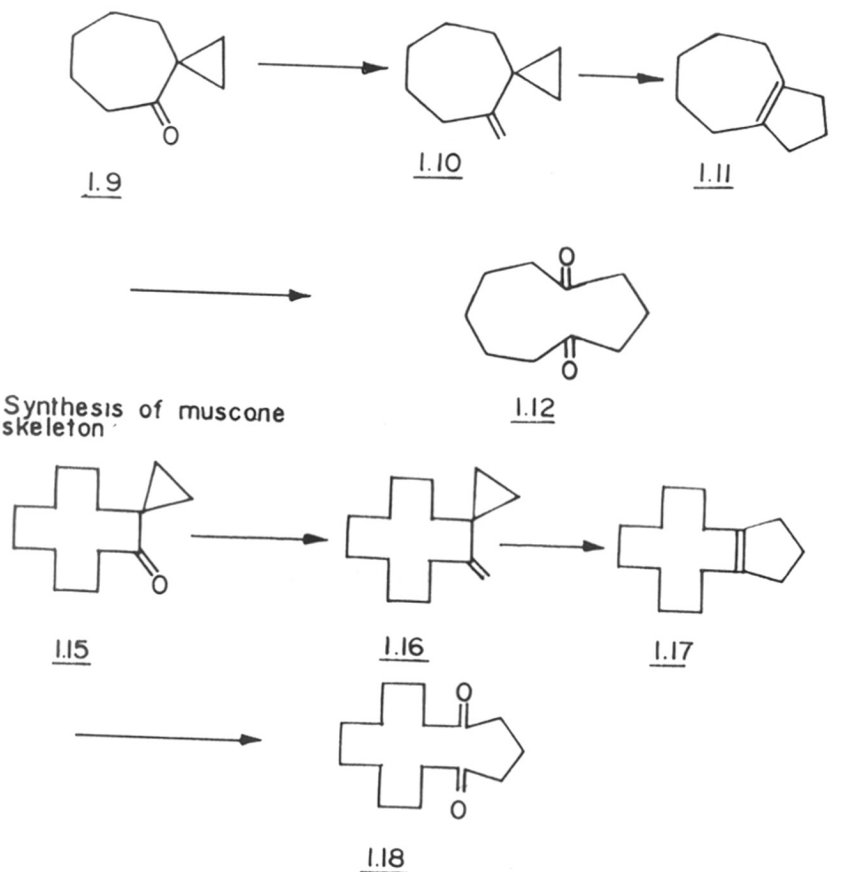


FIG. 11 ^{13}C NMR (300MHz) SPECTRUM OF 1.6

of these bridged alkenes led to the expected C_{10} and C_{15} carbocyclic 1,5-diones, **1.12** and **1.18** respectively. All the intermediates and the final products were well characterized on the basis of their spectral data (see Experimental).

The preparation of the substrates **1.10** and **1.16** and the products obtained from them on thermolysis and $RuCl_3/NaIO_4$ oxidation are shown in Scheme-14.

Scheme 14



The results obtained from these two substrates warrant some comments. At the outset, this protocol has been found to be extremely useful in the construction of medium and large carbocycles.

It may be noted that the highly mobile conformation of the C_{12} carbocycle of **1.16** has not deterred the rearrangement and was as facile as it was in comparatively rigid **1.4**. In addition, the final product **1.12** and its precursor **1.11** from cyclopentanone have synthetic potential in the synthesis of C_{10} natural products.

An attractive feature of the result from cyclododecanone is the attainment of C_{15} cyclic 1,5 dione **1.18** which on monodeoxygenation may lead to exaltone, a key starting material in the synthesis of a valuable perfumery material muscone.[44]

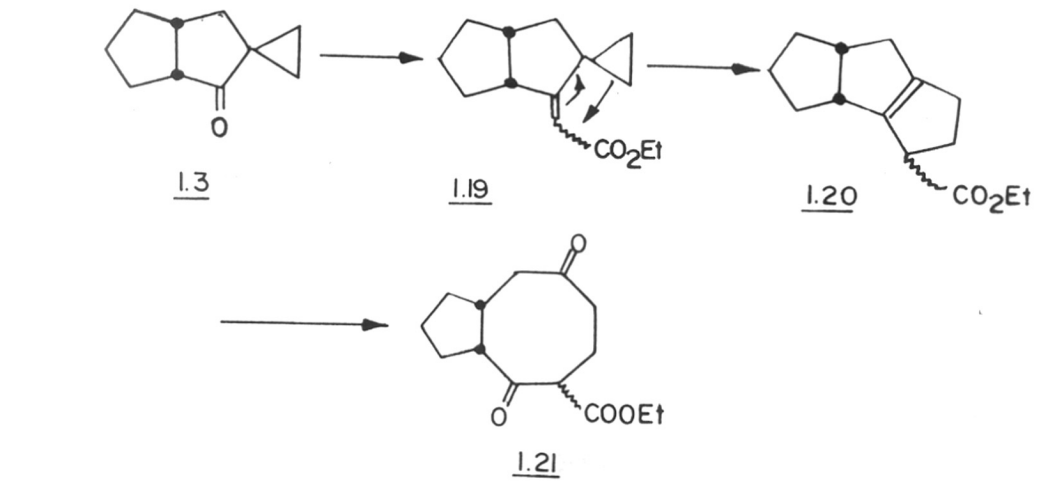
The results from the previous three substrates showed the potentiality of this protocol in realising large sized carbocycles and the efficacy of spirocyclic vinylcyclopropane rearrangement in fusing a five membered ring onto a pre-existing carbocycle. It may be noted that these substrates namely **1.4**, **1.10** and **1.16** did not possess any substituent either on cyclopropane or on the double bond. We, therefore, thought that a study of a couple of substrates with substituents might yield some interesting results. With this objective, the substrate **1.19** with a carboethoxy substituent on the double bond and another with a phenyl substituent on cyclopropane ring **1.24** were prepared. The thermolysis of these substrates afforded the corresponding tricyclic bridged alkenes **1.20** and **1.25** which on oxidative cleavage furnished the final 5-8 fused bicyclic 1,5 diones **1.21** and **1.26** respectively. All the starting materials, the intermediate final products have been characterized by their spectral data. The preparation of these substrates and the results therefrom have been depicted in Scheme-15.

DISCUSSION

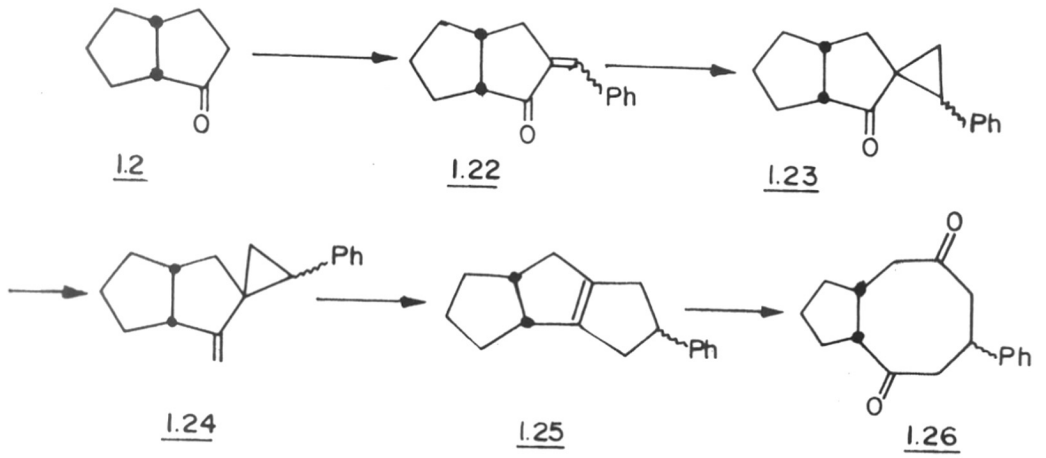
Keeping in mind the facile preparation of these substrates and attractive yields obtained from them in both the thermal rearrangement reaction and the oxidative scission, a few significant remarks need to be made here.

1. The protocol followed for the preparation of these spirocyclic vinylcyclopropanes has been quite satisfactory irrespective of the ring size of the starting cyclic ketone.

Scheme 15



1.3 1.19 1.20 1.21



1.2 1.22 1.23 1.24 1.25 1.26

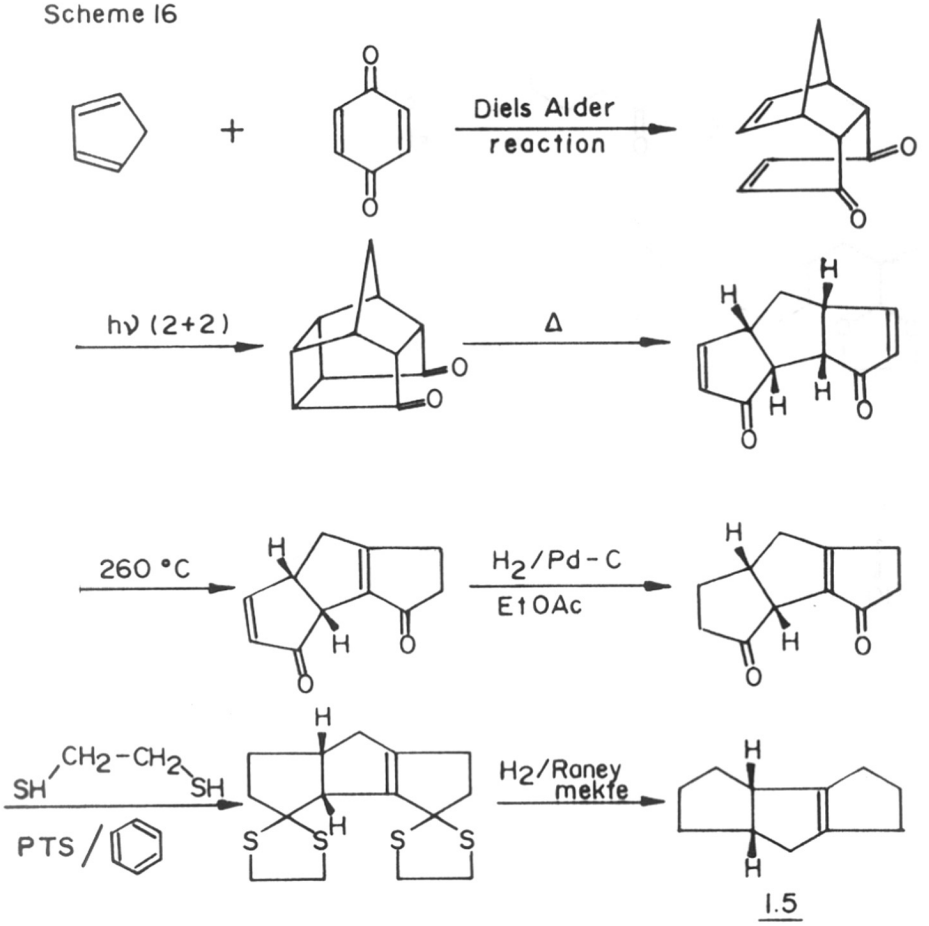
2. The facile transformation of the spirocyclic vinyl cyclopropane into [m.3.0] bridged alkenes indicates a reasonably good orientation of the cyclopropyl bond with *p*-orbitals of the double bond, needed for the rearrangement.

3. These results have led to the development of a convenient methodology for the construction of [m.3.0]alkenes.

4. Ruthenium chloride/$NaIO_4$ oxidation of the bridged alkenes has served to prepare a 5-8 fused carbocyclic systems and also to synthesise C_{10} and C_{15} membered monocyclic ketones.

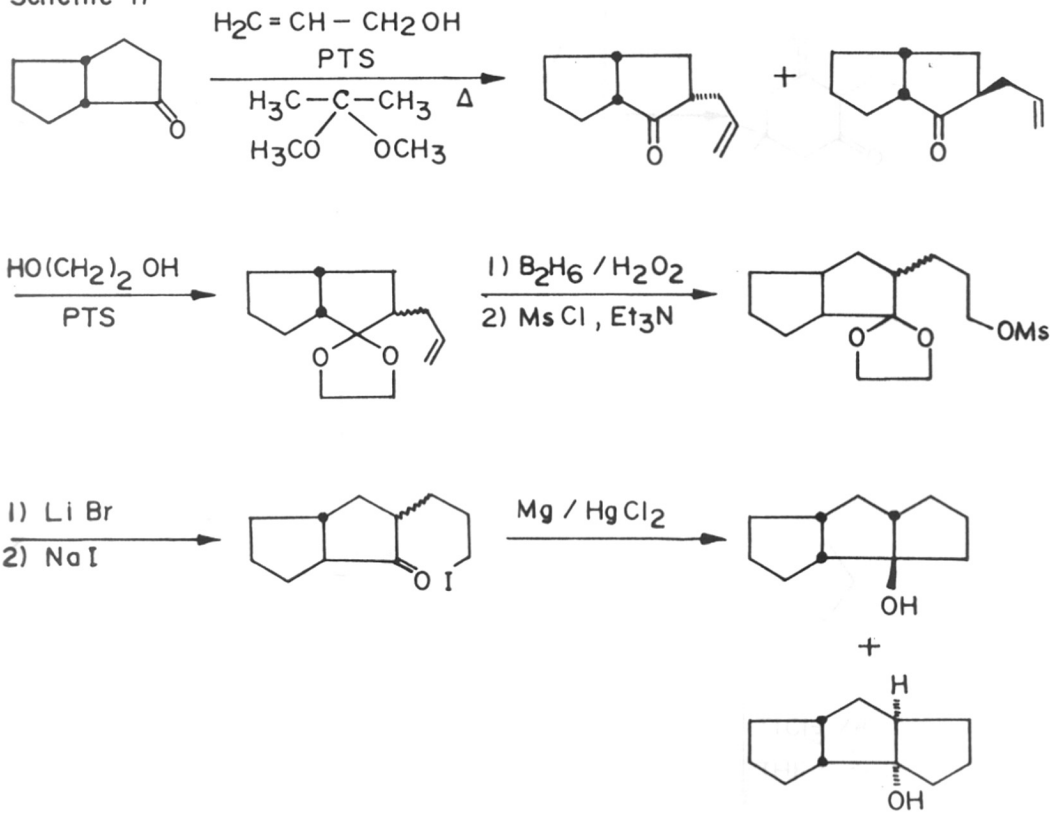
5. In addition to the above general comments, the results obtained from the individual substrates **1.3** (Scheme-13) merit some discussion. The linearly fused triquinane based alkene **1.5** has been a model compound in the synthesis of precapnelladiene reported by Mehta *et al.*[45] It is interesting to find out that the synthesis of **1.5** realized in our study in two synthetic operations from **1.3** has been achieved by an altogether different multistep strategy by the above authors (Scheme-16).

Scheme 16



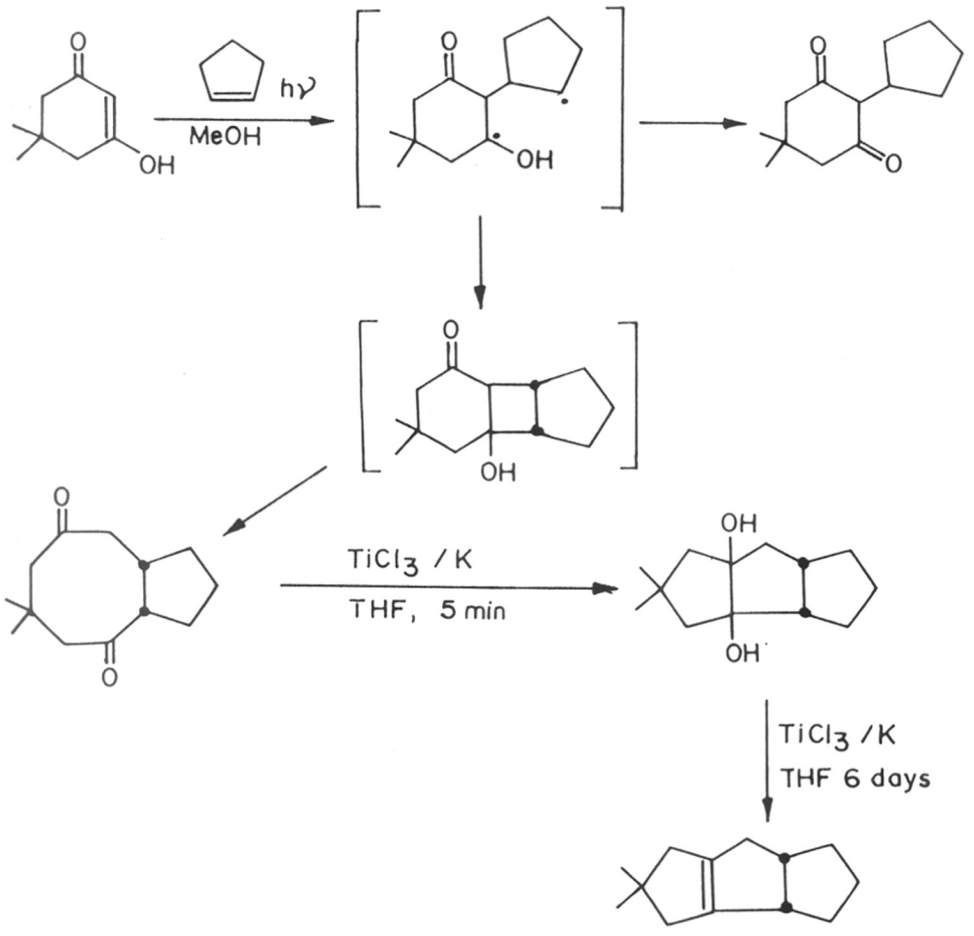
An alternate elegant entry into tricyclo[6.3.0.0^{2,6}]undecane-1-ols system was reported by Kakiuchi *et al.*[42] These authors utilized cis-bicyclo[3.3.0]octan-2-one as starting material and their protocol (Scheme-17) involved two key reactions. An adaptation of Claisen rearrangement led to a mixture of isomeric α-allyl ketones which were transformed into α-ω-iodopropylketone by a sequence of conventional reactions which underwent Barbier cyclization leading to required triquinane alcohols.

Scheme 17



It is to be noted that we obtained the 5-8 fused bicyclo 1,3 dione **1.6** (Scheme-13) from the oxidative cleavage of tricyclo [6.3.0.$0^{2,6}$]undecane system **1.5**. Interestingly enough, Weedon[46] and Pauw have utilized the 5-8 fused bicyclo 1,5 dione to realize the linearly fused triquinane (Scheme-18).

Scheme 18



These authors have harnessed the photochemical generation of radical at a α-site in cyclohexanone and trapped it by cyclopentene. The coupling of 1,4-biradicals led to 5-8 fused 1,5 dione via the intermediacy of the cyclobutanol. McMurry coupling of 1,5 carbonyl groups afforded a tricyclic linearly fused triquinane diol which was transformed to the bridged alkene.

CONCLUSION

The work described in this chapter demonstrates for the first time synthetic potential of spirocyclic vinylcyclopropane-cyclopentene rearrangement in cyclopentane annulation. In addition, this protocol offers a convenient methodology for the construction of [m.3.0] bridged alkenes. More importantly, the oxidative scission of the central bond in these systems furnishes a facile entry into 5-8 fused carbocyclic systems which have recognized potential in the synthesis of natural products.

This protocol is equally applicable in the construction of medium and large carbocycles by variation of the size of the initial cyclic ketone chosen for spirocyclopropyl annulation. The key reaction of vinylcyclopropane-cyclopentene rearrangement does not appear to be deterred by the substituents to either on the double bond or in cyclopropane. In view of the importance of triquinane systems and the occurrence of 5-8 fused carbocycles in natural products, the present strategy assumes significance.

Experimental

General Remarks

1. All melting points (mp) and boiling points(bp) are uncorrected (°C).

2. All solvents and reagents were purified and dried using standard procedures, see: Perrin,D.D.; Armarego,W.L.F.; Perrin,D.R. "*Purification of Laboratory Chemicals*", Second Edition, Pergamon Press, Oxford, **1980**.

3. In general, all reactions requiring anhydrous conditions were carried out under dry, oxygen free, nitrogen atmosphere.

4. Silica gel used for column chromatography was 60-120 mesh.

5. The preparative TLC plates were prepared by spreading an aqueous suspension of silica gel G (200-300 mesh) uniformly over glass plates using applicator (Layer thickness ~ 1.2mm). After initial drying at room temperature, the plates were activated at 100°C for one hr. before use.

6. Elemental analysis (**Anal.**) were carried out using empty tube combustion method on Hoslis rapid carbon hydrogen analyzer.

7. **UV** absorption spectra were recorded on Carl Zeiss UV-VIS model 44069.

8. **IR** spectra were recorded as smears or nujol mulls (in case of solid samples) on a Perkin Elmer Infracord model 137-E. λmax are reported in reciprocal centimeters (cm^{-1}).

9. Proton Magnetic Resonance spectra (^{1}**H-NMR**) were recorded on a Varian T-60, FT-80A, Bruker FT-90, MSL-200 or MSL-300 instrument. Carbon magnetic resonance spectra (^{13}**C-NMR**) were recorded on a Bruker MSL-200 or MSL-300 instrument.
   All spectra were taken in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard.
   ^{1}H-NMR data, using standard notations, are presented in the following order. Chemical shift (δ)/splitting pattern (J = coupling constant)/relative proton ratio/assignment.
   The following abbreviations have been used while presenting the data: s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet and br-broad.

10. The mass spectra (**MS**) were recorded on a CEC mass spectrometer model 21-110B, using an ionization potential of 70 ev and a direct inlet system. The most abundant ions with their relative intensities have been mentioned.

11. Analytical **GLC** of the starting materials and reaction products have been carried out on a Hewlett Packard Gas Chromatograph 5793, with the following columns:
    (i) Carbowax (5%, 6'x1/8", Aluminium column)
    (ii) OV-101 (5%, 6'x1/8" ID, Aluminium column)
    (iii) HP-1 (1m x 0.53mm x 2.65μm, Fused silica capillary column)
12. Usual workup refers to extraction of the reaction mixture with a suitable organic solvent (solvent used is specified in the individual experiments), washing the organic layer with water, followed by brine and drying over anhydrous Na_2SO_4.

Bicyclo[3.3.0]octan-2-one (1.1)

(6.10g, 0.05M) of bicyclo[3.3.0]oct-1(5)-ene-2-one was taken in 100 ml distilled ethanol, followed by addition of Pd-C 10% (600 mg) and hydrogenated under pressure of 40 psi in Parr hydrogenation apparatus for 10 hours and filtered through celite. The celite was washed repeatedly with ethanol. From the combined filtrate, solvent was evaporated and residue was distilled to get the pure product 4.70g, 76% (**b.p.** 70-71°/6mm; lit.[40] 50°C/2.3mm). **IR** (Neat): 2960, 2880, 1745, 1470, 1420, 1320, 1180, 1170, 1150, 1120, 1060 cm^{-1}. **^{1}H-NMR**: 1.24-3.00 (m, 10H).

Spiro[cyclopropane-1,3'-bicyclo(3.3.0)octan-2'-one] (1.3)

This compound was prepared by a reported[39] procedure. A mixture of bicyclo[3.3.0]octanone-2 (12.40g, 0.1M), dimethylamine hydrochloride (38.00g, 0.466M) and paraformaldehyde (9.00g, 0.30M) in 95% ethanol (100 ml) was heated in the presence of a catalytic amount of concentrated hydrochloric acid (1 ml) under reflux for 8 hours. Solvent was evaporated under vacuuo, followed by addition of 100 ml of acetone, the precipitated material was filtered. Treatment of the crude precipitate with excess sodium carbonate in water (50 ml) gave an oil. The aqueous phase was extracted repeatedly with ether (3x30 ml). The combined organic layer was washed with water and dried over anhydrous potassium carbonate, followed by concentration to furnish the aminoketone 11.23g. (62%). Methylation of the amino ketone (11.23g, 0.062M) with methyl iodide (17g, 0.12M) in acetonitrile gave a white precipitate (quantitative) after evaporation of excess CH_3I and the solvent. The product was used as such for cyclopropanation without further purification.

A mixture of oil free sodium hydride [0.1364M, 4.353g. (60%)] and trimethyl oxosulfonium iodide[38] (0.074M, 17g) was treated dropwise with dimethyl sulfoxide (25 ml) at room temperature and under nitrogen atmosphere. After the solution was stirred for 1 hr, a solution of the crude ammonium iodide in DMSO (25 ml) was added dropwise. Stirring was continued for 8 hours at

room temperature and 1 h. at 50-60°C before the mixture was poured onto ice and extracted with ether. After the usual workup, the crude product was purified by column chromatography (silica gel) using pet.ether-ethyl acetate (10:1) as an eluent to furnish the product which was distilled to give 5.26g. (49%), **b.p.** 97-98°C/6mm. **IR** (Neat): 3090, 2980, 2890, 1735, 1450, 1360, 1300, 1100, 1000, 940, 820 cm^{-1}. **^{1}H-NMR**: 0.7-1.00 (m, 2H), 1.10-1.20 (m, 2H), 1.45-2.95 (m, 10H). **^{13}C-NMR**: 16.91(t), 20.38(t), 26.01(t), 28.59(s), 29.95(t), 33.83(t), 35.99(t), 38.85(d), 53.54(d), 223.01(s). **Anal. calcd. for** $C_{10}H_{14}O$: C, 80.00; H, 9.33. **Found**: C, 80.20; H, 9.51.

Spiro[cyclopropane-1,2'-cycloheptan-1'-one] (1.9) and
spiro[cyclopropane-1,2'-cyclododecan-1'-one] (1.15)

These two compounds were prepared starting from cycloheptanone and cyclododecanone by following same procedure except that the molar ratio used for ketone:dimethyl amine hydrochloride:paraformaldehyde was (1:1:1) and reflux time was 36 hours. The yields of the corresponding amino ketones were 60% and 76% respectively. Quarternary salt were prepared in a similar way, as described before, subjected to cyclopropanation reaction in the similar way. However, in these cases, the reaction time was 3 hr. at 50-55°C. After the usual workup, the corresponding cyclopropyl ketones were obtained. The yield of former was 55%, **b.p.** 150-60°C (bath)/4mm and latter was 78%, **b.p.** 160-65°C/4mm. Their spectral data is as follows:

Spiro[cyclopropane-1,2'-cycloheptan-1'-one] (1.9)

IR (neat): 3010, 2960, 2880, 1700, 1460, 1450, 1440, 1380, 1210, 1160, 1120, 920, 840 cm^{-1}. **^{1}H-NMR**: 0.55-0.75 (m, 2H), 1.10-1.30 (m, 2H), 1.50-1.90 (m, 8H), 2.40-2.75 (m, 2H). **^{13}C-NMR**: 19.62(t), 24.56(t), 28.17(t), 30.73(t), 30.93(s), 34.23(t), 44.03(t), 213.53(s). **Anal calcd. for** $C_9H_{14}O$: C, 78.26; H, 10.14. **Found**: C, 78.45; H, 10.29.

Spiro[cyclopropane-1,2'-cyclododecan-1'-one] (1.15)

IR (neat): 3100, 2910, 2880, 1700, 1480, 1450, 1380, 1080, 1060, 1030, 920, 750 cm^{-1}. **^{1}H-NMR**: 0.57-0.73 (m, 2H), 1.02-1.15 (m, 2H), 1.22-1.86 (m, 18H), 2.26-2.55 (m, 2H). **^{13}C-NMR**:

14.62(t), 14.62(t), 22.96(t), 23.63(t), 24.79(t), 25.02(t), 25.45(t), 25.45(t), 25.54(t), 25.79(t), 31.44(s), 33.76(t), 35.33(t), 211.35(s). **Anal. calcd. for** $C_{14}H_{24}O$: C, 80.76; H, 11.53. **Found**: C, 80.78; H, 11.55.

Spiro[2-phenylcyclopropane-1,3'-bicyclo(3.3.0)octan-2'-one] (**1.23**)

This compound was prepared by using 3-phenylmethylidenebicyclo[3.3.0]octan-2-one (**1.22**).The compound (**1.22**) was prepared by following a reported procedure.[47] Bicyclo[3.3.0]octan-2-one (6.2g, 0.06M) and benzaldehyde (5.3g, 0.05M) were taken in 50 ml of 10% aq. KOH solution. The mixture was refluxed for 5 hr. and after cooling, the oily layer was extracted with ether. The ethereal solution was washed with dil. H_2SO_4 and dried over Na_2SO_4. The ether was evaporated and residue was distilled in vacuo. Foreruns were distilled over upto 100°C/8mm. Then the temperature was increased to 200°C/8mm to get the pure product, Yield 6g. (58%). **IR** (neat): 2940, 2880, 1720, 1620, 1500, 1450, 1300, 1240, 1190, 950, 760, 700 cm^{-1}. **^{1}H-NMR**: 1.20-2.11 (m, 7H), 2.53-3.35 (m, 3H), 7.11-7.62 (m for 5 Ar-H and one olefinic H). **MS**: m/z (%): 212 (M^+, 100%), 184(11), 155(12), 141(15), 129(13), 115(42), 91(26).

(0.528g (50%), 0.011M) of NaH was placed in a flask and washed thrice with dry pet.ether under nitrogen atmosphere. The system was evacuated until the last traces of pet.ether were removed. Then (2.64g, 0.012M) of powdered trimethyloxosulfonium iodide was introduced. The system was placed under nitrogen atmosphere, followed by addition of 15 ml dry DMSO dropwise with stirring. A vigorous evolution of H_2 ensued, which ceased after 15-20 minutes to give milky white reaction mixture. To this mixture the enone (2.12g, 0.01M) in 15 ml dry DMSO was added dropwise with stirring. After complete addition, reaction mixture was stirred for 3 h. at 50-55°C, poured over ice-cold water, extracted with ether. After the usual workup, the crude product was purified by chromatography (silica gel) using pet.ether-ethyl acetate (10:1) as an eluent to furnish the product

as a viscous oil 2.14g. (95%). **b.p.** 180-85°C/3.5mm. **IR** (neat): 3020, 2980, 2900, 1735, 1610, 1505, 1470, 1390, 1270, 1130, 1080, 1050, 780, 710 cm^{-1}. **^{1}H-NMR**: 0.77-1.15 (m, 1H), 1.22-2.22 (m, 9H), 2.44-2.88 (m, 3H), 6.95-7.48 (5H). **Anal. calcd. for** $C_{16}H_{18}O$: C, 84.95; H, 7.96. **Found**: C, 84.81; H, 8.14.

General procedure for olefination of spirocyclic ketones

This reaction was done by following a reported procedure.[41] A mixture of activated zinc powder (2.35g, 0.035M), 6 ml dry THF and (2.08g, 0.012M) dibromomethane was stirred under nitrogen atmosphere and cooled to -10°C to -5°C by using ice-salt bath. To the stirred mixture, $TiCl_4$ (0.96 ml, 0.0088M) in dry CH_2Cl_2 (3 ml) was added dropwise. After complete addition of $TiCl_4$, the reaction mixture was stirred for half an hour at -5°C to -10°C, followed by addition of spiroketone (0.008M). After complete addition of ketone, the reaction mixture was allowed to come to room temperature and stirred overnight. A slurry of 20g. of $NaHCO_3$ in minimum amount of water was prepared and cooled to 0°C, followed by addition of the reaction mixture slowly and diluted by n-hexane (50 ml). The organic layer was decanted and the slurry was washed with n-hexane for several times. The combined organic extract was dried over a mixture of anhydrous sodium sulphate - $NaHCO_3$ (5:1) and filtered. Evaporation of the solvent and chromatography of the residue over silica gel using pet.ether as an eluent furnished the pure product. The distillation was avoided because these compounds tend to polymerise fast. Yields and spectral data of these compounds are as follows:

Spiro[cyclopropane-1,3'-bicyclo(3.3.0)octan-2'-methylene] (1.4)

Yield: 66%. **IR** (neat): 3090, 2960, 2880, 1660, 1460, 1440 cm^{-1}. **^{1}H-NMR**: 0.70 (s, 4H), 1.25-3.2 (m, 10H), 4.30 (d, 1H), 4.5 (d, 1H). **^{13}C-NMR**: 15.15(t), 17.38(t), 25.77(s), 25.95(t), 33.22(t), 34.80(t), 41.63(d), 41.82(t), 50.15(d), 97.26(t), 163.11(s). **MS**: m/e M^+, 148 (30%), 133(32), 119(85), 105(67), 91(100), 79(54), 77(47), 67(3), 65(33).

Spiro[cyclopropane-1,2'-cycloheptan-1'-methylene] (1.10)

Yield: 70%. **IR** (neat): 3100, 2920, 2880, 1630, 1455, 1380, 1280, 1040, 900, 850 cm^{-1}. **^{1}H-NMR**: 0.40-0.90 (m, 4H), 1.10-1.90 (m, 8H), 2.10-2.45 (m, 2H), 4.45-4.75 (m, 2H). **MS**: m/e (M^+, 136 (58%), 121(100), 107(89), 95(45), 93(91), 91(51), 79(39).

Spiro[cyclopropane-1,2'-cyclododecane-1'-methylene] (1.16)

Yield: 74%. **IR** (neat): 3100, 2940, 1640, 1480, 1460, 1020, 900, 740, 710 cm^{-1}. **^{1}H-NMR**: 0.20-0.60 (m, 4H), 1.00-1.70 (m, 18H), 1.95-2.20 (m, 2H), 4.70-4.90 (m, 2H). **MS**: m/e M^+ 206 (39%), 191(13), 178(100), 163(17), 149(8), 135(77), 58(29).

Spiro[cyclopropane-1,3'-bicyclo(3.3.0)octan-2'-ethoxycarbonylmethylidene] (1.19)

This compound was prepared by using spirocyclopropane-1,3'-bicyclo[3.3.0]octan-2'-methylenethoxycarbonyl-2'-ol. This tertiary alcohol was prepared by following a reported procedure.[48] A mixture of spirocyclopropane-1,3'-bicyclo[3.3.0]octan-2'-one (1.50g, 0.01M), ethylbromoacetate (0.03M), Zn powder (10g.) and NH_4Cl (4g) was thoroughly ground in an agate mortar and pestle, and the mixture was kept at room temperature for 3 h. The reaction product was treated with aqueous NH_4Cl and extracted with ether. The ether extract was washed with water and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, to get the crude product. **Yield**: 2.20g. (92%). This was used as such for dehydration. The spectral data of the product is as follows:

IR (neat): 3500, 2950, 2860, 1730, 1450, 1380, 1350, 1200, 1040. **^{1}H-NMR**: 0.22-0.44 (m, 2H), 0.80-0.91 (m, 2H), 1.13-2.90 (m, 15H), 3.57 (s, 1H), 4.17 (q, 2H). **MS**: m/z (%): 238 (M^+, 6), 220(18), 210(26), 191(15), 171(10), 164(32), 156(24), 150(61), 133(43), 122(45), 109(35), 91(51), 79(81), 67(100).

Dehydration of the above tertiary alcohol was done by following a reported procedure.[49] To a stirred solution of the tertiary alcohol (2.38g, 0.01M) in CH_2Cl_2 (25 ml) was added triethylamine (3.03g, 0.03M) and 4-dimethylaminopyridine (DMAP) (50 mg). The mixture was cooled to 0°C and methanesulfonylchloride (1.72g, 0.015M) was added dropwise into it. The mixture

was stirred for 1 h. at room temperature, then crushed ice was added and the mixture stirred for 1 hr, after which it was extracted with CH_2Cl_2 (3x25 ml). On usual workup, the crude product obtained was chromatographed (silica gel-10% ethyl acetate in pet.ether) to get the pure product. **Yield**: 1.53g. (70%). **IR** (neat): 2920, 2880, 1710, 1650, 1450, 1370, 1270, 1180 (broad), 1050, 860 cm^{-1}. **^{1}H-NMR**: 0.86 (s, 4H), 1.24 (t, 3H), 1.44-3.60 (m, 10H), 4.11 (q, 2H), 5.04 (two singlets merged 1H). **MS**: m/z (%): 220 (M^+, 27), 205(29), 192(19), 177(33), 147(43), 119(39), 105(47), 91(100), 77(53).

Spiro[2-phenylcyclopropane-1,3'-bicyclo(3.3.0)octane-2'-methylene] (1.24)

Yield (72%); **IR** (Neat): 3010, 2960, 1605, 1460, 1050, 880, 760, 710 cm^{-1}; **^{1}H-NMR**: 0.22-1.00 (m, 2H), 1.12-3.21 (m, 10H), 4.48-4.60 (m, 2H), 7.00-7.48 (m, 5H). **MS** m/z (%): 224 (M^+, 72), 209(19), 195(35), 181(26), 170(57), 155(52), 141(100), 139(27), 129(41), 115(38), 105(19), 91(36).

General procedure for thermolysis: Spirocyclic vinylcyclopropane-cyclopentene rearrangement

The diagram of the thermolysis unit is shown in Fig.6. Thermolysis was done in a vertically-held quartz tube (1.2cm x 40cm) packed with quartz helices; it was washed successively with saturated $NaHCO_3$, water, acetone and n-hexane. The tube was heated to 500°C and thoroughly purged with a stream of nitrogen. A solution of the substrate 0.20g. in 15-20 ml of the specified dry solvent was added dropwise into the column. During thermolysis, a slow stream of nitrogen was maintained through the column. The thermolysate was trapped in a flask cooled by ice-salt bath. After removal of the solvent, the product was purified by column chromatography (silica gel) using same specific solvent as an eluent.

***Cis*-Tricyclo[6.3.0.0^{2,6}]undec-1(8)-ene[42] (1.5)**

Thermolysis of **1.4** carried out, as described above, furnished the product **1.5**. Solvent - dry pet.ether. **Yield**: (88%). **IR** (neat): 2920, 2820, 1440, 1280, 1100, 1010, 800 cm^{-1}. **^{1}H-NMR**: 1.2-2.4

(m, 14H), 2.6-3.2 (m, 2H). **^{13}C-NMR**: 25.84(t), 27.79(t), 28.04(t), 29.28(t), 30.13(t), 35.59(t), 37.27(t), 46.67(d), 47.52(d), 144.24(s), 148.03(s). **MS**: m/z (%): 148 (M^+, 100), 133(42), 119(91), 105(20), 91(20).

***Cis*-Tricyclo[6.3.0.0^{2,6}]undec-10-phenyl-1-(8)-ene (1.25)**

(From the thermolysis of **1.24**).Solvent - dry benzene:dry pet.ether (1:1). **Yield**: (56%). **IR** (neat): 2980, 2800, 1600, 1510, 1360, 1280, 1140, 740, 670 cm^{-1}. **^{1}H-NMR**: 1.13-1.60 (m, 12H), 2.51-3.06 (m, 2H), 7.22 (s, 5H). **MS**: m/z (%): 224 (M^+, 7), 179(6), 167(35), 154(63), 141(100), 128(65), 115(58), 104(33), 91(35).

***Cis*-Tricyclo[6.3.0.0^{2,6}]undec-9-ethoxy carbonyl-1(8)-ene (1.20)**

(From the thermolysis of **1.19**).Solvent - dry benzene:pet.ether (1:1). **Yield**: (59%). **IR** (neat): 2950, 2790, 1745, 1450, 1370, 1350, 1200, 1050, 800 cm^{-1}. **^{1}H-NMR**: 1.26 (t, 3H), 1.40-3.37 (m, 14H), 4.13 (q, 2H), 5.33 (s, 1H). **MS**: m/z (%): 220 (M^+, 17), 169(8), 155(9), 147(100), 119(28), 105(25), 91(54), 77(25).

Bicyclo[5.3.0]dec-1(7)-ene (1.11)

(From the thermolysis of **1.10**).Solvent - dry pet.ether. **Yield**: (66%). **IR** (neat): 2920, 2820, 1410, 1220, 1060, 760, 690 cm^{-1}. **^{1}H-NMR**: 1.15-2.82 (m, 16H). **MS**, m/z (%): 136 (M^+, 7), 105(24), 91(100), 79(89), 67(34).

Bicyclo[10.3.0]pentadec-1(10)-ene (1.17)

(From the thermolysis of **1.16**).Solvent - pet.ether. **Yield**: (68%). **IR** (neat): 2940, 2880, 1480, 1440, 1360, 1280, 1110, 1030, 810, 750 cm^{-1}. **^{1}H-NMR**: 1.00-1.60 (m, 18H), 1.80-2.30 (m, 8H). **MS**, m/z (%): 206 (M^+, 47), 163(4), 149(6), 135(13), 121(22), 107(21), 93(50), 79(100), 67(87), 55(75).

General procedure for the oxidative scission[43] of tricyclic and bicyclic bridged alkenes

A flask was charged with 1 ml of CCl_4, 1 ml of CH_3CN, 1.5 ml of water, 0.5 mmol of the bridged alkene and 440 mg (4.1 equiv.) of sodium metaperiodate. To this biphasic solution, two-three crystals (~ 2 mg) of ruthenium trichloride-hydrate was added and the entire mixture was stirred vigorously for 2 h. at room temperature. Then 5 ml of CH_2Cl_2 was added and the phases were separated. The upper aqueous phase was extracted with CH_2Cl_2 (3x5 ml). The combined organic extracts was dried over Na_2SO_4 and concentrated. The residue was treated with 20 ml of ether and filtered through celite pad and concentrated. The crude product was purified by chromatography over silica gel using pet.ether-ethyl acetate (10:4) as an eluent to furnish the pure product.

Bicyclo[6.3.0]undeca-2,6-dione (1.6)

m.p. 61°C, (Lit. 63-64°C)[16]. **Yield**: (65%). **IR** (KBr): 2950, 1700, 1440, 1240. **^{1}H-NMR**: 1.10-3.20 (m, 16H). **^{13}C-NMR**: 23.08(t), 25.95(t), 32.99(t), 40.81(d), 42.94(t), 43.64(t), 44.64(t), 53.57(d), 212.97(s), 214.79(s). **MS**: m/z (%): 180 (M^+, 12). 152(16), 124(36), 113(69), 97(16), 95(37), 83(71), 67(100), 55(75). **Anal. calcd. for** $C_{11}H_{16}O_2$: C, 73.33; H, 8.88. **Found**: C, 73.12; H, 8.70.

3-Ethoxycarbonyl-bicyclo[6.3.0]undeca-2,6-dione (1.21)

Viscous liquid **Yield**: (68%). **IR** (neat): 2950, 2880, 1740 (broad), 1720 (broad), 1650, 1610, 1450, 1380, 1300, 1200, 1110, 1040, 880, 780 cm^{-1}. **^{1}H-NMR**: 1.30 (two triplets merged, 3H), 1.48-3.70 (m, 15H), 4.21 (two quartets merged, 2H). **MS**, m/z (%): 252 (M^+, 36), 234(9), 206(30), 195(9), 185(36), 178(62), 163(21), 152(79), 139(34), 124(51), 110(41), 99(32), 95(55), 83(49), 67(85), 55(100). **Anal. calcd. for** $C_{14}H_{20}O_4$: C, 66.66; H, 7.93. **Found**: C, 66.32; H, 8.01.

4-Phenylbicyclo[6.3.0]undeca-2,6-dione (1.26)

Viscous liquid **Yield**: (52%). **IR** (neat): 2920, 2880, 1700 (two broad), 1590, 1450, 1360, 1260, 780, 710 cm^{-1}. **^{1}H-NMR**: 0.78 to 3.66 (m, 15H), 7.11-8.22 (m, 5H). **MS**, m/z (%): 256 (M^+, 4), 160(4), 149(8), 139(8), 131(12), 122(58), 111(9), 105(100), 95(15), 83(29), 77(95). **Anal. calcd. for** $C_{17}H_{20}O_2$: C, 79.68; H, 7.81. **Found**: C, 79.43; H, 7.50.

Cyclodeca-1,5-dione (1.12)

Semi-solid material. **Yield**: (65%). **IR** ($CHCl_3$): 2940, 2880, 1715, 1470, 1430, 1380, 1280, 1230, 1110, 1030 cm^{-1}. **^{1}H-NMR**: 1.15-2.62 (m, 16H). **^{13}C-NMR**: 18.77(t), 22.94(t), 26.80(t), 38.71(t), 44.33(t), 53.30(t), 213.89(s). **MS**: m/z (%): 168 (M^+, 14), 150(10), 140(10), 125(25), 112(35), 108(11), 97(100), 83(59), 81(12), 70(20). **Anal. calcd. for** $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. **Found**: C, 71.31; H, 9.80.

Cyclopentadeca-1,5-dione (1.18)

m.p. 61-62°C. **Yield**: (68%). **IR** (nujol): 1720 cm^{-1}. 1480, 1390, 1130, 1050, 1000, 730, 740 cm^{-1}. **^{1}H-NMR**:1.04-2.00 (m, 18H), 2.22-2.66 (two triplets merged, 8H). **^{13}C-NMR**: (symmetrical molecule) 17.83(t), 23.49(t), 26.97(t), 27.22(t), 28.16(t), 41.32(t), 42.01(t), 211.54(s). **MS** m/z (%): 238 (M^+, 16), 195(7), 153(8), 135(12), 128(32), 111(23), 97(85), 83(54), 69(42). **Anal. calcd. for** $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. **Found**: C, 75.39; H, 11.05.

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CHAPTER II

Application of vinylcyclopropane-cyclopentene rearrangement towards the construction of Taxane framework [A/B ring system] and synthesis of (±)β-cuparenone

Objective: *This chapter presents our synthetic efforts towards realising 5-8 fused carbocyclic AB framework of Taxol. The key reaction utilized is spirocyclic vinylcyclopropane-cyclopentene rearrangement. (Section A).*

As a further extension to demonstrate the synthetic potential of this rearrangement reaction, our synthetic inputs aimed at realization of (±)β-cuparenone are also included. (Section B).

Section A: Synthetic efforts towards the construction of Taxane framework [A/B ring system]

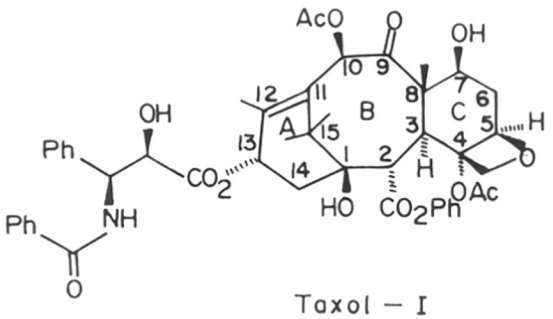
Introduction

The occurrence of 5-8 fused carbocycles in many natural products and various important methodologies for the construction of such systems have been briefly presented in the previous chapter. Attention was also drawn to natural products possessing 5-8 fused ring system, especially to those with well recognised biological profile;[1] this included taxol, taxinine and baccatin.

The results presented in the previous chapter showed the efficacy of spirocyclic vinylcyclopropane-cyclopentene rearrangement in leading to 5-8 fused bicyclo[6.3.0]undecane systems exemplified by a key intermediate to the marine natural product precapnelladiene. These encouraging results prompted us to extend this methodology towards the synthesis of AB framework of taxane system.

Taxol (I) isolated from the yew trees nearly twenty two years ago[2] has attracted tremendous synthetic efforts owing to its great promise in the treatment of cancer, especially breast cancer.[3]

The biological activity combined with the highly functionalised complex framework of Taxol provided a great stimulus for its synthesis. An additional triggering factor is the occurrence of this natural product in trace amounts which would not suffice for structure activity studies. The synthetic interest created by this molecule can be attested by the fact that more than forty research groups are working to realize a total synthesis, all over the world.



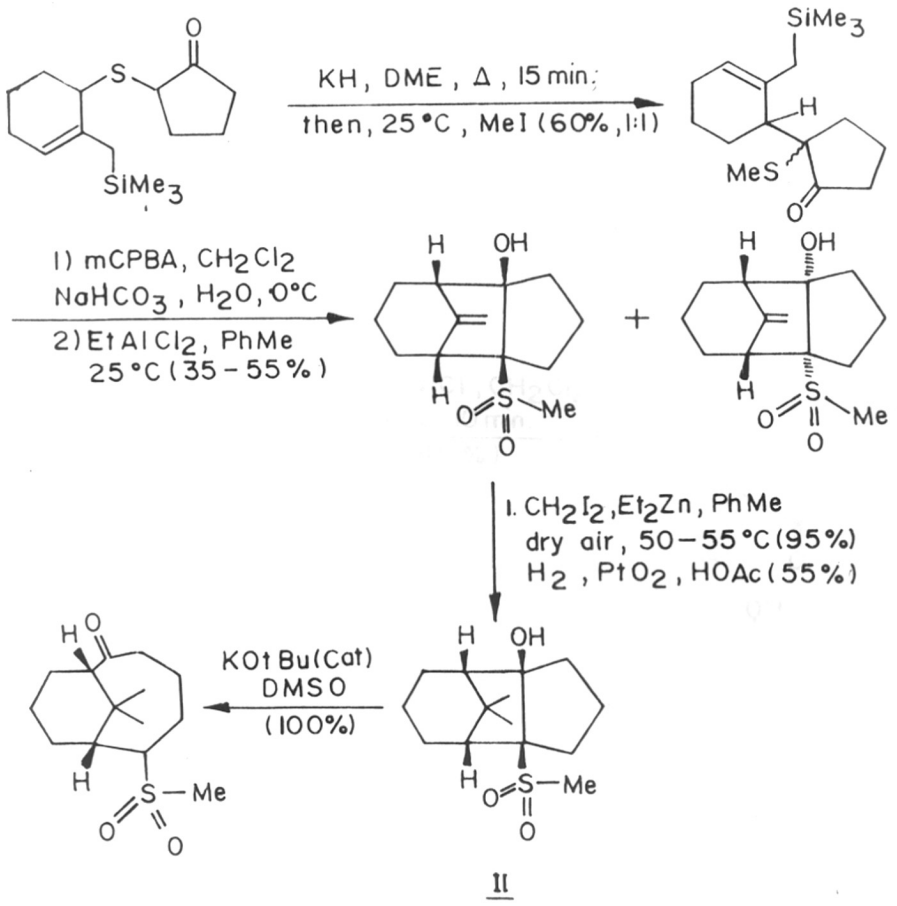
Taxol – I

An examination of the structural features of this molecule bringsforth a few inherent difficulties. The main problem in taxol synthesis has been the construction of the highly functionalized central eight membered ring. Although the gemdimethyl groups at C_{15} and the methyl group at C_8 are not very close to each other in the taxol molecule, most of the methods with pre-fabricated A and C rings were not successful owing to steric resistance offered by the methyl groups.

As our goal was to devise a synthetic methodology for the construction of AB ring system of taxol, a brief literature survey was carried out to understand various strategies employed. There have been numerous designs and tactics towards this end and this topic has been reviewed[4] well. Nevertheless, with a view to highlight the importance of the problem and to present a few interesting strategies, four synthetic designs have been chosen and the key reactions are presented in various schemes.

Trost and Heimstra[5] have elegantly generated the eight membered ring of the taxol skeleton by the cleavage of the central bond of a tricyclic compound (II). It can be seen that this fragmentation reaction takes advantage of the stabilization provided by the sulfone group of the carbanion intermediate involved. In this reaction, the stereochemistry of the substituents at the ring junction does not affect the course of the reaction. It can be noted that the introduction of the gemdimethyl group was initially carried out in the tricyclic intermediate before the fragmentation reaction (Scheme-1).

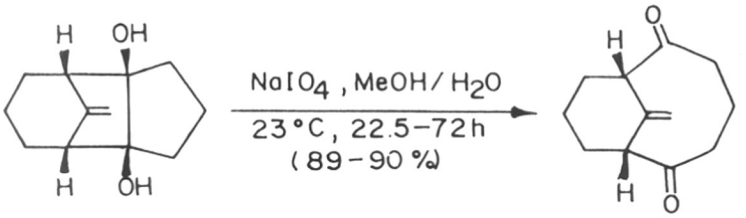
Scheme I



II

In a similar manner, Trost and Fray[6] realized a short entry into the bicyclo [5.3.1] undecane system IV by an oxidative cleavage of the diol III (Scheme-2).

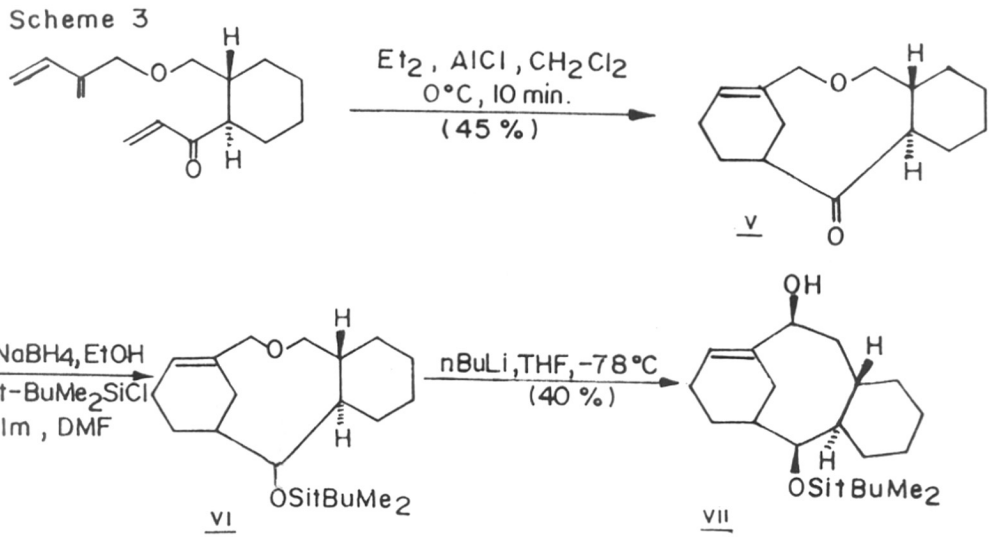
Scheme 2



III IV

Another interesting strategy towards the taxane skeleton based on Wittig rearrangement was recently reported by Yadav and Ravishankar.[7] This approach utilizes intramolecular Diels-Alder reaction to construct the A ring model V (Scheme-3) which was converted to VI by conventional chemistry. A Wittig rearrangement involving ring conflection led to the desired AB ring system (VII) of Taxol.

Scheme 3



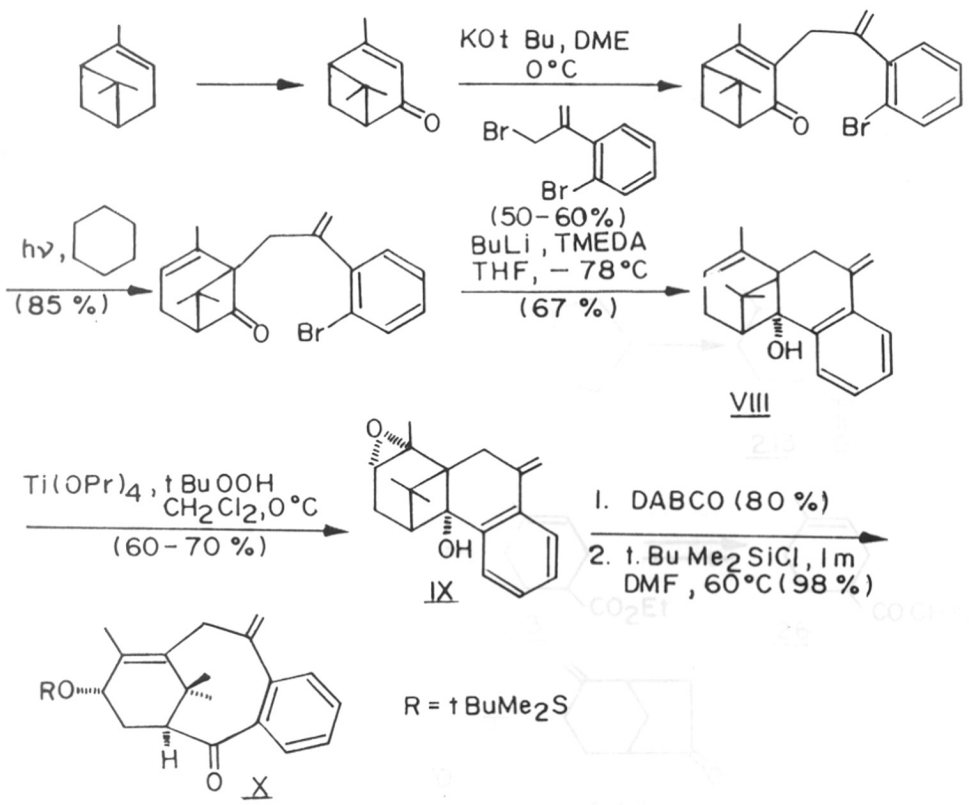
An elegant strategy towards the taxane skeleton was reported recently by Wender and Mucciaro[8] (Scheme-4).

These authors utilized (+) α pinene as a cheap starting material to synthesize the hydroxy epoxide IX, which underwent base induced fragmentation to afford a tricyclic key intermediate X.

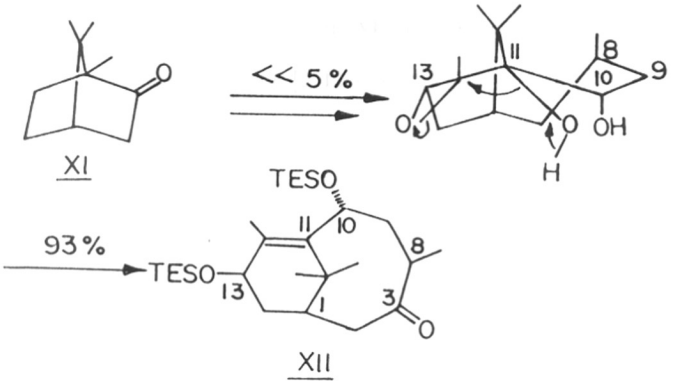
Holten et al.[9] (Scheme-5) constructed the AB framework of taxane (XII) in a linear strategy utilizing fragmentation of β-patchoulene oxides; the latter was synthesized from (-) camphor XI.

With our goal of synthesising a [m.3.0] bridged alkene by spirocyclic vinylcyclopropane rearrangement and realizing the cyclooctane ring by a fragmentation reaction, the literature survey was highly selective with more examples of the fragmentation reactions. With the availability of

Scheme 4

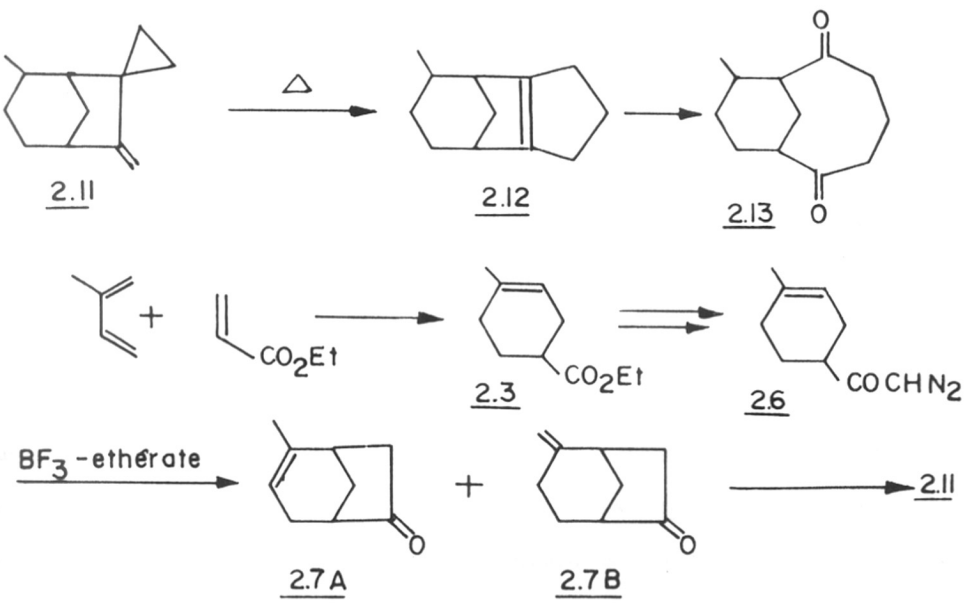


Scheme 5



innumerable strategies for the construction of AB ring system of a taxane skeleton, we would be content in making references to the literature dealing with the fragmentation strategy in realizing A/B ring system. Nonetheless, we realized that this spirocyclic vinylcyclopropane rearrangement was not utilized so far for this purpose.

Scheme 6



A synthetic plan of reactions in which a spirocyclic vinyl cyclopropane rearrangement to furnish a [m.3.0] bridged alkene [2.11 --> 2.12] and the oxidative cleavage of the olefinic bond, constituting the key reactions, is shown in Scheme-6. It can be seen that BF_3 catalyzed reaction of 2.6 should lead to a mixture of bicyclic ketone 2.7 which on hydrogenation followed by spirocyclopropanation and olefination, as described in the previous chapter, should furnish the desired substrate 2.11 for the rearrangement. An occurrence of the expected thermal VCR should lead to 2.12 which can be seen as a ready precursor to bicyclo [5.3.1] undecane system 2.13. At this planning stage, a few special features of this target intermediate may be mentioned. One of the carbonyl groups can be readily utilized for the introduction of the desired acetoxy function; the

other carbonyl group can activate the adjacent bridged C-H bond for the required hydroxylation. Nonetheless, realization of 2.13 just serves as an exercise in building up the AB ring system of taxane skeleton.

Results and Discussion

Diels-Alder reaction[10] of 2-methyl 1,3-butadiene with ethyl acrylate in sealed tube readily afforded a homogeneous product. The use of hydroquinone in the reaction to arrest the polymerization of butadiene enabled us to obtain the Diels-Alder adduct in about 90% yield. The PMR spectrum of the product (Fig.1) displayed a 3H triplet at 1.25, a 2H quartet at 4.15, 1 H multiplet at 2.50 and a 3H singlet at 1.52; besides these signals, the spectrum showed a 4H multiplet at 2.00, a 2H multiplet at 2.20 and a 1H broad signal at 5.40. These spectral data readily enabled the characterization of the product as 2.3.

The alkaline hydrolysis of the above ester readily furnished the corresponding acid which was transformed to the diazoketone 2.6 by the treatment of the acid chloride with diazomethane. The IR spectrum (Fig.2) of the product clearly indicated a strong band at 2150 cm^{-1} typical of a α-diazoketone. The PMR spectrum (Fig.3) was conspicuous by a 1H singlet at 5.20, 3H singlet at 1.60, a 1H broad signal at 5.30 and broad multiplet in the region 1.80 to 2.46 accounting for seven protons. Thus, the IR and PMR spectral data enabled a ready characterization of the product 2.6. With the preparation of α-diazoketone 2.6, two distinct ways of getting the required bicyclic ketones 2.7 occured to us. These possibilities are shown in Scheme-7.

α-diazoketones are known to be efficient precursors to carbenoid species and their reactions with double bonds in presence of either copper or rhodium acetate catalysts lead to cyclopropanation. Such a reaction on 2.6 should lead to the cyclopropanated intermediate which on acid catalysis should result in a mixture of bicyclic ketones 2.7A and 2.7B.

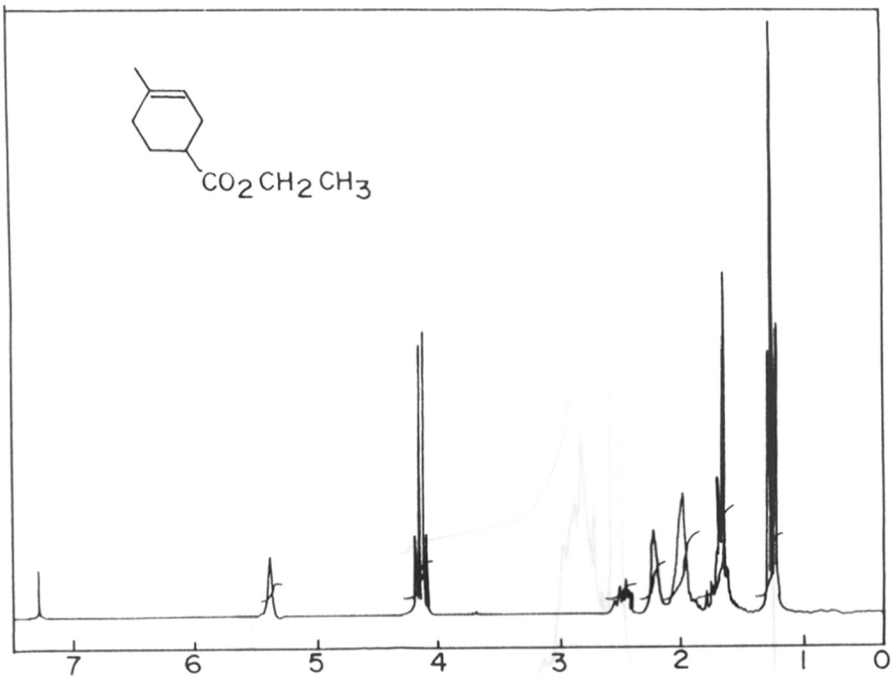


FIG. 1 ^{1}H NMR (200 MHz) SPECTRUM OF 2.3

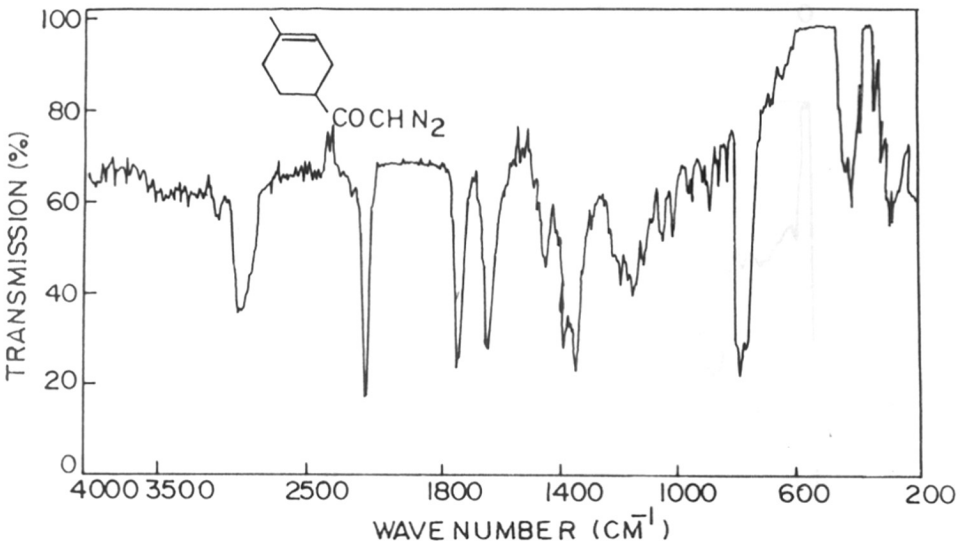


FIG. 2 IR SPECTRUM OF 2.6

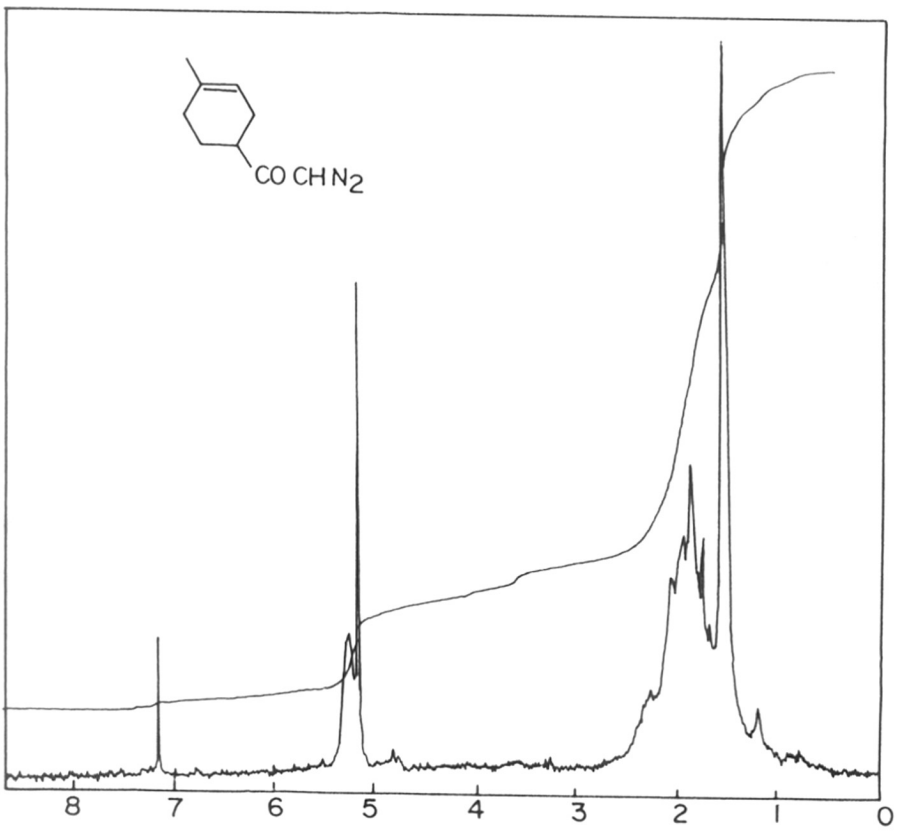


FIG.3 ^{1}H NMR(80MHz) SPECTRUM OF 2.6

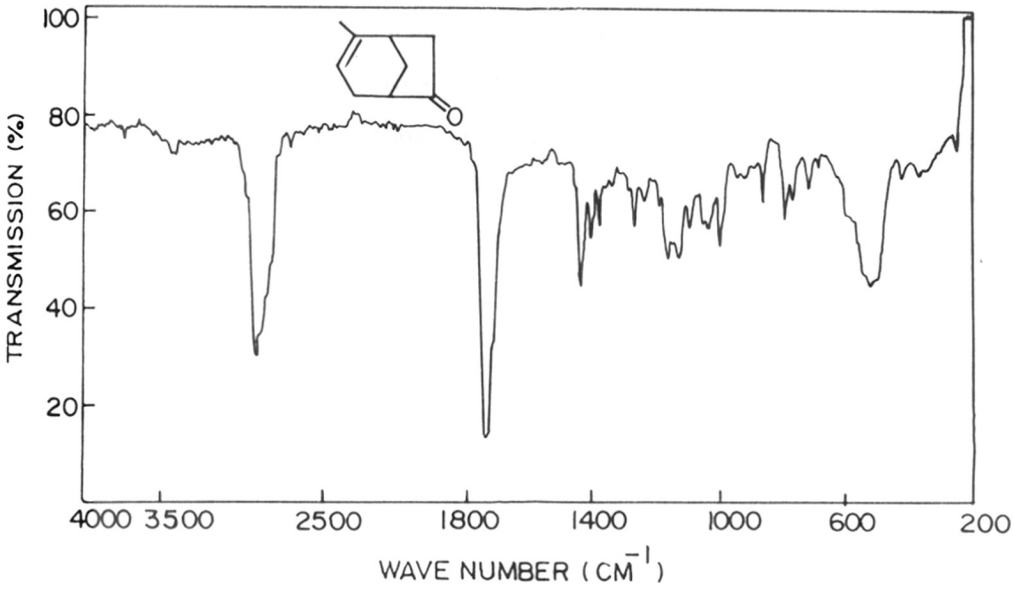
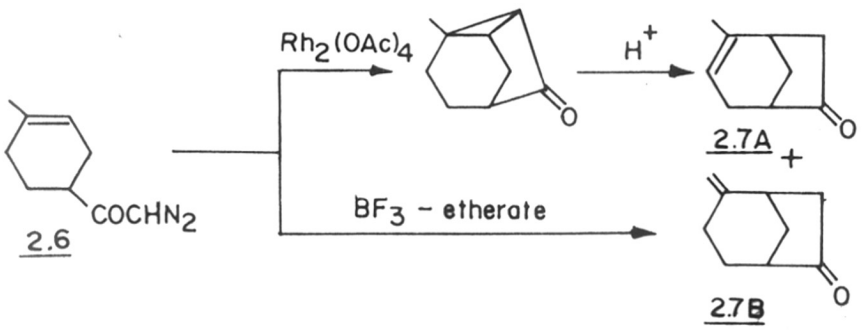


FIG. 4 IR SPECTRUM OF 2.7A + 2.7B

Scheme 7



An alternate possibility is the direct acid-catalyzed intramolecular addition of diazoketone to the double bond. The regioselectivity of this addition will be guided by polarization of the double bond decided by the incipient carbonium ion stability. Such a reaction on 2.6 is expected to result directly in 2.7A/B. This differential reactivity of α-diazoketone has been advantageously utilized by Erman and Stone[11] in devising a general approach for the synthesis of α-patchoulane sesquiterpenes.

It was, therefore, thought worthwhile to subject the α-diazoketone 2.6 to BF_3 etherate directly. Thus, addition of the reagent (2 mole %) into a solution of 2.6 in 1,2-dichloroethane followed by a standard workup furnished a product which was found to be homogeneous by GLC. The IR spectrum (Fig.4) of the product showed a strong band at 1740 cm^{-1} suggesting a presence of a five-membered ketone. In addition, a small hump in the spectrum at 1735 cm^{-1} suggested the presence of a minor amount of an isomeric product. The PMR spectrum of the product (Fig.5) showed a 3H singlet at 1.65 δ and a broad 1H multiplet at 5.05 δ, besides showing signals for 8 protons in the region of 1.80 to 2.60 δ.

With the above ^{1}H-NMR spectral data and the expected occurrence of cyclization in 2.6, the product could be identified as a mixture of 2.7A with a minor amount of 2.7B.

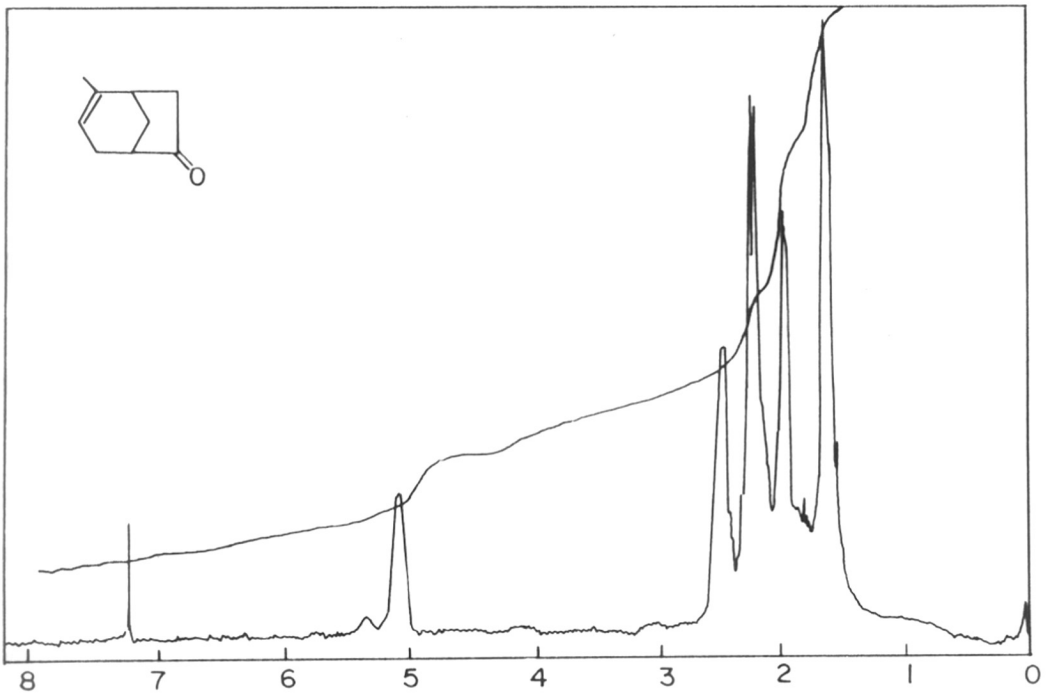


FIG. 5 ^{1}HNMR (80MHz) SPECTRUM OF 2.7A

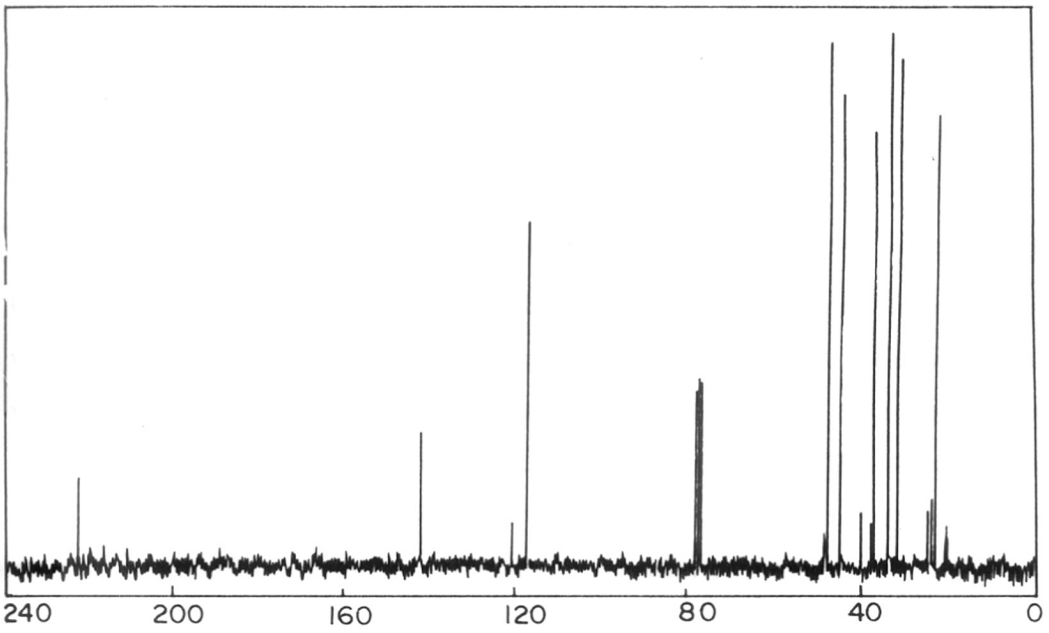


FIG. 6 ^{13}CNMR (200 MHz) SPECTRUM OF 2.7A

Further, structural proof was obtained from the ^{13}C-NMR spectrum (Fig.6), the data of which is given below:

21.61(q), 31.76(t), 33.90(t), 37.46(d), 44.79(d), 47.94(t), 117.40(d), 142.08(s), 221.42(s).

The suspected presence of a minor amount of 2.7B was conspicuously seen by additional equal number of signals in all the region observed for 2.7A in the ^{13}C-NMR spectrum.

It can be seen from our projected protocol (Scheme-6) that a key reaction is the oxidative cleavage of an olefinic bond. In order to prevent undesirable reactions, it was necessary to obtain the saturated ketone and subject it to spirocyclopropyl annulation reaction. Besides this, hydrogenation of the mixture of isomeric ketone 2.7A and 2.7B would lead to a single product. Thus, hydrogenation of 2.7A,B under standard condition (Experimental) afforded a homogeneous product which could easily be characterized by its spectral data as 2.8. ^{1}H-NMR (Fig.7) 0.85 (d, 3H), 1.10-2.35 (m, 11H).

^{13}C-NMR (Fig.7a): 20.26(q), 29.62(t), 30.17(t), 34.76(d), 37.58(t), 38.27(d), 39.21(t), 45.23(d), 221.48(s).

Mannich reaction of the bicyclic ketone 2.8

With our previous experience of preparing α-spiro cyclopropyl ketone by Mannich reaction leading to the α-methylene ketone and a sequential cyclopropanation[12], we thought such a procedure would be equally applicable here. Therefore, a solution of the ketone 2.8 (0.01M) in ethyl alcohol was treated with 0.03M of paraformaldehyde and 0.04M of dimethyl amine hydrochloride under refluxing condition. Surprisingly, monitoring the progress of the reaction by TLC of aliquotes did not show any indication of the desired reaction. Refluxing for prolonged time (10-12 hr.) did not make any change, the starting material was recovered quantitatively.

This negative result was a setback in the scheme of our reactions. It may be noted that Mannich reaction was successful in the case of [3.3.0] bicyclo octanone system previously described while

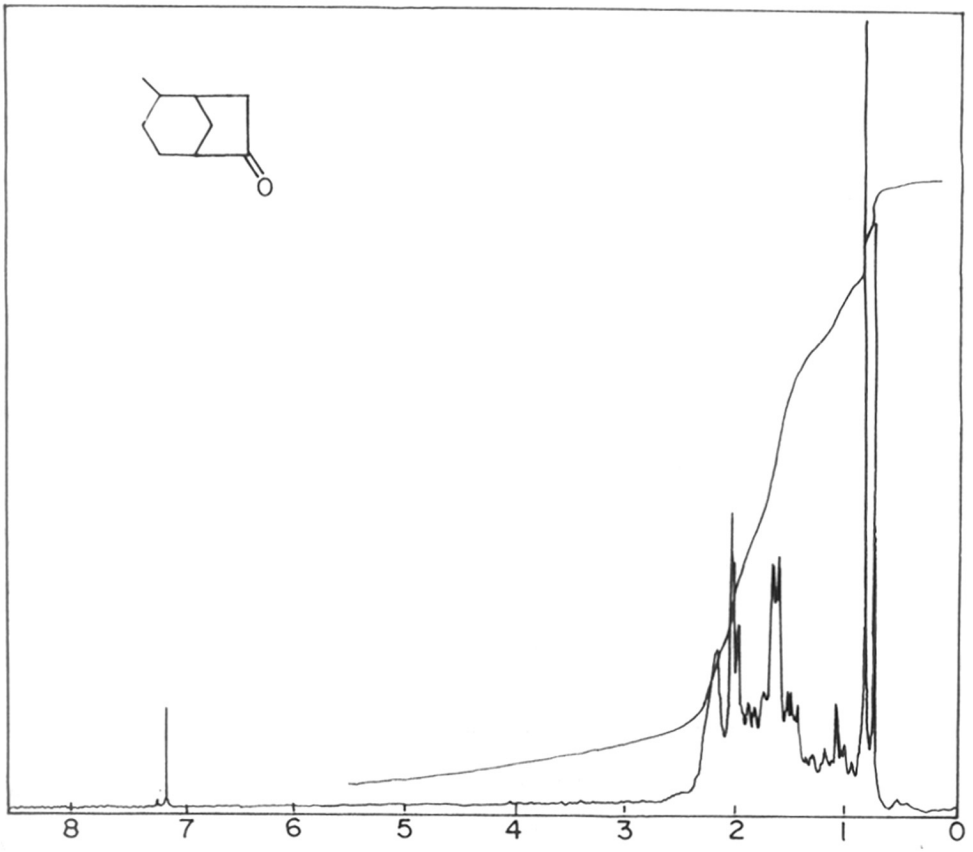


FIG.7 ^{1}H NMR(80MHz) SPECTRUM OF 2.8

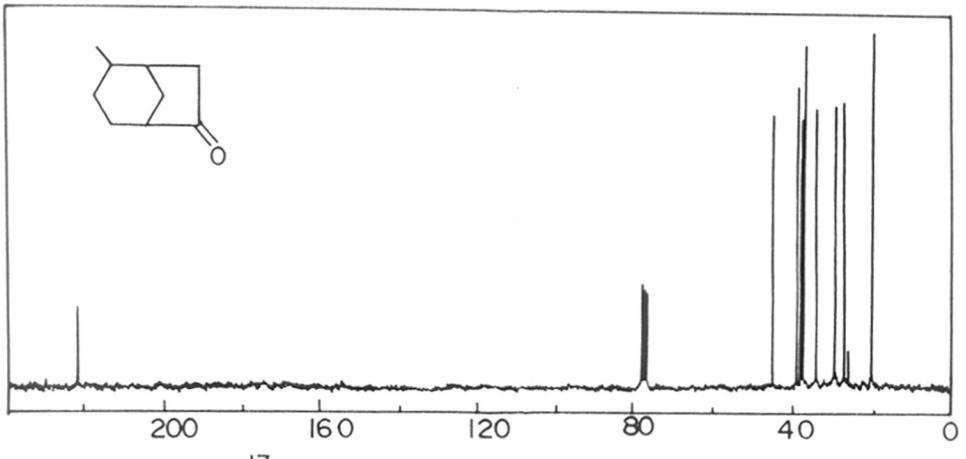


FIG.7a ^{13}C NMR(200MHz) SPECTRUM OF 2.8

it has failed in the present case. A possible explanation can be found in the nature of the bicyclo [3.2.1] octanone system and in this particular substrate, the methyl group may present steric hinderance.

With an interest to realize α-methylenation of the keto group, it was subjected to the previously described reagent namely Trifluoromethyl anilium acetate, although it was not fruitful in the previous case (Chapter-I). Unfortunately, this reagent proved unsuccessful even here as seen by the recovery of the starting material accompanied by undesired polymerized product to some extent.

Similar result was obtained when intramolecular dialkylation of the ketone 2.8 was attempted with 1,2-dibromoethane under phase transfer catalysis condition. With the inability to realize α-cyclopropyl ketone 2.10, a further sequence of reaction envisaged in Scheme-6 was arrested.

Conclusion

Work described in this Section bringsforth the importance of steric factors, especially in bicyclic systems; while Mannich reaction was successful in a bicyclo[3.3.0]octanone system, it was unyielding in a bicyclo[3.2.1]octanone system indicating the effect of change in ring size. In addition, the steric hindrance offered by a methyl group has been considerable enough to preclude the reaction. It can also be said that although the sequence of reaction appeared feasible, one is not certain till one does experimentation.

SECTION B: Efforts towards the synthesis of (±) β-cuparenone

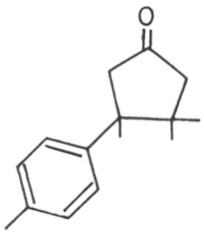
Introduction

The development of a convenient methodology for efficient construction of bicyclic [m.3.0] bridged alkenes and their further transformation to 5-8 fused carbocycles have been dealt with in the first chapter. The key reaction involved was spirocyclic vinylcyclopropane-cyclopentene rearrangement.

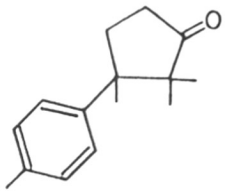
Our attempts in synthesis of AB ring system of taxane skeleton utilizing the above mentioned reaction have been presented in the previous Section of this chapter.

The present Section describes our synthetic efforts towards realization of a well known natural product (±) β-cuparenone **3a** utilizing vinylcyclopropane-cyclopentene rearrangement.

The sesquiterpene α-cuparenone **3b** and β-cuparenone **3a** were first isolated from essential oil of Mayurpankhi tree.[13]



3a



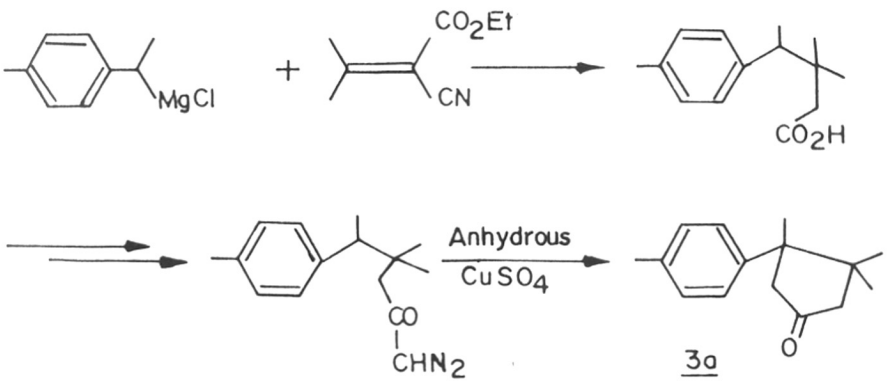
3b

The presence of two contiguous quaternary centres in a cyclopentane ring has provided a synthetic challenge and has served as a testing ground for many synthetic methodologies.[14-20] An additional stimulus for their synthesis is the presence of a quaternary chiral carbon.

With an objective of placing our work in a proper perspective, various reported synthetic strategies employed to realize β-cuparenone have been briefly presented below, indicating the key reactions.

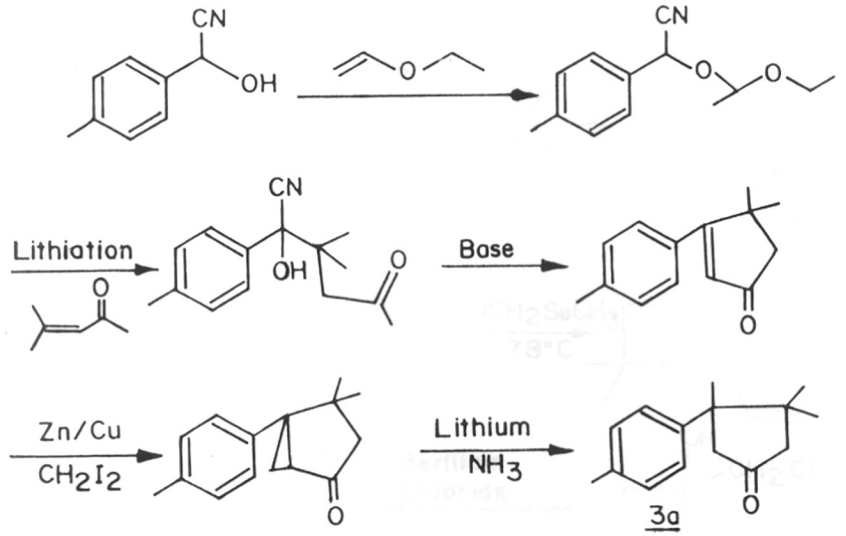
Mane and Krishna Rao[18] devised a general method for the preparation of 1-aryl 1,2,2-trimethyl cyclopentane system by intramolecular α-ketocarbene insertion into the benzylic C-5 hydrogen of a 5-aryl 1-diazo 4,4-dimethyl hexane-2-one. The required substituted valeric acid was prepared by the Michael addition of α-p-tolyl ethyl magnesium chloride to ethyl isopropylidine cyanoacetate.

Scheme 8

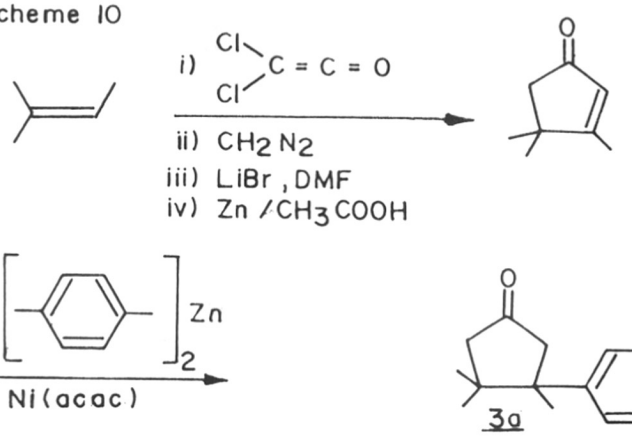


The general method described above is exemplified by the preparation of (±) β-cuparenone (Scheme-8). Casares and Maldonado[16] et al. (Scheme-9) elegantly utilized Stork's protected cyanohydrin reagent in an effective lithiation, followed by a Michael 1,4 addition to mesityl oxide. The intermediate alkylated cyanohydrin on treatment with base afforded the *p*-tosyl substituted cyclopentenone; the latter on cyclopropanation and regioselective hydrogenation furnished the target molecule. It was observed by Caseros and Maldomello that 4,4 dimethyl *p*-tolyl cyclopentenone was inert to both lithium dimethyl cuperate and copper catalyzed methyl Grignard 1,4 additions. On the other hand, Green et al.[15] achieved (Scheme-10) two such straightforward and efficient conjugate addition-based synthesis of β-cuparenone utilizing so for unrecognized potential of organozinc reagent in this type of reaction. The required trimethyl cyclopentenone could be easily obtained through three carbon annulation of β-isoamylene.

Scheme 9



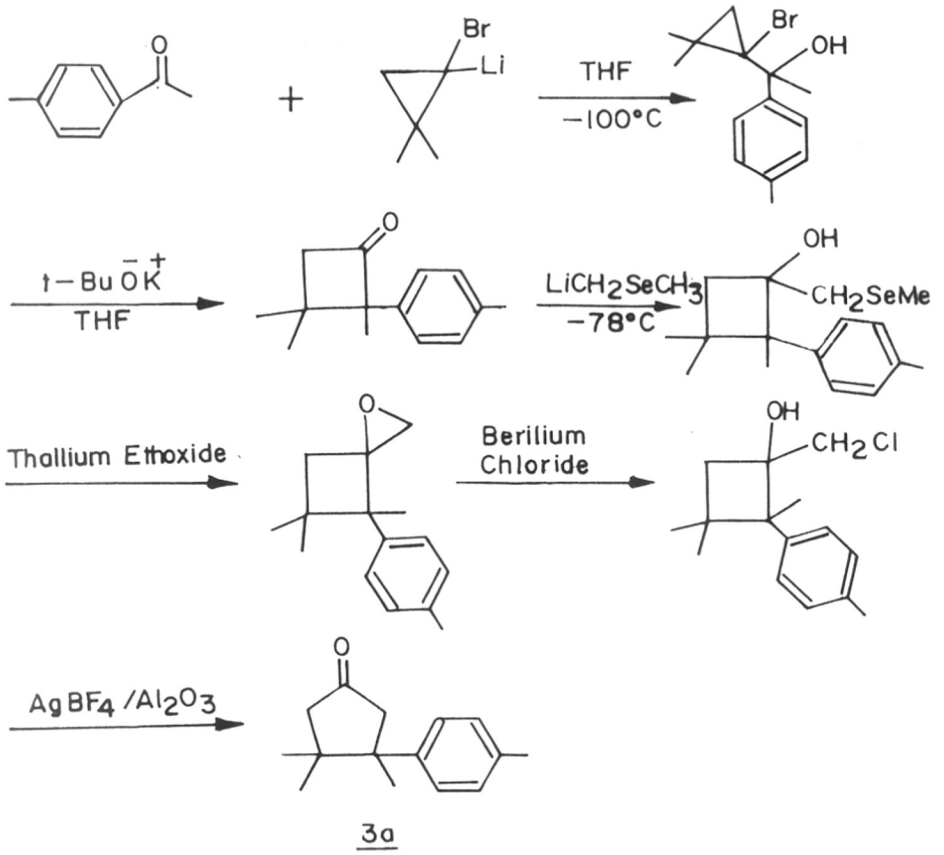
Scheme 10



Nickel acetyl acetonate-catalyzed conjugate addition of readily prepared dipara tolyl zinc was found to proceed smoothly resulting in the target molecule.

Krief et al.[20] realized the synthesis of β-cuparenone by a regioselective formation of cyclopentane ring from *p*-methyl acetophenone via two ring expansion reactions (Scheme-11).

Scheme II



3a

It can be seen from the above Scheme that the bromohydrin formed by the reaction of α-lithiated cyclopropyl bromide with *p*-methyl acetophenone undergoes base-catalysed ring expansion leading to the substituted cyclobutanone. A second rearrangement of substituted cyclobutanol by silver fluoroborate leads to the target molecule.

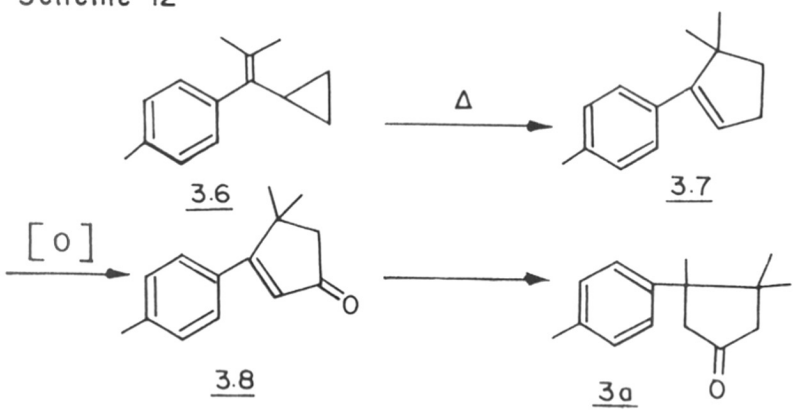
Various asymmetric synthesis of β-cuparenone have been reported during the past decade. Mention may be made of synthesis of chiral β-cuparenone involving stereospecific Rhodium catalyzed intramolecular C-H insertion[21] on an optically pure tertiary centre. Posner et al.[22] utilized enantiocontrolled conjugate addition by chiral sulfoxide. While Mayers and Lafker[23] based their synthetic strategy on alkylation of chiral bicyclic lactams derived from S-valinol. Optically pure α

and β-cuparenones were synthesised from a common optically active precursor by Fedel et al.[24] These authors utilized a single chiron obtained by simple enzymatic hydrolysis of a prochiral malonate.

Foregoing literature survey indicates that vinylcyclopropane-cyclopentene rearrangement has not been utilized so far in the synthesis of **3a**. It can be recalled that our previously reported[25] work on this rearrangement showed the intermediacy of biradicals in the reaction. Thus, realization of **3a** by this strategy would provide an example of a first radical method in β-cuparenone synthesis.

The sequence of reactions that we envisaged towards this end is shown in Scheme-12.

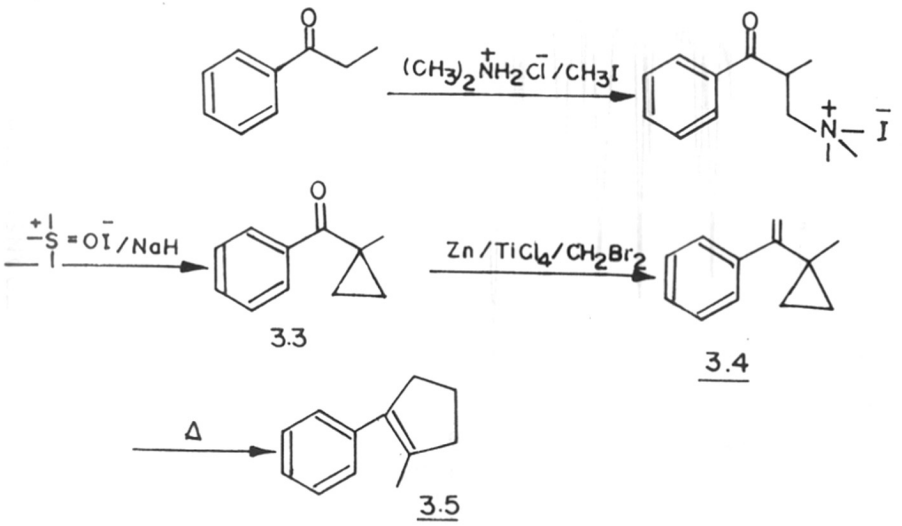
Scheme 12



The thermal VCR of vinylcyclopropane **3.6** was expected to furnish cyclopentane-annulated key intermediate **3.7**; an allylic oxidation of **3.7** would lead to the enone **3.8**, a well known precursor[16] to **3a**.

It can be seen from the scheme that the occurrence of VCR reaction in substrate 3.6 involves a radical addition to a geminally substituted carbon. Although the steric requirements for free radical reactions are less stringent than those for ionic processes, there have been steric hindrance reported[26] in many free radical reactions. From this point of view, it was thought to investigate the reaction in a model vinylcyclopropane (Scheme-13) relatively free from steric problems.

Scheme 13



3.3 3.4 3.5

Results and Discussion

Preparation of vinyl cyclopropane 3.4

Readily available propiophenone was reacted with formaldehyde and dimethyl ammonium chloride in typical Mannich reaction condition. Further, quaternization of the same amine with CH_3I and the sequential treatment of the quaternary salt with dimethyl oxosulfonium methylide (Corey's reagent) in presence of NaH furnished a product in a moderate yield. The IR spectrum (Fig.8) of the product showed typical C-H stretching band of cyclopropane around 3000 cm^{-1} along with an intense band at 1690 cm^{-1}. The PMR spectrum (Fig.9) displayed a 3H singlet at 1.40, a 2H multiplet in the region 0.66-0.84 along with another 2H multiplet in the region 1.17 to 1.33 δ. In addition, the spectrum showed a 3H multiplet in the region 7.20-7.48 and a 2H multiplet in the region 7.64-7.80. These spectral features sufficed to identify the product as **3.3**. Further structural support

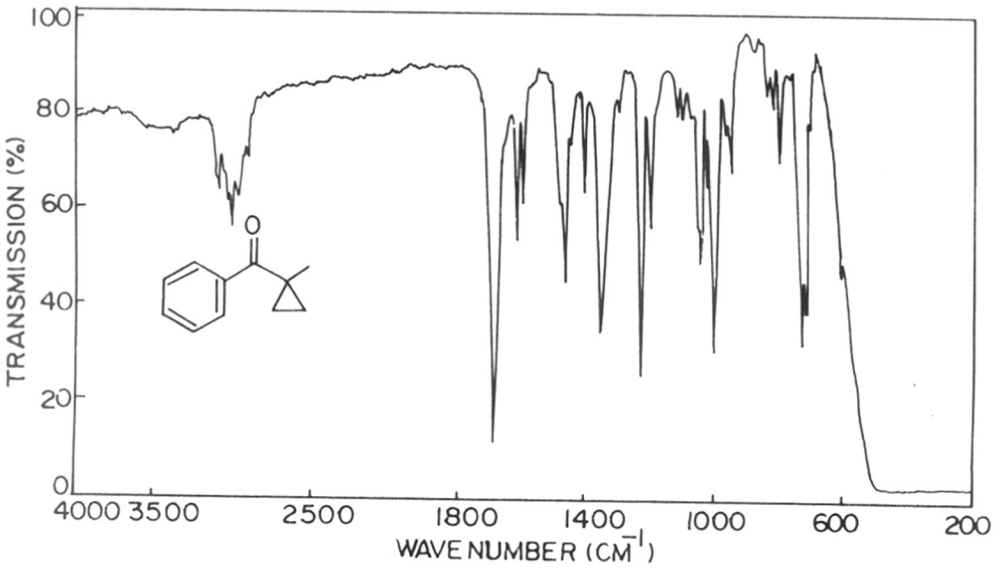


FIG. 8 IR SPECTRUM OF 3.3

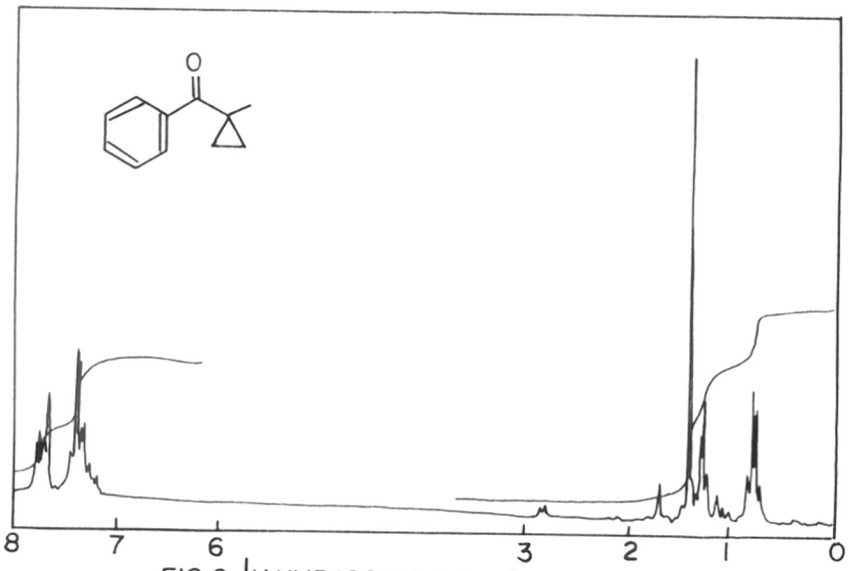


FIG. 9 ^{1}H NMR (90MHz) SPECTRUM OF 3.3

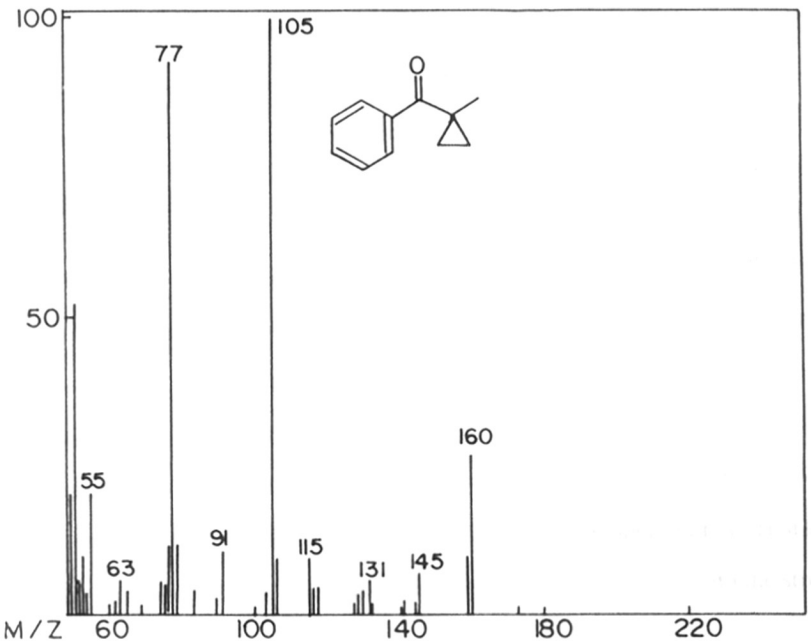


FIG. 10 MASS SPECTRUM OF 3.3

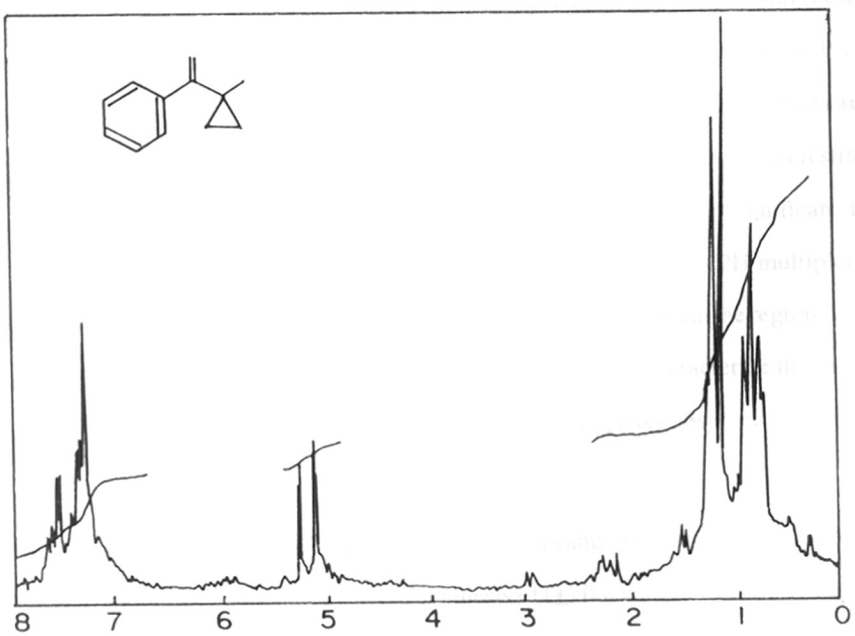


FIG. 11 ^{1}HNMR (90 MHz) SPECTRUM OF 3.4

was obtained from its mass spectrum (Fig.10) which showed the required molecular ion peak at m/z 160; the base peak at m/z 105 and a prominent peak m/e 77 indicated expected loss of methyl cyclopropyl moiety and further loss of carbon monoxide.

Lambardo reaction[27] of 3.3

The reaction of α-cyclopropylketone 3.3 with dibromomethane in presence of Zn and $TiCl_4$, followed by standard workup afforded a product in moderate yield. The IR spectrum was conspicuous by its absence of the carbonyl absorption. The PMR spectrum (Fig.11) was supportive of the transformation of the carbonyl group into the methylene, by two 1H doublets centered at 5.11 and 5.26 δ; the other resonances in the spectrum were a 2H multiplet in the region 0.71-0.97 and another 2H multiplet in the region 1.04-1.35, the latter being overlapped with a 3H singlet and a 5H multiplet in the region 7.00-7.66. These spectral data were well in accord with the structure **3.4**.

Vinylcyclopropane-cyclopentene rearrangement[28] of 3.4

A solution of 150 mg of **3.4** in pet.ether was slowly dropped into the pyrolysis unit (described earlier in Chapter-I) maintaining a temperature of 500°C. The product was collected in a well-cooled receiver. Passage of this material in pet ether through a short column of silica gel furnished a refined product (yield - 60%). The PMR spectrum (Fig.12) of the product was extremely interesting and supported the occurrence of the expected rearrangement. The spectrum was significant by the absence of resonances for the cyclopropyl and olefinic protons. It displayed a 2H multiplet in the region 1.73-2.20, which was overlapped by a 3H singlet at 1.80, a 4H multiplet in the region 2.33-2.93 and a 5H broad singlet centered at 7.28. These spectral data sufficed to characterize the product as **3.5**. The observed molecular ion peak at m/z 158 and the prominent peaks observed at m/z 143 and 105 gave further support to the structural assignment.

The occurrence of vinylcyclopropane cyclopentene rearrangement in the model compound 3.4 prompted us to adopt this methodology in the synthesis of (±) β cuparenone **3a**. Such a protocol has already been shown in (Scheme-12) which necessitates the preparation of substrate 3.6.

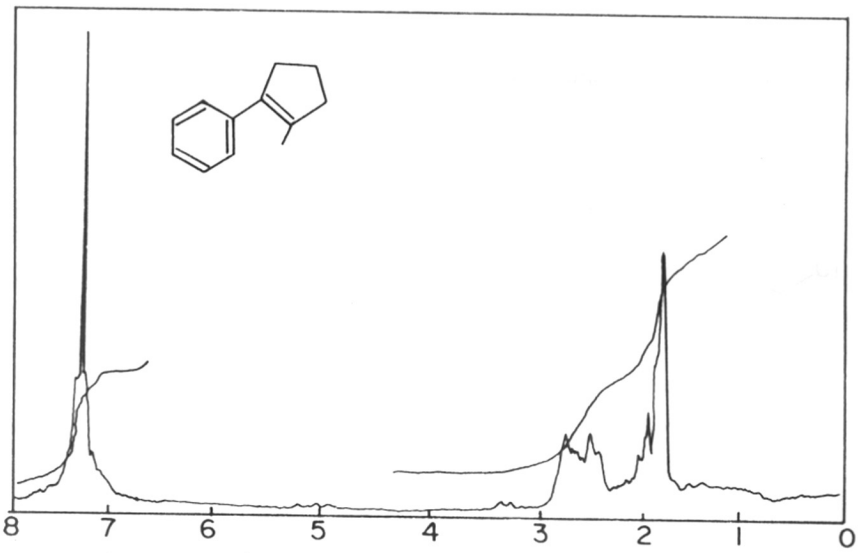


FIG.12 ^{1}H NMR (90 MHz) SPECTRUM OF 3.5

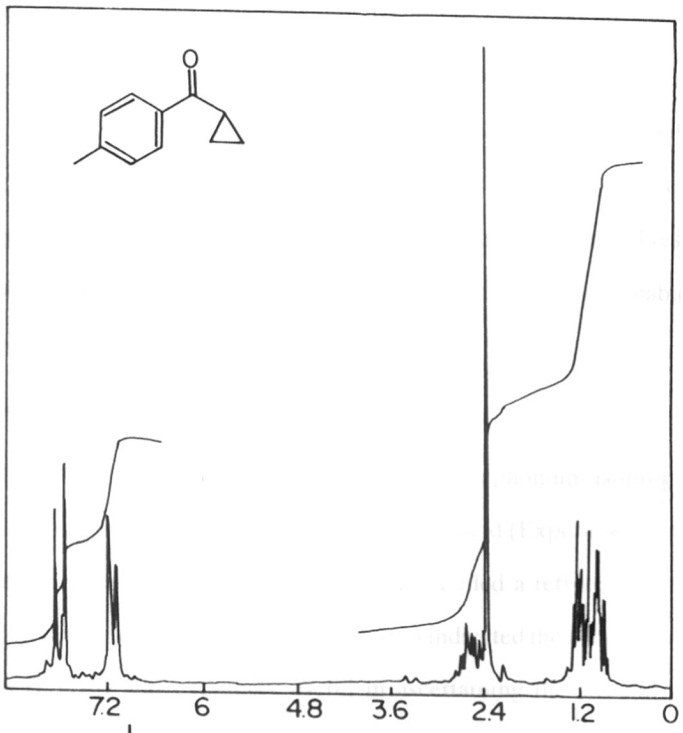
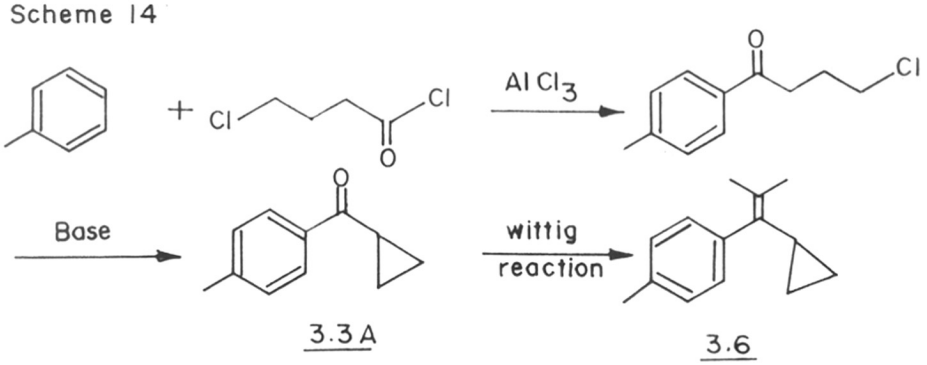


FIG. 13 ^{1}H NMR (80 MHz) SPECTRUM OF 3.3A

Preparation of the substrate 3.6

The sequence of reactions that we planned to utilize to synthesize the substrate **3.6** is shown in Scheme-14.

Scheme 14



3.3A 3.6

Friedel craft acylation of toluene with γ-chlorobutyryl chloride was carried out as per reported procedure[29] and the product therefrom was treated with ethanolic KOH. A normal workup furnished a product in a very good yield (83%). The IR spectrum showed an intense band 1680 cm^{-1}. The PMR spectrum (Fig.13) displayed a 1H multiplet in the region 2.49-2.73, a singlet at 2.40 and 4H multiplets in the region 0.81-1.20 δ, in addition the spectrum showed a typical 4H resonance pattern of *p*-disubstituted phenyl derivatives in the region 7.20 and 7.70. These data enabled the identification of products as **3.3A**.

Wittig olefination of cyclopropyl ketone 3.3A

Treatment of 0.02M of ketone in THF with triphenyl phosphonium isopropyl bromide[30] in presence of n-butyl lithium afforded a product in a moderate yield (Experimental). Passage of the crude product in pet.ether through a column of silica gel yielded a refined material. The disappearance of the carbonyl absorption band in the IR spectrum indicated the occurrence of olefination. The PMR spectrum (Fig.14) was extremely useful in ascertaining the structure of the product unambiguously. Two intense 3H singlet at 1.60 and 2.00 accounted for the expected olefinic methyl

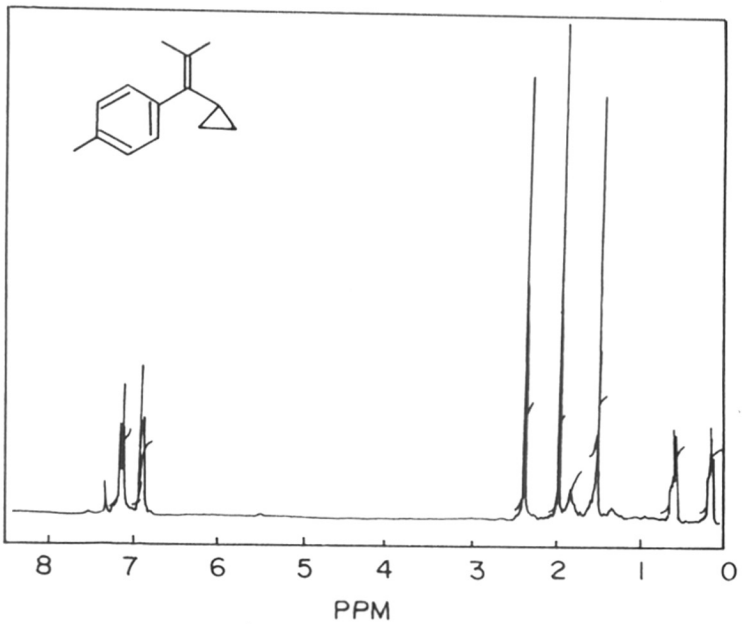


FIG. 14 ^{1}H NMR (200MHz) SPECTRUM OF 3.6

methyl groups; a similar 3H singlet at 2.50 obviously indicated aromatic methyl group. A conspicuous upfield shift of the cyclopropyl protons in comparison with those of starting cyclopropyl ketone, resulting into 2H multiplets in the region 0.15-0.30 and 0.60-0.70 further supported the olefination. The other features of the spectrum were 1H multiplets at 1.85 and two well-separated 2H doublets in the region 6.90-7.20. The mass spectrum showed the molecular ion peak m/e 186, the base peak at m/e 115 and peak arising from successive loss of methyl groups.

The above mentioned spectral data adequately supported the structure **3.6** for the product.

Thermolysis of 3.6

As mentioned previously, this rearrangement reaction constitutes the key step in building up the cyclopentane framework of (±) β-cuparenone **3**. A solution of 200 mg of 3.6 in pet.ether was introduced in a dropwise manner into the thermolysis unit maintained at about 490-500°C. The products of the reaction were collected in a flask kept in a freezing mixture. The residue obtained after the removal of solvent was passed through a short column of silica gel and a cleaner product was obtained. The GLC of the total product (Fig.15) was, however, disappointing. When a single product was expected, the GLC showed the total product to comprise about 40% of the unreacted **3.6** along with three more products, more or less, to a similar extent together accounting for 50% of the total. The PMR spectrum of the total product (Fig.16) essentially showed the resonances expected for the unreacted **3.6**; nonetheless, two signals at around 1.20-1.3 and two broad signals in the region 5.0-5.50 indicated the presence of the required cyclopentane annulated product **3.7**. Attempts to isolate the required product were not, however, fruitful.

In an alternate attempt to realize the desired VCR reaction, pet.ether solution of 3.6 was subjected to photolysis with 300 nm light using acetone as a sensitizer.

However, even prolonged irradiation did not show the occurrence of the rearrangement as seen by the quantitative recovery of the starting material (judged by PMR); use of different sensitizers such as benzophenone, benzene was of no avail.

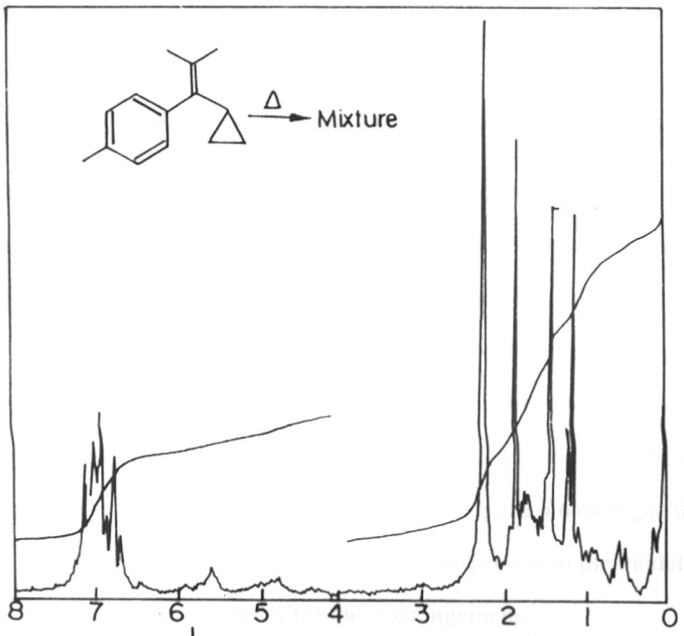


FIG. 16 ^{1}H NMR (80 MHz) SPECTRUM OF THE THERMOLYSIS PRODUCT FROM 3.6

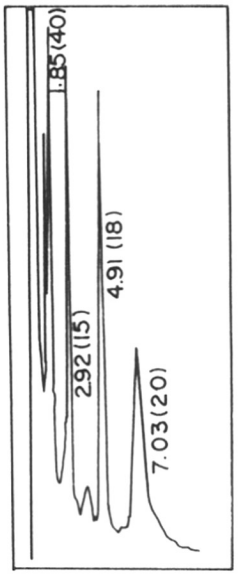


FIG. 15 GLC OF THE THERMOLYSATE OF 3.6 RRT (%)

Conclusion

The work presented in this Section can briefly be summarized as follows:

Prompted by the success that we realized in devising a methodology for [m.3.0] bridged alkenes (Chapter I) by the use of vinylcyclopropanecyclopentene rearrangement, we explored the potential of this reaction in the synthesis of (±)β-cuparenone. A successful realization of this objective would have provided the first example of use of VCR reaction in synthesising **3a**. It is interesting to note that this rearrangement occured in a facile manner with the model compound **3.4** while the target molecule was not amenable to this strategy. In all probability, this result could be the consequence of steric hindrance offered by vinylcyclopropane **3.6** owing to the presence of gem dimethyl group. Nonetheless, the occurrence of the rearrangement in the model compound **3.4**, all the more suggests the steric requirements for the rearrangement.

Experimental

General remarks remain the same as described in Chapter I.

4-Methyl-3-cyclohexenecarboxylic acid;[10] ethyl ester (2.3)

A mixture of (15g, 0.22M) isoprene (15g, 0.15M) ethyl acrylate and hydroquinone (1g) was heated at 150-160°C for 7-8 hr in a sealed tube and then distilled to get 22.17g of the product (88%). **b.p.** 80-90°C(bath)/5.00mm. **IR** (neat): 3000, 2940, 1740, 1450, 1390, 1310, 1260, 1180, 1040, 910, 760 cm^{-1}. ^{1}**H-NMR**: 1.25 (t, 3H), 1.52 (s, 3H), 2.00 (m, 4H), 2.20 (m, 2H), 2.50 (m, 1H), 4.15 (q, 2H), 5.40 (broad s, 1H).

4-Methyl-3-cyclohexeneearboxylic acid (2.4)

The above ester (22.17g, 0.132M) was saponified in 50 ml methanol with 20 ml 50% KOH aq. After refluxing for 5 hr, the corresponding acid was obtained by neutralization. The crude solid was recrystallised from water. **m.p.** 97-98°C (reported 97-99°C)[10]. **Yield** 14.75g (80%). **IR** (nujol): 2580, 1710, 1450, 1380, 1310, 1240, 1200, 950, 800 cm^{-1}. ^{1}**H-NMR**: 1.66 (s, 3H), 1.84-2.62 (m, 7H), 5.33 (broad s, 1H), 8.46 (broad s, 1H, exchangeable with D_2O).

2-Methylbicyclo[3.2.1]oct-2-ene-6-one (2.7A) (major) **and 2-Exomethylene bicyclo[3.2.1]octan-6-one (2.7B)** (minor)

To 4-methylcyclohexanoic acid (2.4) (2.80g, 0.02M) taken in dry pet.ether (20 ml) was added oxalyl chloride (3.72g, 0.03M) taken in dry pet.ether (15 ml) dropwise with stirring under dry conditions. After complete addition of acid chloride, the reaction mixture was stirred for 6 hr and the solvent and excess of oxalyl chloride were removed in vacuo. The residual crude product was used as such for the next step. The α-diazoketone **2.6** was prepared by following reported procedure.[11]

To diazomenthane (4.2g, 0.1M) in ether (150 ml) was added the above acid chloride in dry pet.ether (10 ml) dropwise with stirring at 0°C. After complete addition of the acid chloride, the

reaction mixture was stirred at room temperature for 12 hr. and solvent was removed in vacuo. The residual diazoketone was used without purification for cyclization reaction. **IR** (neat): 2970, 2150, 1750, 1650, 1450, 1400, 1350, 1200, 1160, 1120, 1050, 1020, 900, 860, 790 cm^{-1}. **^{1}H-NMR**: 1.60 (s, 3H), 1.80-2.46 (m, 7H), 5.20 (s, 1H), 5.30 (broad s, 1H).

Cyclization of the diazoketone (2.6)

Cyclization of the diazoketone was done by following a reported[11] procedure. To the above diazoketone taken in dry 1,2 dichloroethane (100 ml) was added BF_3-etherate (0.2-0.3 ml) by syringe under dry condition at 0°C with stirring. The reaction mixture was stirred overnight at room temperature and washed repeatedly with saturated $NaHCO_3$. After removal of the solvent the crude product was purified by column chromatography (silica gel - 10% ethyl acetate in pet.ether). **Yield** 1.74g. (64%) based on **2.4**, **b.p.** 150-55°C(bath)/10mm. **IR** (neat): 2950, 1740, 1440, 1400, 1380, 1220, 1120, 1160, 1000, 860, 800 cm^{-1}. **^{1}H-NMR**: 1.65 (s, 3H), 1.80-2.60 (m, 8H), 5.05 (broad s, 1H). **^{13}C-NMR**: 21.61(q), 31.76(t), 33.90(t), 37.46(d), 44.79(d), 47.94(t), 117.40(d), 142.08(s), 221.42(s).

2-Methylbicyclo[3.2.1]octan-6-one (2.8)

(3.40g, 0.025M) of mixture of above unsaturated ketones **2.7A** and **2.7B** was taken in 100 ml of distilled ethanol, followed by addition of Pd-C 10% (340 mg) and hydrogenated under pressure of 40 lb/inch in Parr hydrogenation apparatus for 25 hr. and filtered through celite. The celite was repeatedly washed with ethanol. Solvent was evaporated and residue was distilled under diminished pressure to afford the pure product, **Yield** 2.92g. (85%), **b.p.** 150-55°C(bath)/10mm. **IR** (neat): 2940, 2880, 1750, 1460, 1410, 1260, 1180, 1040, 1000, 880, 840, 700 cm^{-1}. **^{1}H-NMR**: 0.85 (d, 3H), 1.10-2.35 (m, 11H). **^{13}C-NMR**: 20.26(q), 29.62(t), 30.17(t), 34.76(d), 37.58(t), 38.27(d), 39.21(t), 45.23(d), 221.48(s). **Anal. calcd. for** $C_9H_{14}O$: C, 78.26; H, 10.14. **Found**: C, 78.11; H, 10.31.

1-Methyl,1-benzoylcyclopropane (3.3)

This compound was prepared by a reported procedure.[12a] A mixture of propiophenone (5.36g, 0.04M), dimethylamine hydrochloride (15.20g, 0.186M) and paraformaldehyde (3.6g, 0.12M) in 95% ethanol (30 ml) was heated in the presence of a catalytic amount of conc. HCl (0.5 ml) under reflux for 10 hr. Solvent was evaporated under vacuo, followed by addition of acetone (30 ml), the precipitate was filtered; treatment of the crude precipitate with excess of 10% Na_2CO_3 in water (50 ml) gave an oil. The aqueous phase was extracted with ether repeatedly (3x25 ml). The combined organic layers were washed with water and dried over anhydrous K_2CO_3, followed by concentration to furnish the aminoketone 4.13g. (54%). Methylation of this crude amino ketone (3.33g, 0.01M) with methyl iodide (2.13g, 0.015M) in acetonitrile (15 ml) gave a product (quantitative) after evaporation of excess CH_3I and solvent. This salt was used as such for cyclopropanation reaction.

A mixture of oil free NaH (0.022M, 0.528g.) and trimethyl sulfoxonium iodide (2.64g, 0.012M) was treated dropwise with dimethyl sulfoxide (15 ml) at room temperature and under nitrogen atmosphere with continuous stirring. After the reaction mixture was stirred for 1 hr, a solution of the crude ammonium iodide obtained above was added dropwise in the same solvent (15 ml). After complete addition, the stirring was continued at 50-55°C for 6 hrs. and the mixture was poured onto ice and extracted repeatedly with ether (3x25 ml). The usual work-up furnished a residue which was purified by column chromatography over silica gel using pet.ether-ethyl acetate (10:0.50) as an eluent, **b.p.** 140-145°/1mm. **Yield** (60%). **IR** (neat): 3100, 3000 cm^{-1}, 2980, 1690, 1620, 1600, 1470, 1350, 1220, 1020, 1000, 940, 790 cm^{-1}. **^{1}H-NMR**: 0.66-0.84 (m, 2H), 1.17-1.33 (m, 2H), 1.40 (s, 3H), 7.15-7.82 (m, 5H). **MS**, m/z (%): 160 (M^+, 27), 145(6), 131(5), 115(10), 105(100), 91(11), 77(91).

1-Phenyl, 1(1'-methylcyclopropyl)ethylene (3.4)

For the preparation of this compound, a reported procedure[27] was followed. A mixture of activated zinc powder (2.938g, 0.045M), 5 ml dry THF and (2.61g, 0.015M) dibromomethane was stirred under nitrogen atmosphere and cooled to -10°C to -5°C using ice-salt bath. To the stirred

mixture, $TiCl_4$ (2.08g, 0.011M) in dry CH_2Cl_2 (4 ml) was added dropwise. After complete addition of $TiCl_4$, the reaction mixture was stirred for half an hour at -5°C to 0°C and ketone **3.3** (1.60g, 0.01M) in THF (5 ml) was added in a dropwise manner. After complete addition of the ketone, the reaction mixture was stirred at room temperature for 12 hr. A standard workup afforded a crude product which was purified by column chromatography (silicagel-pet.ether) to furnish a refined material. **Yield**: 0.930g. (59%). **IR** ($CHCl_3$): 3100, 3020, 2980, 1620, 1500, 1450, 1390, 1220, 1020, 910, 780. **^{1}H-NMR**: 0.71-0.97 (m, 2H), 1.04-1.35 (m, 5H), 5.11 (d, 1H), 5.26 (d, 1H), 7.00-7.66 (m, 5H). **MS**, m/z (%): 158 (M^+, 4), 145(13), 129(27), 115(43), 105(100), 91(66), 77(52).

1-Methyl-2-phenylcyclopentene-1 (3.5)

Thermolysis[28] of the above vinylcyclopropane (200 mg) was done by following the same procedure as described earlier (Chapter-I). The crude product was purified by column chromatography (silica gel-pet.ether) to afford a refined product. **Yield**: 98 mg (50%). **IR** (neat): 2940, 2850, 1612, 1490, 1450, 1350, 1060, 1040, 805 cm^{-1}. **^{1}H-NMR**: 1.73-2.20 (m, 5H), 2.33-2.93 (m, 4H), 7.28 (s, 5H). **MS**, m/z (%): 158 (M^+, 67), 143(76), 129(62), 115(80), 105(100), 91(63), 77(54).

***p*-Methylphenyl cyclopropyl ketone (3.3A)**

Anhydrous $AlCl_3$ (4.25g, 0.317M) was suspended in dry toluene (20 ml) and cooled to 10-15°C. To this reaction mixture, γ-chlorobutyryl chloride (4.25g, 0.30M) in dry toluene (5 ml) was added in dropwise manner with continuous stirring by maintaining the temperature between 10-15°C. After complete addition of the acid chloride, the reaction mixture was further stirred for 20 minutes and poured over crushed ice. Organic layer was separated. The aqueous layer was extracted separately with ether (25x3 ml). From the combined organic layer, solvent was removed under vacuo. The crude product was treated with alcoholic KOH (3g. KOH in 12 ml methanol) solution and kept for 30 minutes with stirring. Methanol was removed under vacuo and 100 ml water added and the reaction mixture was extracted with ether repeatedly (50x3 ml). The usual work up afforded a crude product which was purified by distillation. **B.P.** 185-90(bath)/15mm.

Yield 4g. (83%), [lit.[30] **b.p.** 127°C/9mm]. **IR** (neat): 3000, 2940, 1680, 1620, 1470, 1430, 1400, 1250, 1140, 1060, 1010, 850, 770 cm^{-1}. ^{1}**H-NMR**: 0.81-1.20 (m, 4H), 2.40 (s, 3H), 2.49-2.73 (m, 1H), 7.20 (d, 2H), 7.70 (d, 2H).

1-(cyclopropyl),1-(*p*-methylphenyl)2-methylpropene-1 (3.6)

Isopropylphenylphosphonium Bromide[30]: 3.1g. of isopropyl bromide and 6.6g. of triphenylphosphine was heated at 150°C in a sealed tube for 12 hrs. The crystalline product weighed 6g. It was recrystallized from a small amount of ethanol with ether m.p. 237-238°C (Reported[30]: 238-239°C).

Triphenyl phosphine isopropylidine reagent:[30]

The reagent was prepared from (6.93g, 0.024M) of isopropyl triphenyl phosphonium bromide, 22 ml of 1.5M of n-butyllithium in hexane and 40 ml of anhydrous THF by stirring overnight under nitrogen atmosphere.

To the above alkylidene reagent was added (3.2g, 0.02M) of ketone **3.5** in 20 ml dry THF. The reaction mixture was stirred under nitrogen atmosphere for 15 hrs. To quench the reaction, 150 ml ether and 100 ml cold water was added with stirring. Organic layer was separated and washed repeatedly with water till neutral. Usual work-up afforded a crude product which was purified by column chromatography (silica gel-pet.ether) **Yield** 1.45g. (39%). **IR** (neat): 3100, 2920, 1520, 1460, 1100, 1040, 850. ^{1}**H-NMR**: 0.15-0.30 (m, 2H), 0.60-0.70 (m, 2H), 1.60 (s, 3H), 1.85 (m, 1H), 2.00 (s, 3H), 2.50 (s, 3H), 6.90 (d, 2H), 7.20 (d, 2H). **MS**, m/z (%): 186 (M^+, 5), 171(17), 156(17), 143(80), 120(83), 115(100), 105(62), 91(55), 77(35).

Thermolysis of (3.6)

Thermolysis of **3.6** (200 mg) in dry pet.ether (15 ml) was performed by following same procedure (Chapter-1). The thermolysate which was trapped in flask cooled by ice-salt bath after evaporation

of the solvent gave a crude residual oil which was purified by using column chromatography (silica gel-pet.ether) **Yield**: 102 mg (51%). The GLC of the product showed mixture. The RRT and % of various products are shown in the following Table:

GLC conditions		Product Composition			
140°C/Carbovax Col.	RRT	*1.85	2.92	4.91	7.03
	%	40	15	18	20

*unreacted 3.6

The ^{1}H-NMR spectrum of the total product (Fig.16) showed ~ 10-15% of the required product. However, attempts to separate this product by chromatographic technique was unsuccessful. Even silver nitrate-impregnated silica gel was used to separate these individual components, but again in vain.

Photolysis of (3.6)

I) 0.15g. of **3.6** taken in 15 ml of n-hexane was degassed by passing N_2 for a couple of minutes and irradiated for 10 hr. in Rayonet photoreactor with 300 nm lamp. The starting material was almost quantitatively recovered with some polymerized material.

II) When irradiated at 254 nm for 12 hr, it led to recovery of 50% starting and 50% polymerized material.

III) When irradiated at 300 nm and 254 nm with a sensitizer (acetone, 1-2 ml), there is again recovery of the starting material with some amount of the polymerized products. Similar types of results were obtained even when benzene was used as a solvent.

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CHAPTER III

Photochemical investigation of α-substituted propiophenones

Objective: *The present study is intended to explore the effect of different leaving groups α to the carbonyl, and also the effect of different m-substituents in the phenyl rings in the photochemistry of propiophenones. Such a study is expected to help in understanding the mechanistic aspects.*

This chapter presents an account of the results that emerged from a detailed photochemical investigation of four classes of substituted propiophenones:

1. differently α-substituted *p*-isobutylpropiophenones
2. *p*-isobutyl-α,α-dihalopropiophenones
3. *m*-substituted-α-chloropropiophenones
4. phenylsubstituted-αmethoxypropiophenones

With a view to putforth the objective of this investigation in its true spirit and to place the work described here in a proper perspective, a concise introduction on the synthesis of α-arylpropionic acids involving rearrangement reactions is presented, as this class of nonsteroidal antiinflammatory agents is of immense current interest.

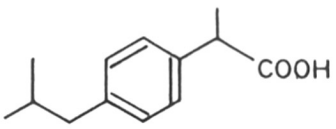
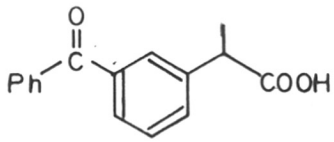
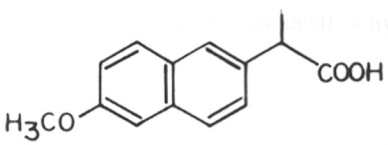
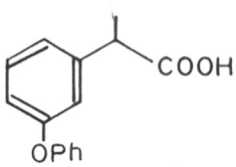
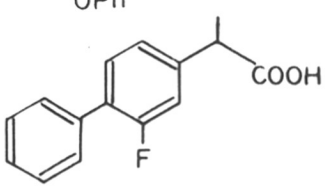
This programme is essentially initiated to understand further the various parameters that affect the photoinduced rearrangement of α-substituted propiophenones to α-arylpropionic acids discovered recently in our group.[1]

Introduction

Nonsteroidal antiinflammatory agents have gained tremendous importance during the past two decades specially due to their significant antiinflammatory and analgesic activities with reduced toxicity.[2] This situation is adequately attested by the fact that Ibuprofen, Ketoprofen, Neproxen, Fenoprofen, Fluorbiprofen and related group of α-aryl propionic acid constitute the fourth largest class of drugs marketed today, globally.[3]

Table-1: Some α-Aryl propionic acids in current world market

TABLE-I

Name	Structure	Year	Manufacturer (Country)
Ibuprofen		1972	Boots (U.K)
Ketoprofen		1973	Specia (USA)
Naproxen		1974	Syntex (USA)
Fenoprofen		1974	Lilily (USA)
Flurbiprofen		1977	Boots (UK)

Such a market has, therefore, led to frenetic and synthetic efforts to devise better methodologies for this class of drugs. This picture is evidenced by numerous publications and patents emanating from academic institutions and commercial research and development centres.[3]

Synthetic methodologies exemplified by Ibuprofen and Naproxen

Disconnection approach:

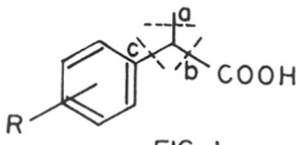


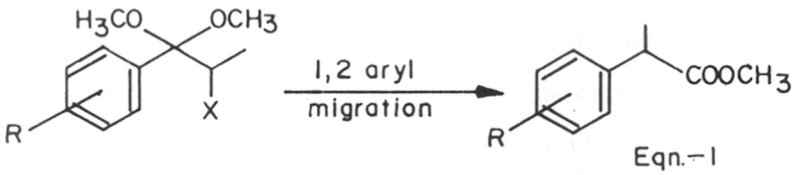
FIG-1

Three distinct types of bond scissions shown in the Figure-1 immediately suggest the right chemical reaction to be adopted for the synthesis of this class of compounds. Disconnection 'a' suggests a following reaction: methylation of α-aryl acetic acid, hydrogenation of α-aryl acrylic acid, epoxidation of α-methyl styrene and its further transformations.

A bond scission as shown in 'b' indicates the need of hydroformylation/hydrocarboxylation of appropriate styrene derivatives.

Finally, 'c' mode of disconnection apparently necessitates an aryl-alkyl bond formation, indicating either a Grignard coupling or alkylation of appropriate aryl compound. A survey of literature reveals that all the strategies indicated above have been investigated well.[4]

Surprisingly enough, despite the various methodologies developed based on the above rationale, the one that led to a commercial process involved an altogether different type of reaction. The key reaction here is a 1,2-aryl migration in differently α-substituted propiophenone: dimethyl acetals (Eq.1).

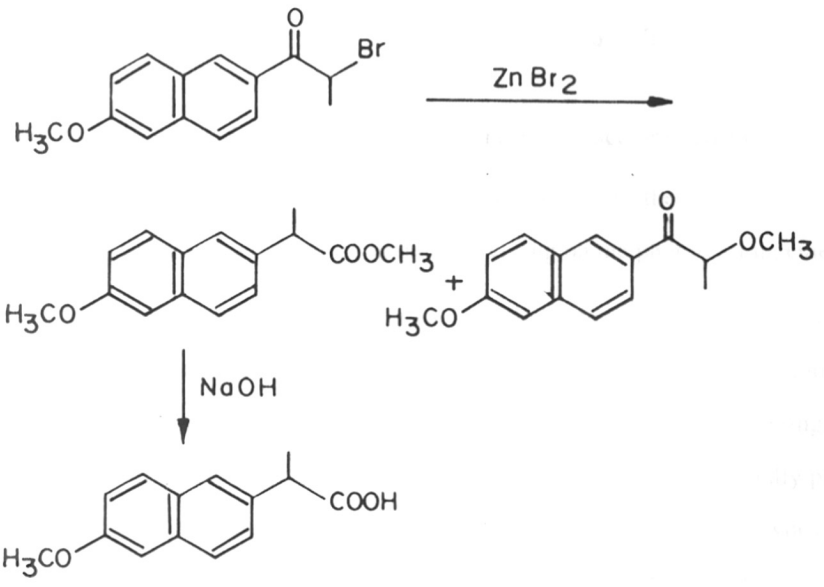


Eqn.–1

Early examples of 1,2-aryl migration leading to this class of compounds involved the use of thallium nitrate,[5] lead tetraacetate[6] and polyvalent iodine derivatives[7] such as $PhI(OAC)_2$. A more recent example involved the transformation of propiophenone into corresponding enamine and its 1,2 rearrangement.[8]

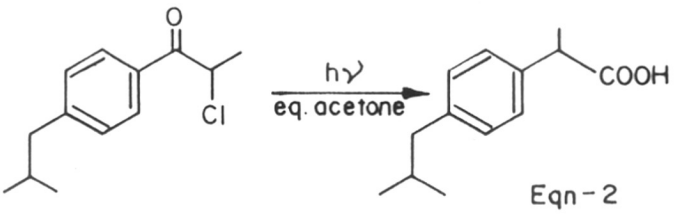
A breakthrough in devising a practical method for α-aryl propionic acid occured when Giordino et al.[9] replaced silver salts that were previously used for rearrangement by inexpensive zinc bromide. The method comprised heating a mixture of concentrated solution of an α-bromo alkyl aryl ketone and zinc bromide in methanol. (Scheme-1).

Scheme I



Another significant stride in this direction was the mechanistic understanding of this reaction by Higgins and Thomas,[10] who showed the involvement of a ketal intermediate in the rearrangement. Such a mechanistic picture suggested the need of protecting the carbonyl group as a ketal prior to the rearrangement. This prerequisite and the need of an efficient leaving group for 1,2-aryl group migration have been presented in greater detail (vide Chapter IV). The need of ketalization suggested

the transformation of trigonal SP^2 geometry of the carbonyl group into tetrahedral SP^3-hybridized state as in the ketal. Such a finding immediately suggested the potential of a photochemical rearrangement reaction in α-halopropiophenones in leading to α-aryl propionic acids. As the configuration of a carbonyl group in its excited state is known to be a SP^3 hybridized one, this reaction appeared attractive. Such a conjecture prompted us to undertake the photochemical investigation of *p*-isobutyl-α-chloro propiophenone (Equation 2).



Eqn - 2

Photolysis of *p*-isobutyl-α-chloro propiophenone in aq. acetone led to the realization of Ibuprofen in a significant yield.[11] Such a finding prompted us to probe the effect of both the electron donating and electron withdrawing groups in the phenyl ring on the photorearrangement reaction.

Results from such a study is presented in Table-2. (Scheme-2).It can be seen from the results that the primary photoprocesses of reduction of the C-Cl bond, 1,2 aryl migration and the photosolvolysis have been influenced to a considerable extent by the nature of the ring substituent. It is significant to note that the electron donating alkyl substituents have essentially promoted the aryl migration while the electron withdrawing chloro substituent furnished other types of products, more or less, in equal amounts. This result suggested a deterring effect of the chloro substituent on aryl migrations. At the same time, it is noteworthy that the unsubstituted ketone yielded almost equal amounts of reduction and the rearrangement product. It is also remarkable that methoxy substituent essentially lead to photosolvolysis.

Scheme 2

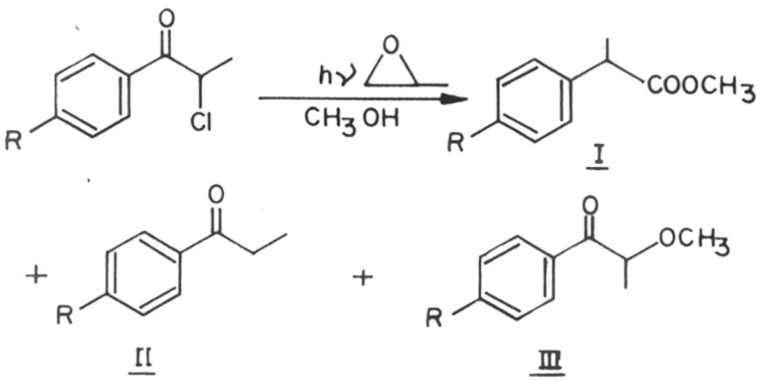


Table-2

Entry	Substrate	R	I	II	III
1	a	H	39	30	--
2	b	CH_3	76	8	--
3	c	C_2H_5	74	9	--
4	d	n-C_3H_7	77	9	--
5	e	i-C_4H_9	65	15	--
6	f	t-C_4H_9	69	8	--
7	g	Cl	30	24	30
8	h	Ph	18	26	35
9	i	OCH_3	8	12	70

This type of reaction selectivity guided by the substituents may be understood in terms of the involvement of different excited states. The reactions of substituted ketones leading to 1,2 aryl migration are supposed to arise from n-π^* transition state. Analogously, photosolvolysis process favoured by the methoxy substituent is assumed to originate from the polar π-->π^* excited state. Such an involvement of different excited states caused by electronic nature of the substituents is well documented.[12]

The study referred to above not only led to the development of a photochemical method for (±)-Ibuprofen, but also suggested its use for realizing asymmetric synthesis. Photolysis of quite a few alkyl substituted chiral α-chloro propiophenones led to the corresponding α-aryl propionic acids in significant enantiomeric excess.[11]

It must be mentioned that the photochemical investigation discussed above was restricted to *p*-substituted-α-chloropropiophenones.

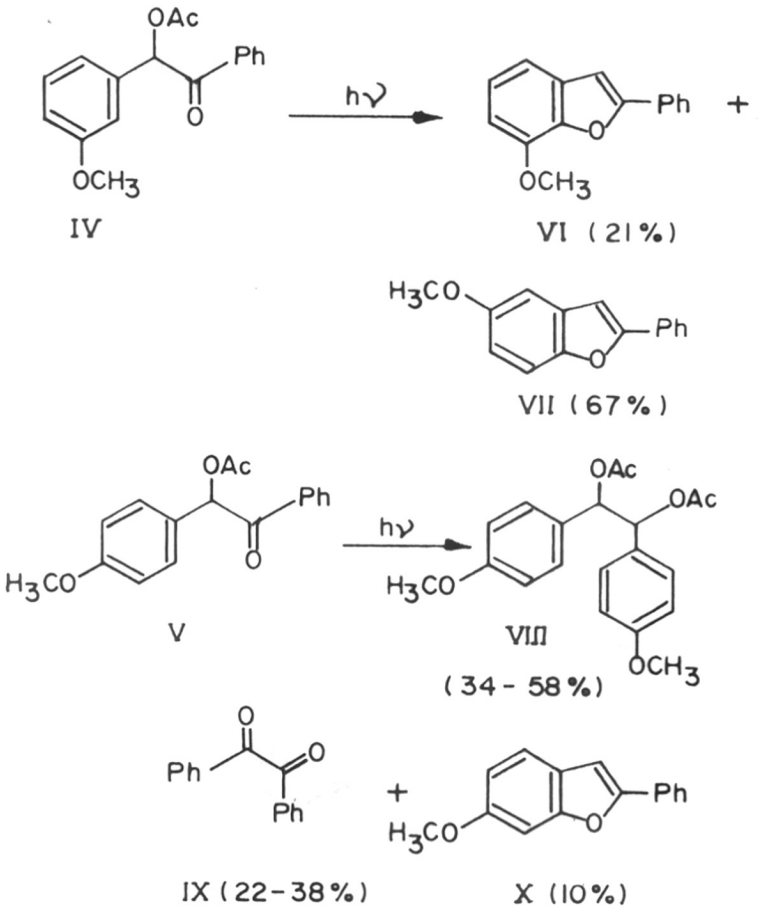
At this juncture, it occurred to us that a photochemical study of differently α-substituted propiophenones may be both educative and useful. The susceptibility of a C-X bond towards homolysis or heterolysis is known to be guided by the nature of the C-X bond. Thus, we envisaged to study photobehaviour of different *p*-isobutyl-α-substituted propiophenones.

Besides the above consideration, a *m*-substituent in the phenyl ring may have its own peculiar directing effect on the different photoprocesses. In this context, a brief survey of literature concerning photolysis of *m*-substituted phenyl derivatives revealed some interesting features.

The photolytic study of methoxy-substituted benzoin esters reported by Sheehan et al[13] is extremely interesting in terms of directing effect of the substituent on the photochemical course in relation with the involvement of different excited states.

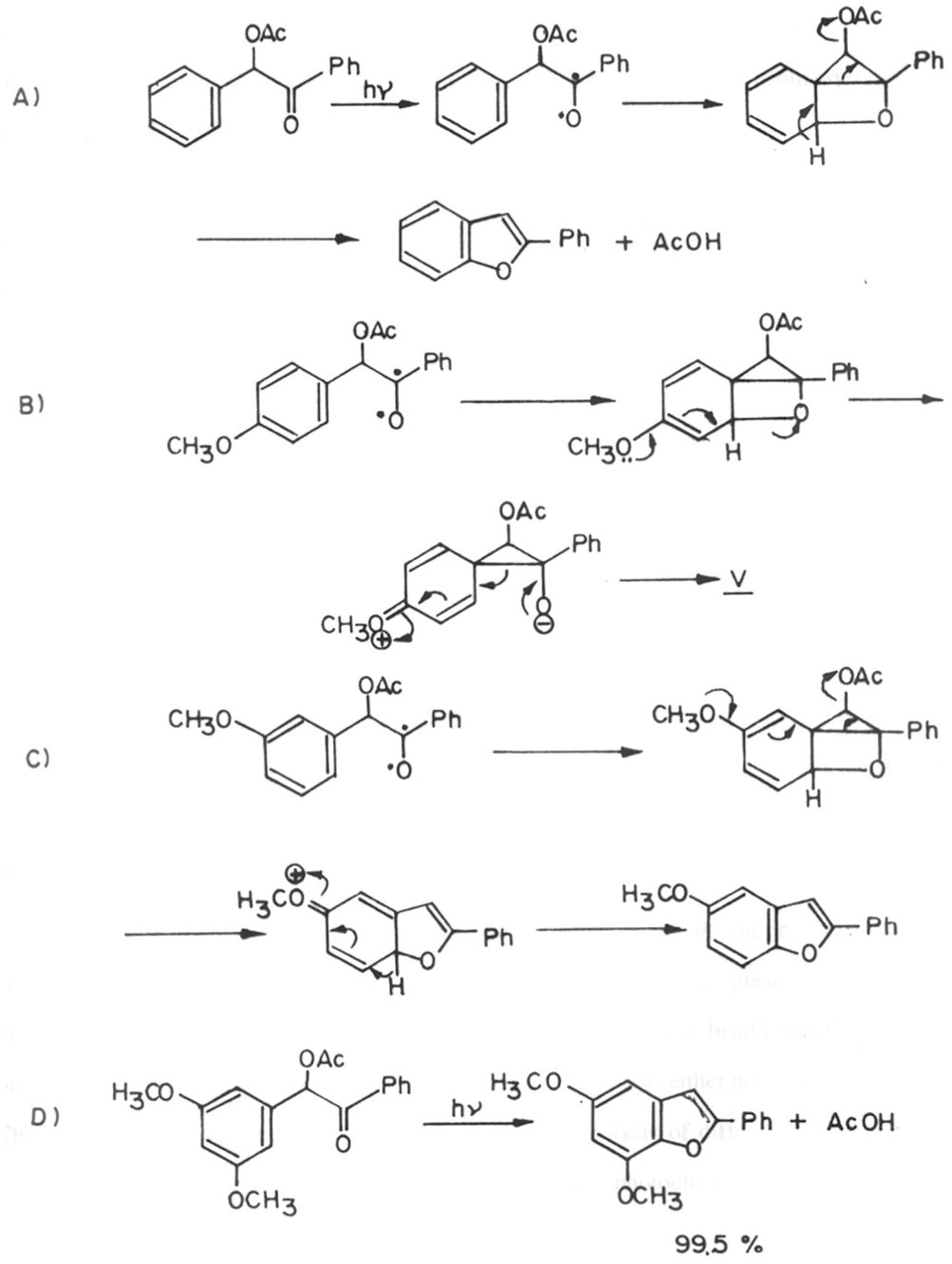
These authors photolysed both 3'-methoxy IV and 4'-methoxy benzoin acetate V and obtained from them an altogether different types of photoproducts (Scheme-3). It can be seen that the 4'-methoxy compound V affords a small quantum of the cyclized product X, while the dimerization products are predominant. This result is understood in terms of the facile formation of the dimeric products VIII and IX arising from α-cleavage of V leading to benzoyl and 4-methoxy phenyl acetoxy methyl radicals. However, it is noteworthy that the 3'-methoxy benzoin ester IV essentially furnished isomeric cyclized benzofurans VI and VII. A mechanistic rationalization for such diverging results has been proposed (Scheme-4).

Scheme 3



The formation of benzofuran is supposed to involve an electrophilic attack on the phenyl ring by the alkoxy radical followed by bond reorganization as depicted in Scheme 3 and 4A. It can be seen that the 4-methoxy substituent in V promotes the rupture of the C-O bond, regenerating the starting ketone (Scheme-4B). On the other hand, 3'-methoxy substituent in IV promotes the benzofuran formation, as shown in (Scheme-4C). Thus, the methoxy substituents in different positions has led to different types of products. It is remarkable that 3',5'-dimethoxy benzoin ester on photolysis furnished the cyclized product exclusively (Scheme-4D).

Scheme 4.



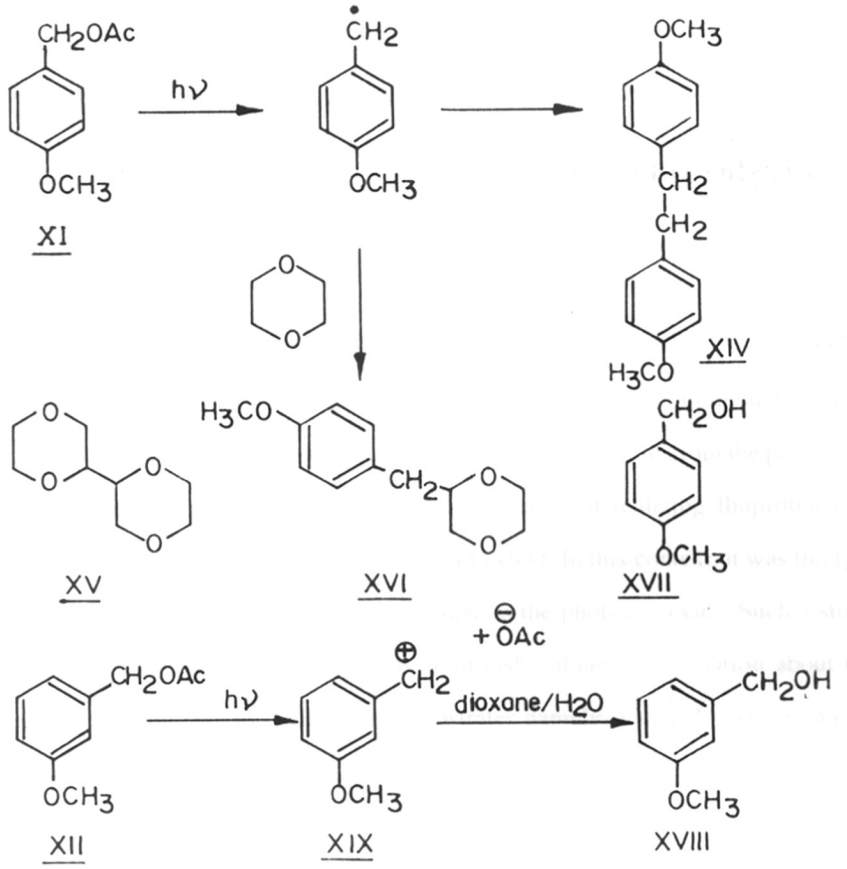
Another important observation made by these authors was the involvement of n-->π^* triplet excited states in the formation of VI and VII as evidenced by quenching of the reaction by piperylene. However, such a quenching was not observed in the reaction of dimethoxy benzoin ester indicating the probable involvement of a n-π^* singlet state.

An elegant example of the substituent effect especially from a meta group comes from Zimerman and Sandell,[12] who investigated the photobehaviour of meta and para methoxy substituted benzyl acetates. It can be seen from the results (Scheme-5A) that the *p*-methoxy benzyl acetate XI on photolysis furnished products XIV, XV and XVI, essentially arising by a radical path; in addition, a minor amount of the photosolvolysis product XVII was observed. On the other hand, the m-methoxy substituted XII yielded a greater quantum of the solvolysis product XVIII. A further enhancement in the solvolysis product XX to the exclusion of the radical products was realised in the photolysis of 3,5-dimethoxy benzyl acetate XIII. Such a remarkable influence of meta methoxy substituents on the photosolvolysis has been rationalised by the authors, as shown in (Scheme-5B).

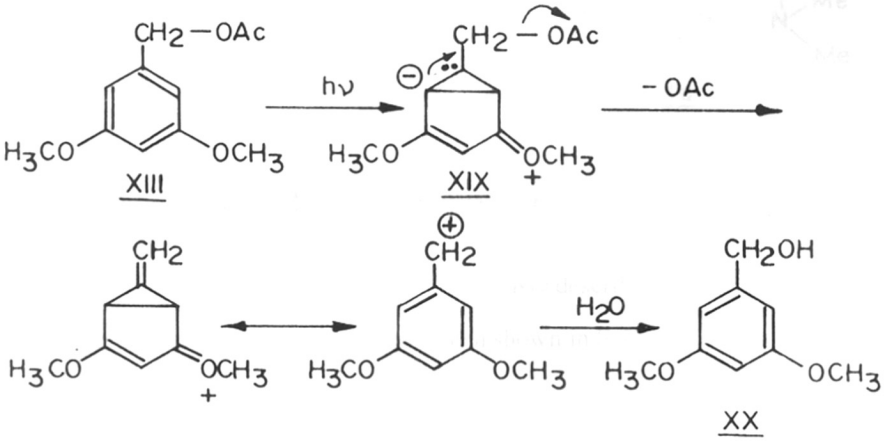
It is apparent that an intermediate (XIX) arising from π-π^* excitation has an anionic character on the carbon α to the acetoxy methyl group which expells the acetate function. Such a situation is not available for the 4-methoxy compound. Such a picture arising from the results has also been supported by molecular orbital calculations indicating an increased electron density at the carbon referred to above.

The above discussion brings out certain points clearly. A substituent on phenyl ring has a definite directive effect on the photochemical course of the chromophores present in the molecules, the effect being different depending on the meta or the para substitution. In addition, the substitution pattern in aromatic ring has a bearing on the type of photocleavage, either homolytic or heterolytic. These considerations along with the results from our photolysis of differently *para*-substituted α-chloropropiophenones suggested that a systematic photochemical study of various

Scheme 5A



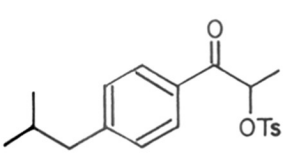
Scheme 5B



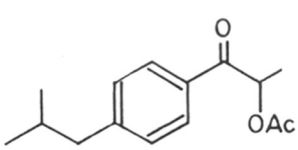
propiophenones with different α-leaving groups and also with meta substituents in the phenyl ring would be interesting; such a study may also throw some light on the mechanistic aspects. The results thus obtained are described in the following sections.

Section A: Photochemistry of *p*-isobutyl-α-substituted propiophenones

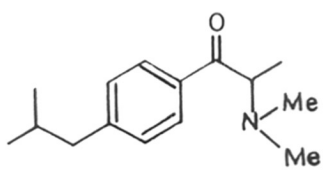
It can be recapitulated that the earlier study reported by us[11] pertained to α-chloro phenyl substituted propiophenones. It was observed that photolysis of these substrates in methanol led to photoreduction, 1,2 aryl migration and photosolvolysis. Particularly, the results from the photolysis of *p*-isobutyl-α-chloropropiophenone 1a was encouraging in terms of realizing Ibuprofen in a significant yield, along with the reduction product to a small extent. In this context, it was thought worthwhile to explore the effect of different leaving groups on the photoprocesses. Such a study might either enhance the desired 1,2 aryl migration or furnish valuable information about the mechanistic aspect of the photoreaction. Thus, three substrates namely α-tosyl **1b**, α-acetoxy **1c** and α-dimethylamino **1d** *p*-isobutylpropiophenones were chosen for the study.



1b



1c

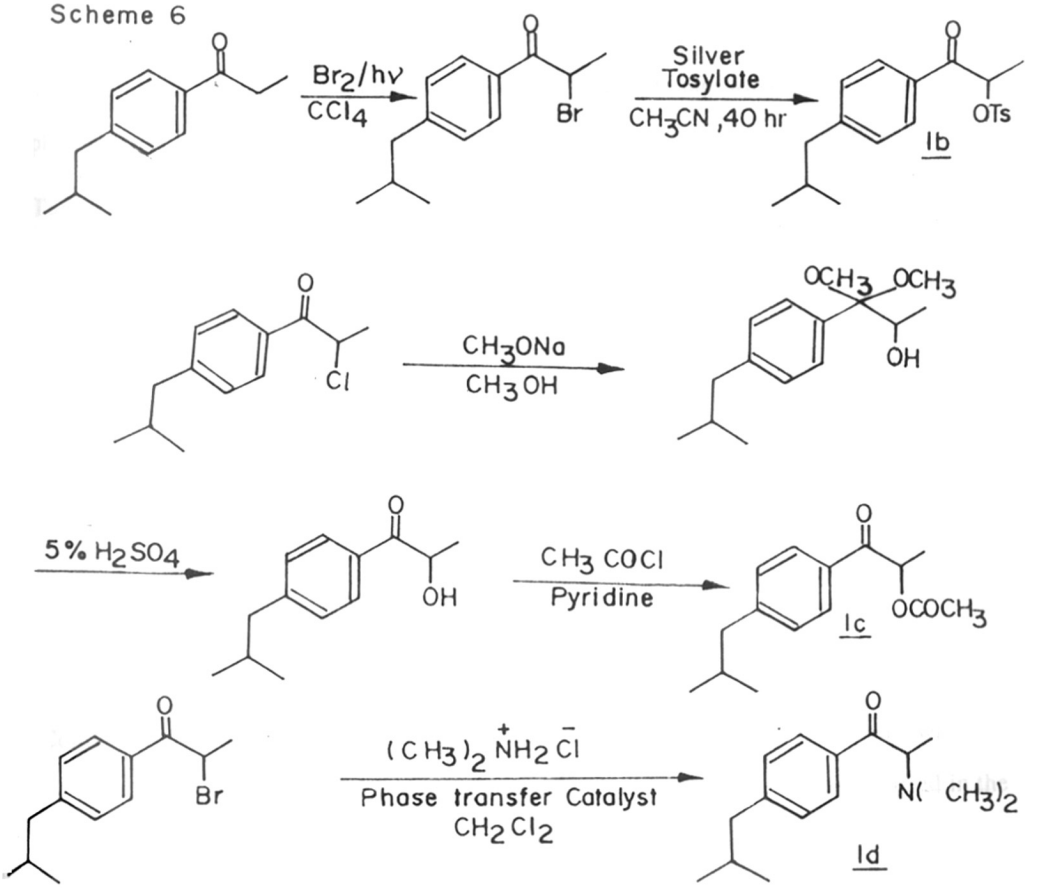


1d

Results and Discussion

Preparation of 1a-1d: The preparation of 1a has been previously described.[11] The sequence of the reactions adopted to prepare the other substrates have been shown in Scheme-6.

Scheme 6



The chemical purity of the substrates were ensured by their homogeneity on two different GLC columns (except 1b) which decomposed on the GLC column). These compounds displayed satisfactory IR and NMR spectral data and analysed well for carbon and hydrogen (Experimental).

Exemplifying ^{1}H-NMR features of these compounds, the PMR spectrum of α-tosyl (*p*-isobutyl) propiophenone is given (Fig.2). The spectral data is given below:

^{1}H-NMR: 0.90 (d, 6H), 1.60 (d, 3H), 1.68-2.10 (m, 1H), 2.40 (s, 3H), 2.52 (d, 2H), 5.70 (q, 1H), 7.10 (d, 2H), 7.20 (d, 2H), 7.60 (d, 2H), 7.70 (d, 2H).

Table-3 presents the UV spectral data of 1b-1d. Based on these absorptions, it was decided to perform the photolysis experiments generally with 300 nm wave length using a Rayonet photoreactor.

Table-3: UV data of **1a** to **1d** (Solvent methanol)

Compound	X	λ_{max} - nm (ε)		
1a	-Cl	207 (8982)	262 (10778)	304 (449)
1b	-OTS	212 (15184)	245 (16360)	310 (519)
1c	-OAC	215 (5317)	255 (12744)	300 (91)
1d	$-N(Me)_2$	212 (9475)	255 (15801)	300 (921)

Control Experiments: All these substrates were subjected to control experiments wherein a 3% solution of the substrate containing propylene oxide (1-2 ml) in methanol was stirred in the dark for 24 hours. It was found that there was no observable reaction as seen by a quantitative recovery of the starting materials.

Photolysis of 1b-1d:

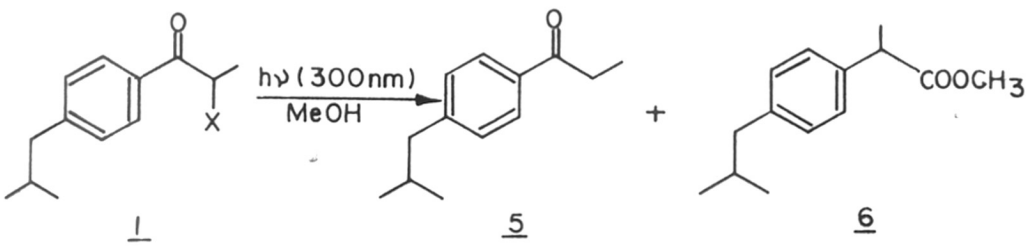
General irradiation procedure:

The photolytic experiments were generally carried out using a 50 ml quartz tube suspended in a Rayonet photoreactor. A 3% solution of the substrate in dry methanol (0.6g, 20 ml CH_3OH) was degassed by a slow bubbling of nitrogen, followed by addition of propylene oxide (1-2 ml). The tubular reactor was stoppered and subjected to irradiation with 254/300 nm lamps. The progress of the reaction was monitored by periodic thin layer chromatography and many a time by GLC analysis. To avoid any acid-catalyzed reaction of the substrate or the products, a totally neutral

reaction medium was maintained during the course of photolysis. After about 6-8 hours of irradiation, excess methanol was stripped off and the product was purified by distillation under diminished pressure. In most of the cases, the products were separated by preparative TLC. With the objective of comparing the results from the substrates 1b-1d, with that of *p*-isobutyl-α-chloropropiophenone 1a previously reported[11], its photolysis was carried out again and results therefrom are also included in Table-4, Scheme-7. It can be noticed from the Table that *p*-isobutyl propiophenone, **5** has been the sole product from all the three substrates. The identity of the product was established by its ^{1}H-NMR (Fig.3) spectral data given below:

^{1}H-NMR: 0.91 (d, 6H), 1.22 (t, 3H), 1.60-2.10 (m, 1H), 2.53 (d, 2H), 2.98 (q, 2H), 7.20 (d, 2H), 7.90 (d, 2H).

Scheme 7



1 5 6

Table-4: Product distribution from the photolysis of α-substituted propiophenones 1a-1d

Substrate	X	Conversion	Composition	
		%	**5**	**6**
1a	Cl	100	25	75
1b	Tosyl	50	99	--
*1c	OAC	15	99	--
1d	$N(Me)_2$	30	99	--

*Irradiated at 254 nm

Further support for the structure was provided by a direct comparison of the PMR data with those reported[11] for **5**.

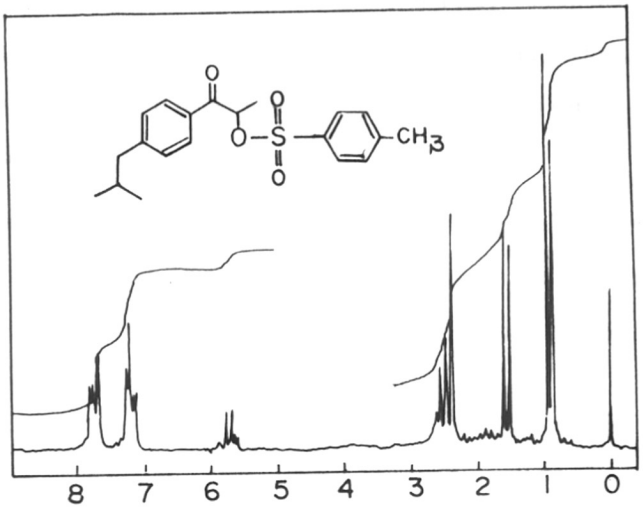


FIG. 2 ^{1}H NMR (80MHz) SPECTRUM OF 1b

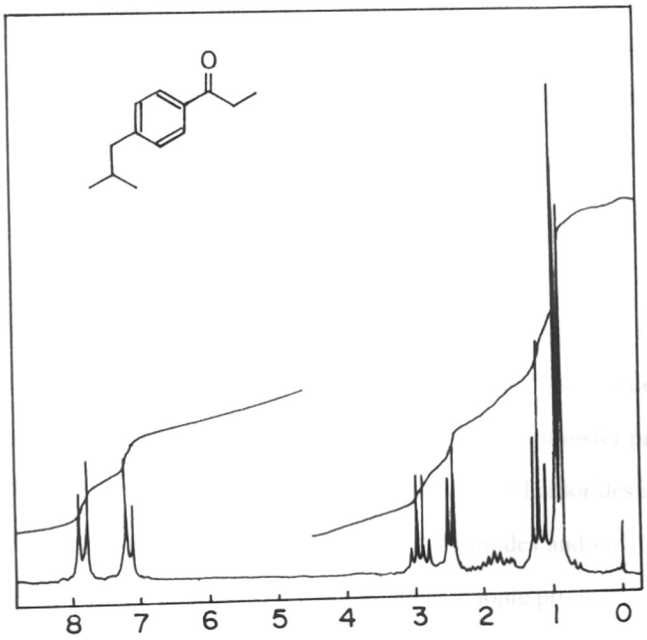


FIG. 3 ^{1}HNMR (80MHz) SPECTRUM OF 5

At the outset, it can be seen that both the chloro and tosyl substituted ketones have(> 50%) converted themselves into products, the conversions in the case of acetoxy and dimethyl amino substituted compounds has been rather poor. As the irradiation was carried out for 6-8 hours, no further photo products were anticipated.

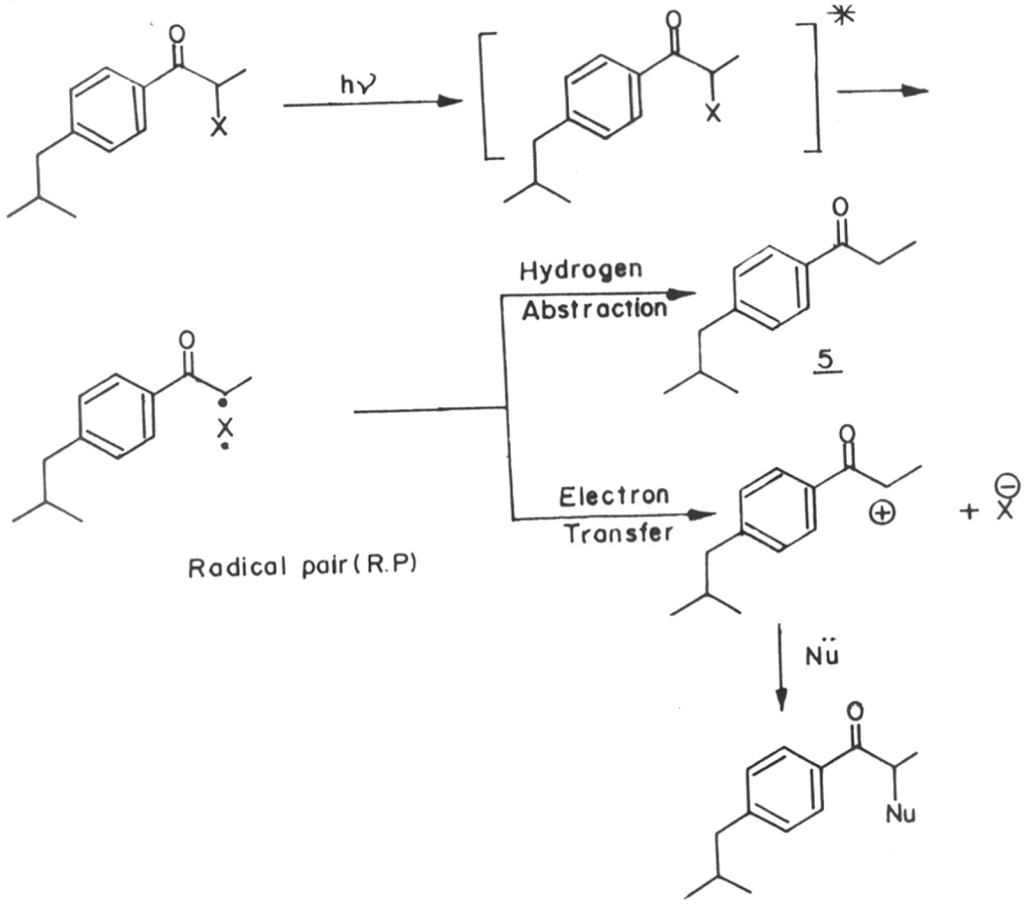
The prominent feature that emerges from a perusal of the Table is the exclusive formation of a single product **5** from 1b to 1d. This result is in contrast with that observed from the chloroketone **1a** which essentially underwent 1,2 aryl migration leading to Ibuprofen. This result from the chloro compound appears to be a special feature of the C-Cl bond.

Genesis of 5: From the extensive work of P.J.Kropp et al.[14] on the photochemistry of alkylhalides, a mechanistic picture has emerged to rationalize the formation of both the radical and ionic products that one obtains. Based on such a scheme, a probable gross mechanistic picture is given below to account for the formation of **5** (Scheme-8).

From such a mechanistic picture, the exclusive formation of the reduction product suggests a total proclivity for the homolysis of C-heteroatom bond in these substrates. These results thus clearly revealed that the nature of the α-substituent has an important role on the course of the photoprocess.

A reasonable explanation for obtaining mostly ionic products with the α-chlorosubstituent alone may be offered in terms of the facile electron transfer in the radical pair (Scheme-8 RP) due to high electron affinity of chlorine atom when compared to the other α-substituents viz. OAc, OTS and $N(CH_3)_2$. Taniguchi et al.[15] have invoked such a facile electron transfer process in obtaining higher proportion of ionic products in the photolysis of certain vinyl chlorides in methanol. In this context, it is pertinent to note that the corresponding vinyl bromides and vinyl iodides have been found to furnish radical products in higher proportion than the ionic products.

Scheme 8

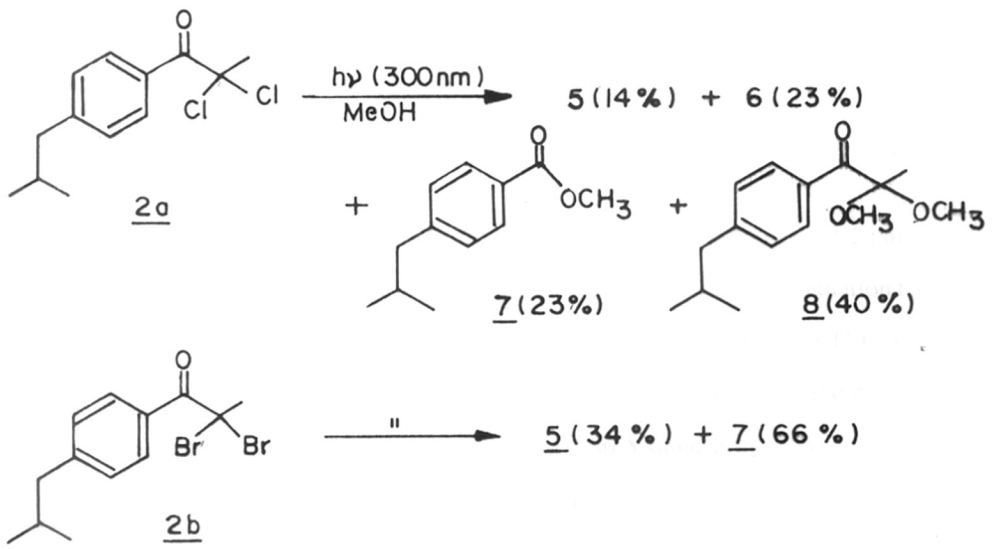


From the synthetic standpoint, these results assume importance since the nature of the α-substituent serves as a switch in bringing about the selective transformation of this class of propiophenones; the deoxygenation (1b and 1c) (Table-4) and deamination (1d) could be of special value.

Section B: Photolysis of *p*-isobutyl-α,α-dihalopropiophenones

This section describes the results from the photochemical investigation of *p*-isobutyl-α,α-dichloropropiophenone **2a** and *p*-isobutyl-α,α-dibromopropiophenone **2b** (Scheme-9).

Scheme 9



Such a study was undertaken primarily for two reasons. Inspite of extensive photochemical studies reported on α-substituted aryl alkyl ketones, there has not been any study on the photochemical behaviour of α,α-dihalo alkyl aryl ketones so far, to the best of our knowledge. On the other hand, there have been some isolated reports on photobehaviour of α,α,α-trichloro acetophenones (vide infra). In the context of *p*-isobutyl-α-chloropropiophenones essentially furnishing 1,2 aryl migrated products on photolysis, we thought it interesting to subject the corresponding dihalo derivatives.

The required substrate **2a** was prepared by chlorination of monochloro derivative following a reported procedure[16]; similarly, bromination of *p*-isobutylpropiophenone afforded **2b**. Both the substrates gave satisfactory spectral data (Experimental). Fig.4 presents the NMR spectral features of **2b**. The UV spectral data of **2a** and **2b** are furnished below:

2a: λ_{max} - nm (ε): 210(6229), 268(13606), 328(409)

2b: 210(7094), 272(12030), 330(488).

As in the case of previous substrates, dark reaction of **2a** and **2b** under comparable conditions were carried out and no reaction was detected.

Results and Discussion:

Photolysis of the dibromo compound **2b** afforded essentially two products in 1:2 ratio (GLC). The minor product was readily identified as the reduction product **5** by peak accentuation technique by GLC on two different columns as well as by its spectral data. The preparative TLC of the total product on silica gel enabled us to isolate the major product in pure form. The PMR spectrum of the product (Fig.5) was conspicuous by a 3H singlet at 3.80 δ suggesting $-CO_2.CH_3$ group. The spectrum was totally comparable with that of the starting dibromo compound, but for the total disappearance of 3H singlet, that was observed at 2.65 δ. The spectrum was obviously suggesting the structure **7**. Further structural support was obtained from the alkaline hydrolysis of the ester. The PMR spectrum of the hydrolysis product (Fig.6) matched well with that of *p*-isobutylbenzoic acid.[11]

Photolysis of 2a: Irradiation of **2a** was carried out as in the case of **2b** and the total distilled photoproduct was analysed by GLC. The chromatogram showed the total product to comprise four components accounting for 14%, 23%, 23% and 40% of the total respectively in the order of increasing retention times. The first three components could be readily recognized as *p*-isobutyl propiophenone **5**, methyl α(*p*-isobutylphenyl) propionate **6** and methyl *p*-isobutylbenzoate **7** from their retention times and also from the mixed GLC experiments. The last component which was

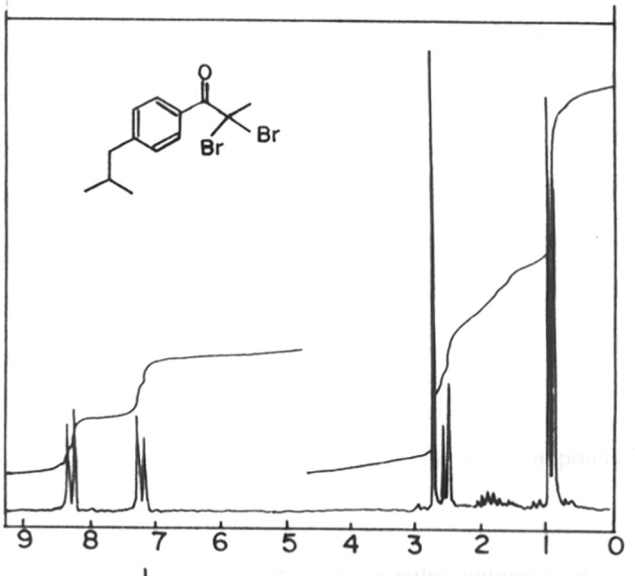


FIG. 4 ^{1}HNMR SPECTRUM OF 2b

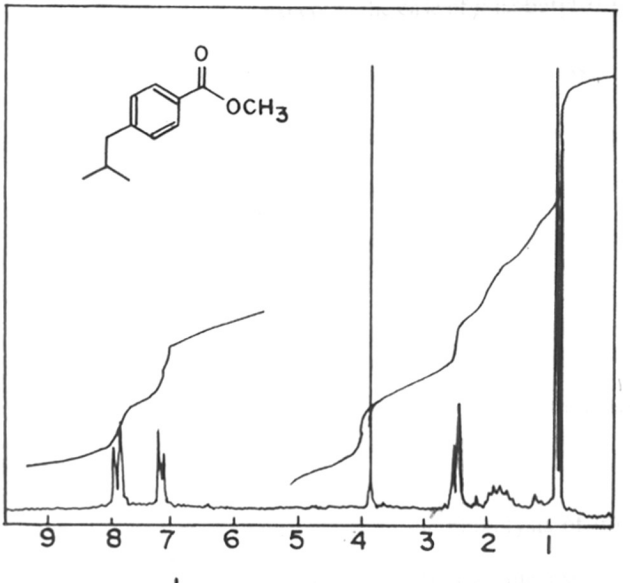


FIG. 5 ^{1}HNMR(80 MHz) SPECTRUM OF 7

separated by preparative TLC showed in its IR spectrum (Fig.7) showed an intense band at 1690 cm^{-1} and 1170 cm^{-1} suggesting the presence of a carbonyl group and an ether linkage respectively. The PMR spectrum (Fig.8) was strikingly peculiar in displaying a 6H singlet at 3.30 and the rest of the spectrum being similar to that of **2a**. Another significant feature was the upfield shift of a 3H singlet from 2.25 δ to 1.55 δ. These spectral features immediately suggested the occurrence of photoinduced methanolysis leading to *p*-isobutyl-α,α-dimethoxypropiophenone **8**. This structural assignment was buttressed by the mass spectrum (Fig.9) which displayed the molecular ion peak at m/z 250 and prominent peaks at m/e 219 (20%) and m/z 161 (40%). Such a fragmentation is well in accord with structure **8**.

Mechanistic aspects: An analysis of the results from the dichloro compound **2a** (Scheme-9) brings forth several interesting features:

1. The formation of methyl benzoate **7** has been rather unique in that none of the previously studied substrates furnished this product except in the case of *p*-isobutyl-α-bromopropiophenone.[11]

2. Photosolvolysis of the geminal dihalide has been a major process.

3. The formation of the reduction product **5** and 1,2 aryl migrated product **6** can be easily understood to arise from the secondary photolysis of mono chloro ketone, which in turn arises from the mono reduction of **2a**. Monohaloketone formation was detected in aliquotes during the course of photoreaction.

As mentioned above, the formation of methyl benzoate **7** is rather intriguing. In this context, the report by Tomioka et al[17] on the photoinduced alcoholysis of trichloroacetophenone is pertinent to be mentioned (Scheme-10).

These authors obtained methylbenzoate from the photolysis of trichloroacetophenone and suggested the genesis of this product from the reaction of the exciplex with oxygen. Such a

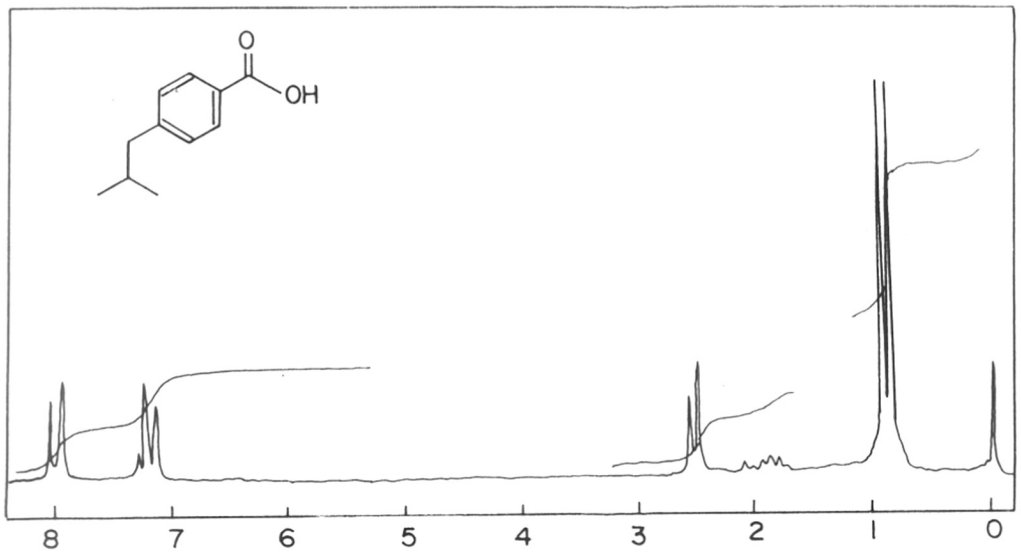


FIG.6 ^{1}HNMR(80MHz) SPECTRUM OF p-ISOBUTYL BENZOIC ACID

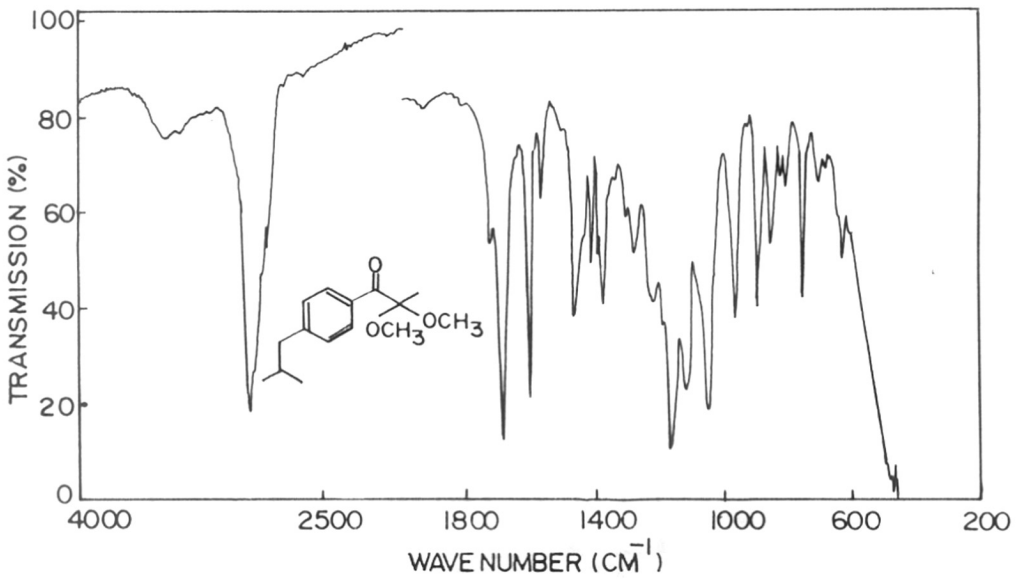


FIG.7 IR SPECTRUM OF 8

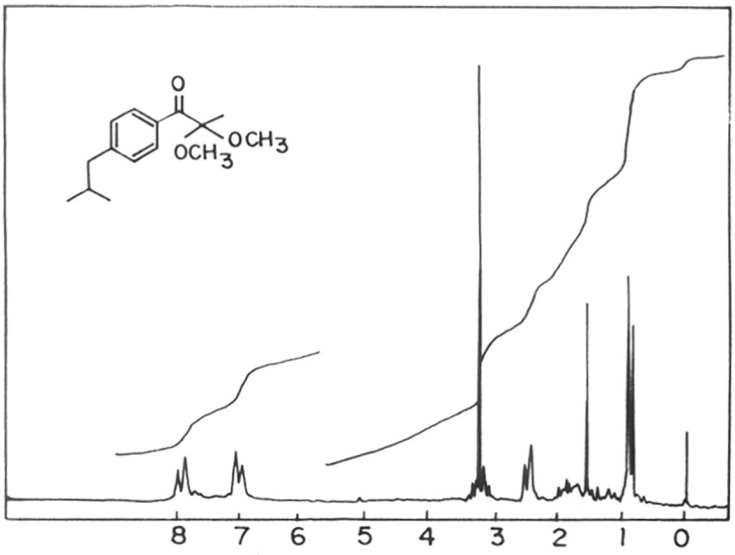


FIG. 8 ^{1}HNMR (80 MHz) SPECTRUM OF 8

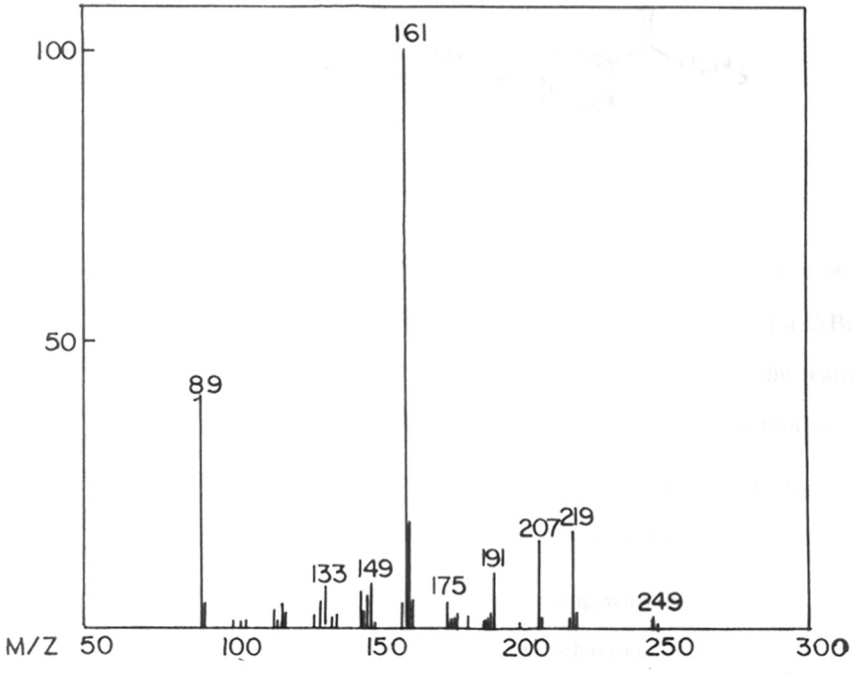
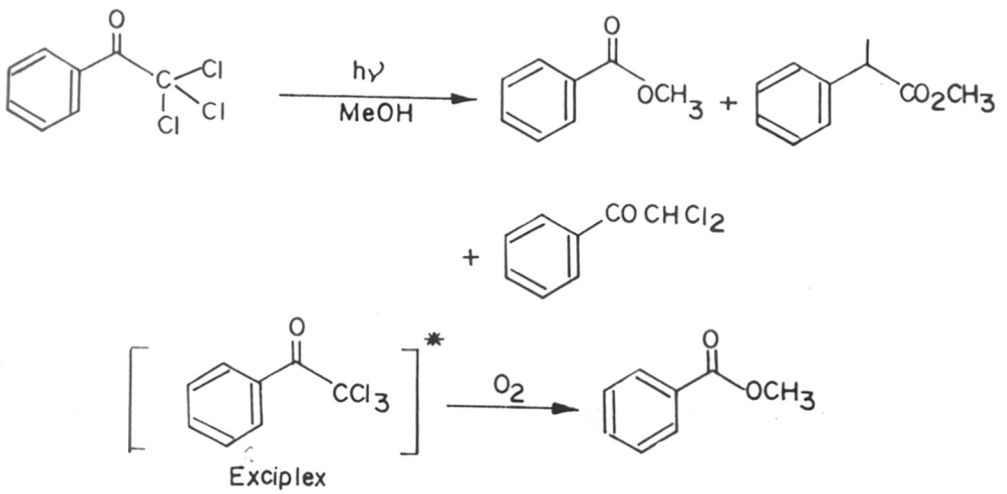


FIG. 9 MASS SPECTRUM OF 8

mechanism may be operating in the case of 2a and 2b.A similar explanation has been offered by Tomioka et al.[18] again to rationalize the formation of methyl benzoate in the photolysis of α,α,α-tribromoacetophenone as well.

Scheme 10



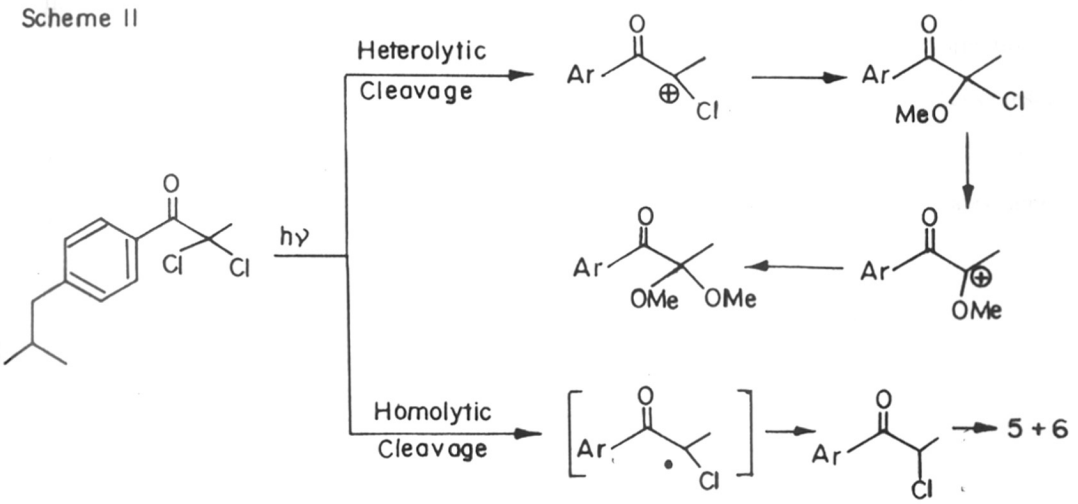
It is interesting to note that the dibromoketone **2b** has yielded the reduction product to a greater extent than **2a**. This can be easily explained in terms of the proclivity of a C-Br bond for homolysis. This situation is further supported by the total absence of either the rearrangement product or the solvolysis product which are known to be derived from an ionic process.

The predominance of photosolvolysis in **2a** deserves some discussion. At the outset, it can be grossly understood to result from a sequence of events as depicted in (Scheme-11).

The observed photosolvolysis in **2a** is quite contrasting with that of **1a** wherein 1,2 aryl migration was the major process. This differential photobehaviour of **2a** leading to **8** may be understood in terms of involvement of a facile aryl participation to undergo rearrangement in the case of **1a** and the expulsion of chloride ion in **2a** leading to α-chloro-stabilized carbocation; the

latter on nucleophilic capture by methanol may lead to α,α-chloromethoxy intermediate which further undergoes methanolysis to furnish the observed **8**. This result may be highlighted in terms of generating highly stabilized α-keto carbenium ions.

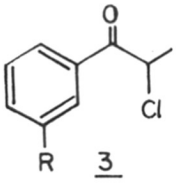
Scheme II



The work described in this Section thus brings out clearly the differential photobehaviour of the monochloro, dichloro and dibromo ketones. While the mono chloro substitution favours a rearrangement reaction, the dichloro predominantly leads to solvolysis. On the other hand, the dibromo derivative preferentially yields reduction product. Both the dihaloketones on photolysis lead to an altogether different type of product namely methyl benzoate.

Section C: Photochemistry of *m*-substituted-α-chloropropiophenones

Representative examples depicting the role of ring substituents on the photochemical behaviour of benzoin acetates have been adequately presented earlier [Introduction: Scheme-3]. It can be recapitulated that the para methoxy substituents favoured the formation of radical products that arise from the triplet excited state in the photochemistry of substituted benzoin acetates. At the same time, a meta methoxy substituent directed the photolysis towards the formation of photocyclization products. Similar observations were made by Zimmerman et al.[12]. These results prompted us to undertake a systematic photochemical study of different meta substituted α-chloro propiophenones. This section presents the results from the photolysis of four such substrates namely 3a-3d and also discusses plausible modes of product formation.



3

R = $-OCH_3$ (3a), $-OPh$ (3b)
$-CH_3$ (3c), $-NO_2$ (3d)

Preparation of the substrates: The substrates were prepared by following the sequence of reactions indicated in Scheme-12.All the substrates analysed well for their elemental composition and exhibited satisfactory IR and NMR spectral data. As a representative example, the PMR spectrum of *m*-methoxy-α-chloropropiophenone **3a** is shown in Fig.10. Table-5 represents the UV spectral data of **3a-3d**.

Scheme 12

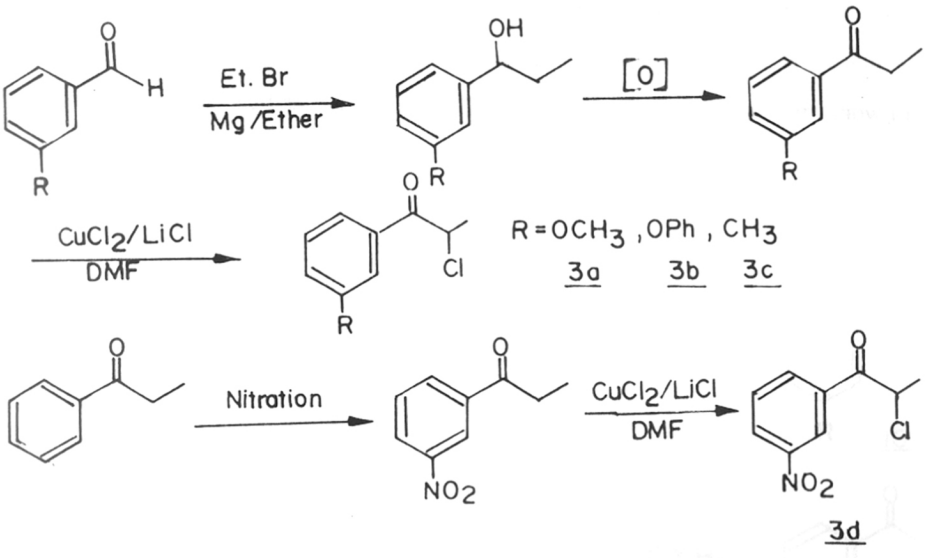


Table-5: Solvent : methanol UV Spectral Data of 3a-3d:

Compound	R	λ_{max} - nm (ε)		
3a	$-OCH_3$	218 (4241)	255 (7297)	315 (1883)
3b	-OPh	226 (19428)	250 (9694)	300 (2649)
3c	$-CH_3$	210 (13300)	252 (12528)	300 (1538)
3d	$-NO_2$	210 (8695)	234 (15312)	300 (855)

No product could be detected in the control experiment of **3a-3d**.

Photolysis of 3a-3d:

The photolysis of these substrates were performed as previously described. As formation of hydrochloric acid was expected, propylene oxide was invariably used as an acid scavenger. The products were isolated as usual and purified by distillation. The results are shown in Scheme-13 and (Table-6).

Scheme 13

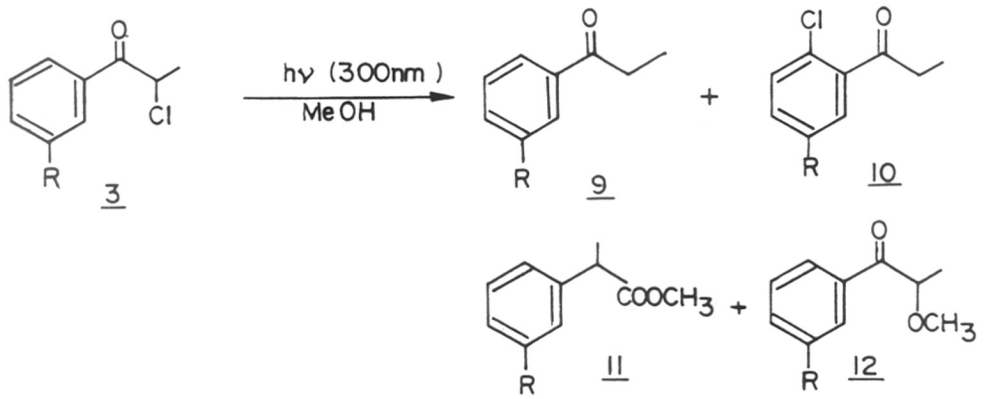


Table-6: Product distribution from the photolysis of 3a-3d

Substrate	R	Conversion %	Composition (%)			
			9	10	11	12
3a	m-OCH_3	100	13	68	--	19
	*p-OCH_3	100	12	--	08	70
3b	m-OPH	100	70	21	08	--
3c	m-CH_3	70	33	--	66	--
	*p-CH_3	100	08	--	76	
3d	#mNO_2	20	100	--	--	--

*This result is extracted from our previous paper.[11]

#Irradiated at 254 nm.

Products from the photolysis of *m*-methoxy-α-chloropropiophenone 3a (Scheme-13, Table-6).

The GLC of the total photoproduct (Fig.11) indicated it to comprise three components of relative retention times, 5.99 (13%), 9.10 (19%) and 10.62 (68%). The PMR spectrum of the total distilled material was extremely useful in suggesting the structural features of the products. The prominent features of the spectrum (Fig.11a) were three distinct 3H singlets in the region 3.82 to 3.90 δ, more or less, in the same ratio of products as observed in GLC. This clearly suggested the presence of aromatic methoxy groups in the products. Another interesting feature was two overlapping 3H triplets at 1.15 δ and corresponding two overlapping 2H quartets centered at 2.93 δ indicating the presence of ethyl groups.

Finally, a secondary methyl doublet centered at 1.46 δ, a 3H singlet at 3.37 and quartet like structure at 4.54 δ indicated the probable formation of the solvolysis product. Thus, the photolysis appeared to have resulted in two reduction products along with the solvolytic one.

The preparative TLC of the total products enabled the separation of all the three components in pure form.

Our initial assumption of the formation of solvolysis product was proved right by the PMR spectrum (Fig.12) of the pure isolated fraction (RRT 9.10). The observed resonances comprised a 3H doublet at 1.46, two 3H singlets at 3.33 δ and 3.82 δ, a 1H quartet at 4.57 combined with a typical meta-disubstituted aromatic pattern of signals accounting for four protons in the region 7.00-7.66 δ. These spectral data enabled us to characterise this product as **12a**.

Further structural evidence was provided by the preparation of an authentic sample of **12a** (vide Experimental) and a direct comparison of its PMR data with those reported above and also its coinjection in GLC with the present compound.

The PMR spectrum of the component with RRT 10.62 displayed a 3H triplet at 1.15 δ, 2H quartet at 2.85, a 3H singlet at 3.70 and a multiplet in the region 6.70 to 7.25 integrated for 4 protons.

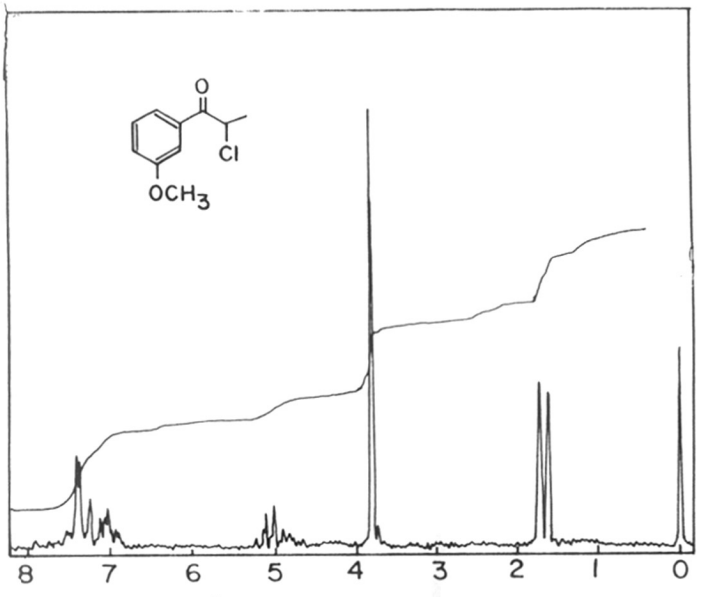


FIG.10 ^{1}HNMR (60MHz) SPECTRUM OF 3a

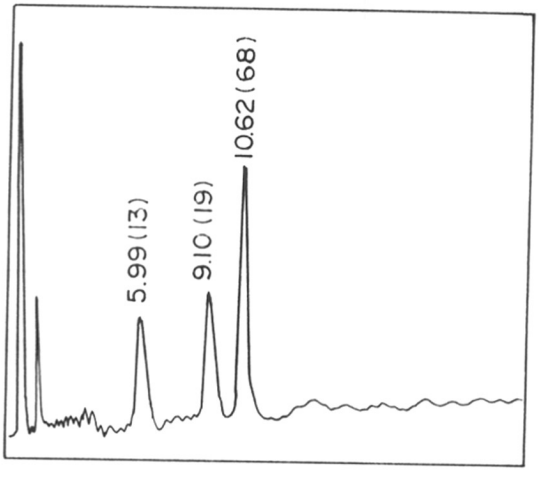


FIG. 11 GLC OF TOTAL PHOTO PRODUCTS OF 3a RRT (%)

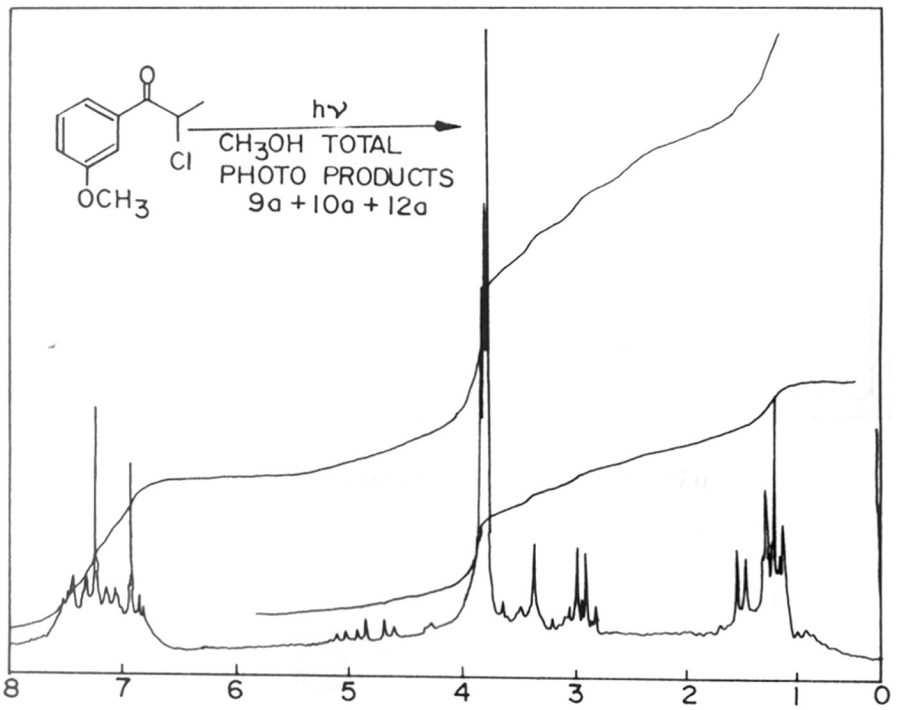


FIG. 11a NMR(90MHz) SPECTRUM OF TOTAL DISTILLED MATERIAL

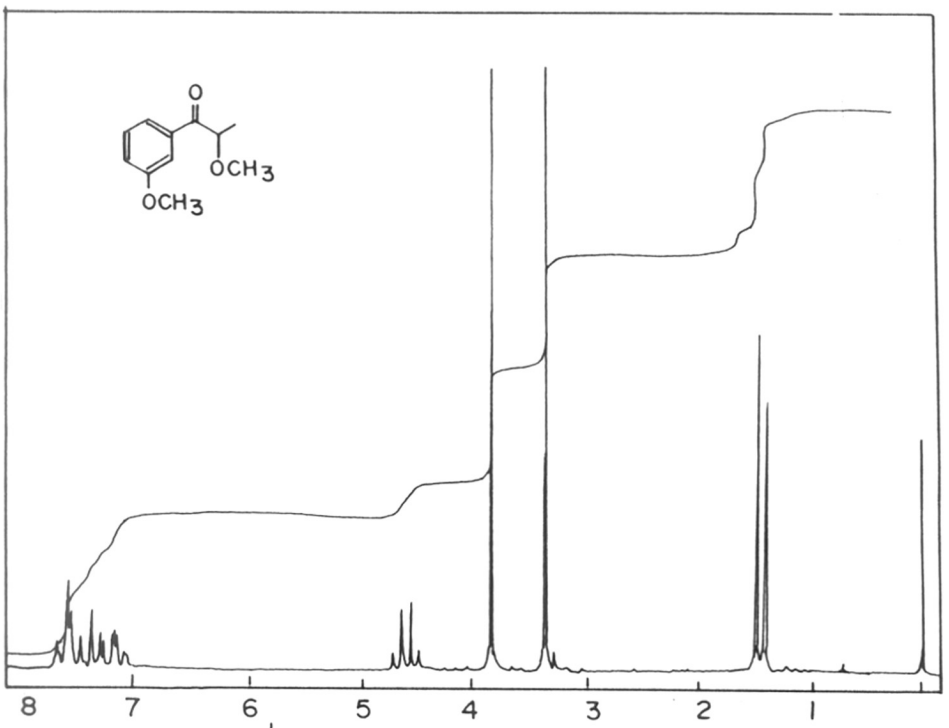


FIG.12 ^{1}HNMR(90MHz) SPECTRUM OF 12a

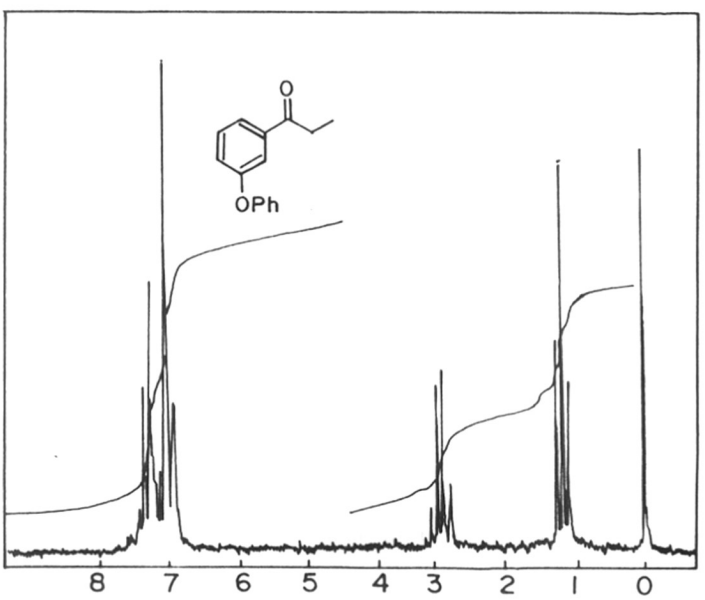


FIG.13 ^{1}HNMR(80MHz) SPECTRUM OF 9b

The mass spectrum of this component indicated the molecular ion peak at m/z, 198 along with a peak m/z, 200 with one third the intensity of the former; the fragments observed at m/z, 169 and 171 indicated a loss of an ethyl group from the molecular ion. Thus, the mass spectral data and the PMR spectral features clearly enabled the identification of this component as **10a**. The PMR spectrum of the minor component with RRT 5.99 was totally similar to that of **10a**, but for showing multiplets for 4 protons in the aromatic region, thus enabling its identity as **9a**. In addition, this assignment was further confirmed by peak accentuation technique with an authentic sample of **9a**.

Thus, the photolysis of *m*-methoxy-α-chloropropiophenone in methanol afforded primarily the reduction product with the preponderance of chlorine incorporated into aromatic nucleus, along with a minor amount of solvolytic product. At the same time, it should be noted that the rearrangement reaction leading to **11** was totally absent. The mechanistic aspects of the formation of products is presented in a later portion. At this juncture, it may be mentioned that the corresponding *p*-methoxy substrate on photolysis essentially furnished the solvolysis product.

Photolysis of *m*-phenoxy-α-chloropropiophenone 3b (Scheme-13, Table-6):

Total distilled product on GLC analysis showed it to comprise three components contributing 21%, 8% and 70% of the total. At the outset, it should be mentioned that the peaks corresponding to the major component was enhanced when mixed with an authentic sample of *m*-phenoxy propiophenone (vide infra). Similarly, the component of 8% composition was accentuated when mixed with authentic sample of methyl α(m-phenoxyphenyl) propionate. The preparative TLC of the total product afforded all the components pure.

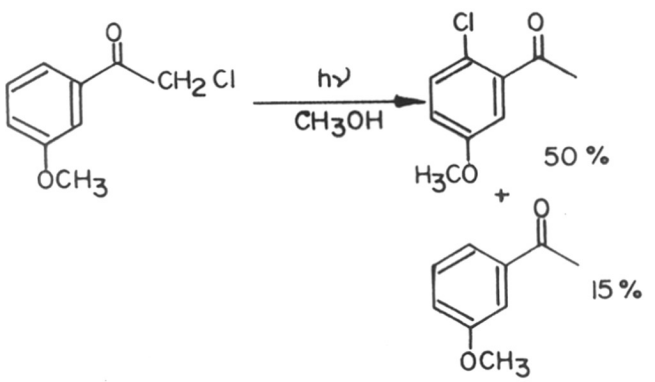
The PMR spectrum of the major component (Fig.13) was extremely obvious in suggesting structure **9b** for the product. It showed a typical 3H triplet and 2H quartet to be expected for the reaction product; multiplet integrating for 9 protons in the aromatic region confined with the signals referred to above made us to identify the component as **9b**. The

PMR spectrum of the second component was totally similar to that of **9b**, but for a slightly reduced area for the aromatic signals. Its mass spectrum was valuable in its structural assignment, it displayed a molecular ion at m/e 260 and m/e 262 with one third intensity. The observed photobehaviour of **3a** and similarity of NMR spectral data of this component to that of **9b** and the molecular ion peaks as noted above collectively pointed out the structure **10b** for the product.

The PMR spectrum (Fig.14) of the last component was significant in displaying a secondary methyl doublet at 1.40, a 3H singlet at 3.64 and an ill resolved 1H quartet at 3.80, besides showing multiplets for nine protons in the aromatic region (7-8 δ).The NMR data immediately indicated structure **11b** for the product. Obviously, this has arisen from 1,2 aryl migration. This structural assignment was further buttressed a direct comparison of the NMR data with that of an authentic sample of **11b** (Chapter-IV).

In the context of the formation of **10a** and **10b** (with the chlorine in the phenyl ring) from the photolysis of **3a** and **3b**, it is relevant to refer to the results of Anderson and Riece.[19] These authors similarly observed the formation of 2-chloro-5-methoxy acetophenone as one of the products from the photolysis of *m*-methoxy phenacyl chloride alongwith the C-Cl reduced products. (Scheme-14).

Scheme 14



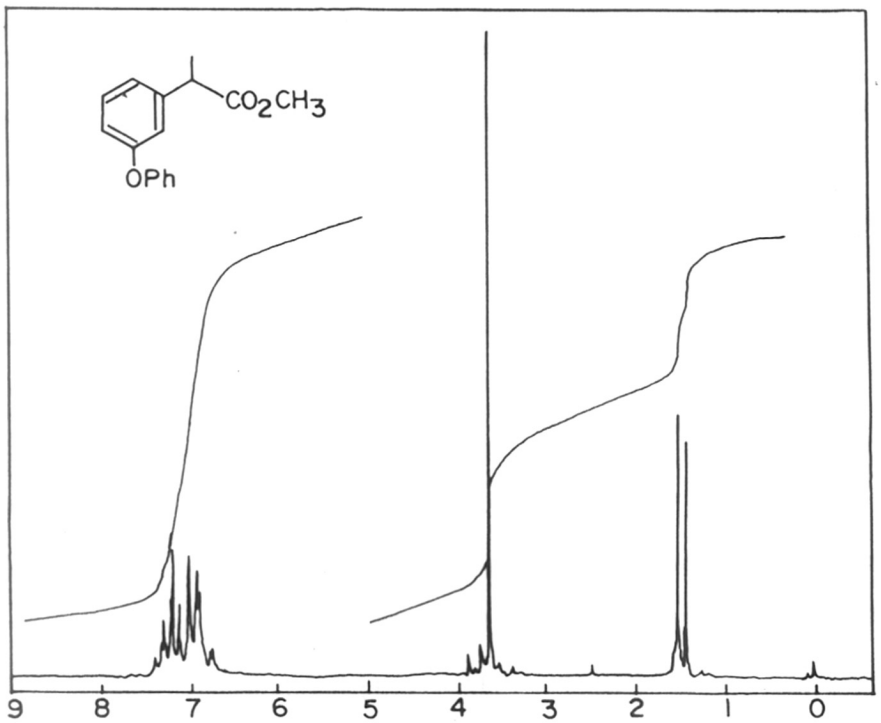


FIG. 14 ^{1}H NMR (80 MHz) SPECTRUM OF 11b

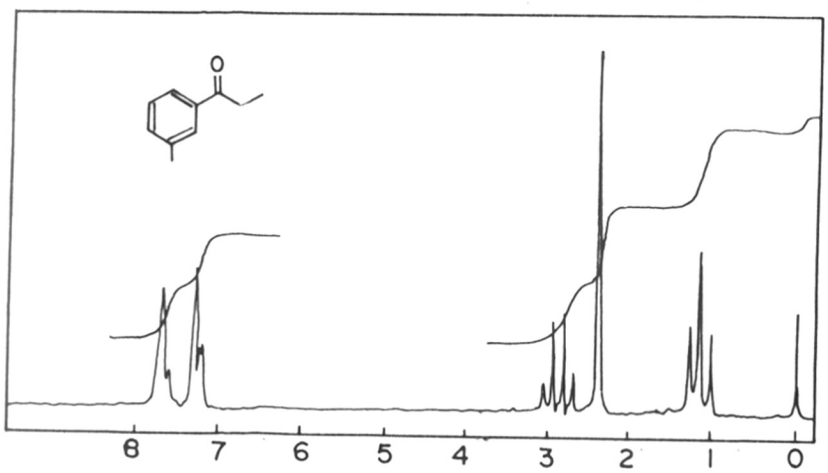


FIG. 15 ^{1}HNMR (60 MHz) SPECTRUM OF 9d

Photolysis of *m*-methyl-α-chloropropiophenone 3c

The composition of the photo product from **3c** was much simpler; the GLC of the total material showed it to comprise two components in a 1:2 ratio. The preparative TLC enabled the isolation of both the components in pure form. The PMR spectrum of the minor component indicated adequately the structure **9c** for the product (Fig.15). This structural assignment was further supported by direct comparison of these PMR data with those obtained for the authentic **9c**. It may be recalled that the latter compound **9c** was utilised in the preparation of **3c**.

The major component could be easily characterized as **11c** by its typical PMR spectrum showing the expected secondary methyl, ester methyl, tertiary methine resonances.

It is necessary to observe here that the alkyl group in the phenyl ring has directed the photolysis in favour of 1,2 aryl migration in contrast with the corresponding methoxy or phenoxy substituents.

Photolysis of *m*-nitro-α-chloropropiophenone 3d

Photolysis of **3d** in methanol with 300 nm light for continuous period did not show the occurrence of any photoprocess as seen by the total recovery of the starting material. On the other hand, photolysis when carried out with 254 nm light resulted in the formation of a single product even after 6 hours of irradiation; nonetheless, the conversion was rather meagre. The GLC of the total product (Fig.16) indicated a single product (20%), along with the unreacted **3d**. A preparative TLC done as usual afforded the product in pure form. The characterization of the product as **9d** was very obvious from the PMR spectrum (Fig.17). The unique feature of the photobehaviour of **3d** is its low reactivity and the formation of a single product arising from reductive cleavage of C-Cl bond. Implications of this result are discussed in detail in a later section.

Mechanistic considerations

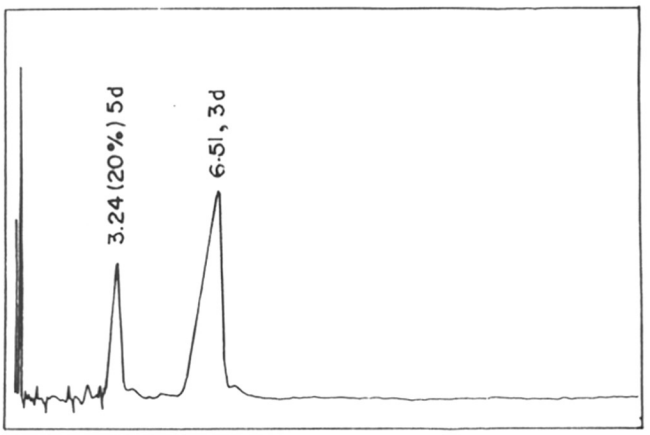


FIG.16 GLC OF THE TOTAL PHOTO PRODUCT OF 3d RRT(%)

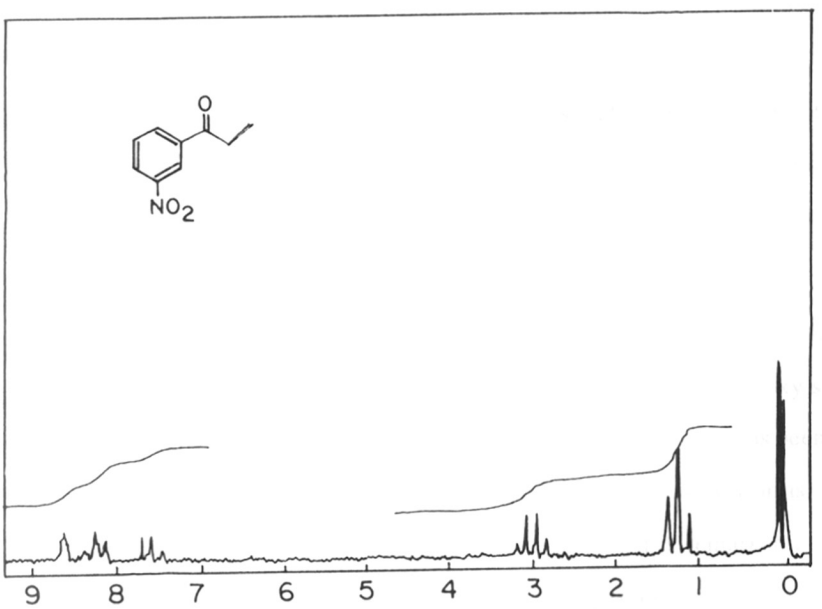


FIG.17 ^{1}HNMR(60MHz) SPECTRUM OF 9d

The primary objective of the photostudy of meta substituted α-chloropropiophenones was to gain a further insight into the mechanistic aspects and also to compare the photobehaviour of these with that of *p*-substituted compounds. A quick reference to the results shown in (Table-5) brings forth some significant features.

1. The *m*-methoxy ketone **3a** has essentially led to **9** and **10** with a preponderance of the latter, incorporating chlorine into the aromatic nucleus; on the other hand, the corresponding *p*-methoxy ketone on photolysis afforded primarily the photosolvolysis product.

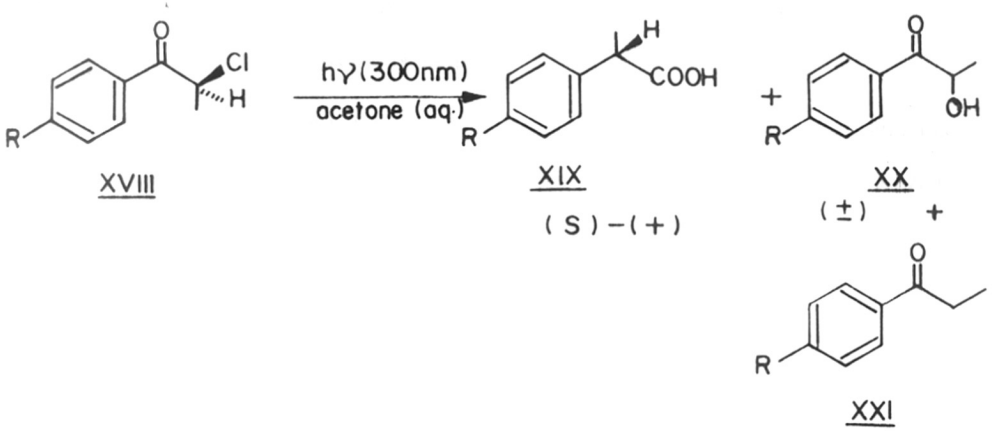
2. The methyl substituted **3c** has shown a proclivity for 1,2-aryl migration leading to **11**, although to a less extent than the corresponding *p*-methyl ketone.

3. Significantly enough, *m*-nitro ketone **3d** has been extremely sluggish and furnished the reduction product **9** exclusively.

The above results merit some comments. In order to understand the mode of formation of the products and also the differential reactivity of 3a-3d, our previous results from chiral α-chloro propiophenones become useful. A comparative study might help to present a cogent picture (Scheme-15).

An analysis of these results show that the alkyl substrates preferentially lead to 1,2 aryl migrated products; the solvolysis has been totally absent. Contrary to this, a methoxy substituent afforded more of the solvolysis product. It can be mentioned that a similar trend has been observed from the compounds of the *m*-series. More important than the above observation is the fact of chirality transfer to different extents depending on the substituents. It is remarkable that α-aryl propionic acids alone show optical activity while solvolysis products are racemic. In addition, 1,2 aryl shift appears to be operating in two competitive ways; stereospecific one leading to inversion of configuration and the other non-stereospecific mode being of ionic nature leading to racemic products.

Scheme 15



XVIII

XIX

(S) −(+)

XX

(±) +

XXI

Table-6

Substrate XVIII	R	Products (+)-XIX Yield %	ee %	(±) XX Yield %	XXI
b	CH_3	78	36	--	23
c	$-C_4H_9$	70	40	--	6
a	H	55	20	--	6
d	OCH_3	30	5	50	9

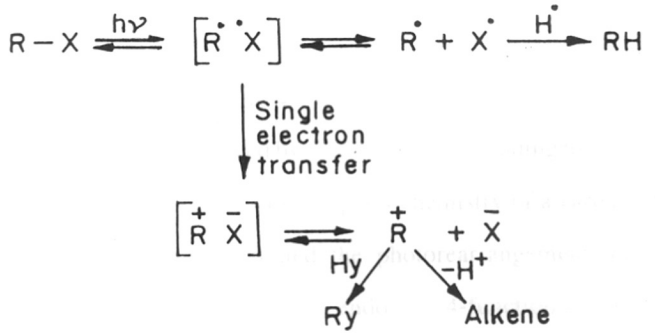
These results have been rationalized in terms of involvement of different triplet excited states. The electron-donating alkyl substituents enhance the nucleophilicity of the aromatic ring leading to a fast 1,2 aryl migration before the migration terminal gets planar and lead to optical induction. In such a case, an n-π^* excited triplet state is known to be involved.[20] On the other hand, the methoxy substituent not only leads to the formation of a π-->π^* triplet excited state,[20] but creates a localized electron deficiency in the aromatic ring. This reduced nucleophilicity deters the 1,2 aryl migration.

The above mechanistic considerations pertained more to the transfer of chirality in the photolysis of chiral α-chloropropiophenones, in addition, the nature of the excited state whether

triplet or singlet is considered. On the other hand, from the point of view of entire results presented in this Chapter on the photochemistry of differently substituted propiophenones, a presentation of a general mechanistic picture would be helpful.

Photochemistry of alkyl halides has been extensively studied over the years and a generally accepted mechanism suggested by Kropp et al.[21] involve an initial homolytic cleavage of the C-halogen bond followed by competing electron transfer within the resulting caged radical pair and diffusion from the cage (Scheme-16A).

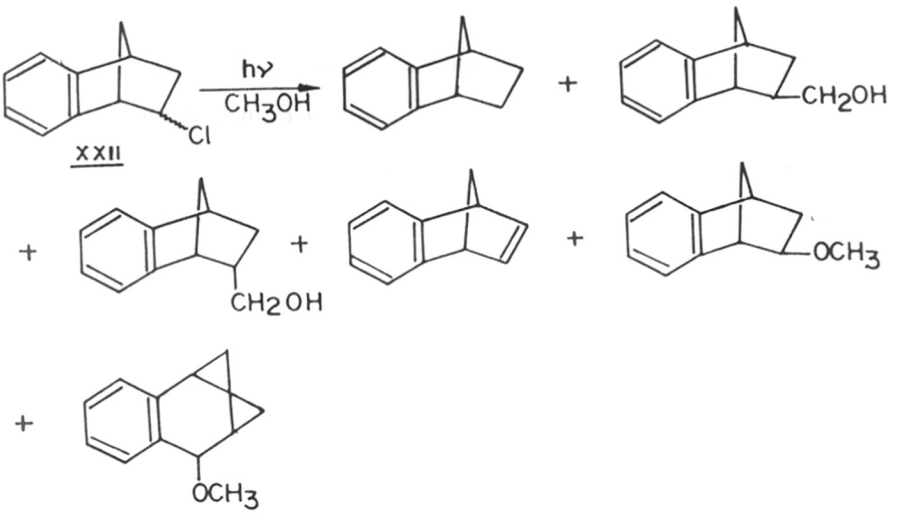
Scheme 16A



Morrison and coworkers[22] have made significant contribution especially in photolytic cleavage of remote functional leaving groups in polyfunctional molecules such as exo/endo-2, benzonorbornenyl chlorides XXII and sulfonate esters (Scheme-16B).

For example, these authors observed the formation of various types of products arising from reduction, solvolysis and rearrangement in the photolysis of exo and endo 2, benzonorbornyl chloride. A remarkably large exo:endo reactivity ratio (700:1) is attributed to the stereoelectronic aspects of the remote activation due to the aromatic ring of the benzo systems. These authors suggested a mechanism which incorporated both direct heterolytic fission as well as a homolytic

Scheme 16B

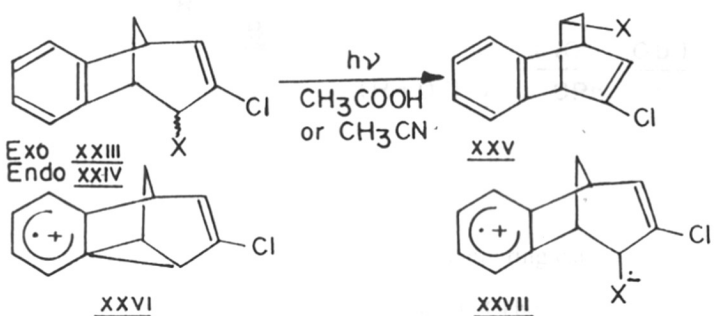


XXII

Reactivity ratio Exo : Endo 700 : 1

fission to a polarized radical pair followed by electron transfer leading to ion pair. In this connection, a reference to the work of Cristol et al.[23] on the photochemistry of a variety of rigid benzobicyclic systems is relevant. These authors studied the photorearrangement and solvolysis in acetic acid/acetonitrile of exo and endo 4-functionalized derivatives of 3-chloro-6,7-benzobicyclo[3.2.1]octa-2,6-dione XXIII and XXIV. They observed (Scheme-16C)

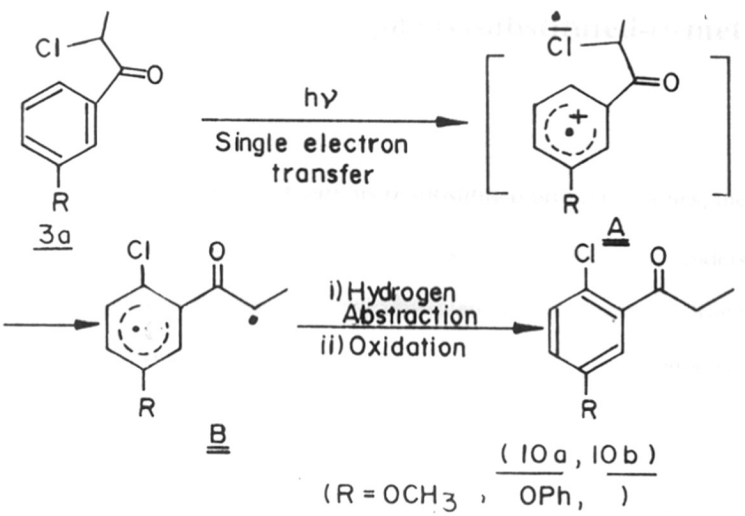
Scheme 16C



that the photolysis of XXIII and XXIV in acetonitrile essentially led to anti-7 functionalized 2-chloro-5,6-benzobicyclo[2.2.2]octa-2,5-diene XXV, through the intermediacy of XXVI. Again, the authors proposed the reaction path may not lead to XXVI directly, but rather *via* $\pi \rightarrow \pi^*$ excited state of XXIII and XXIV in which radiation excitation must originally reside in the benzene ring, decays by intramolecular electron transfer to a state represented by Zwitterion biradicals XXVII.

In this context, the observed incorporation of chlorine into the aromatic ring in the photolysis of *m*-methoxy-α-chloropropiophenone can be rationalized in terms of a possible electron transfer mechanism (Scheme-17).

Scheme 17



A photoinduced single electron transfer from the aromatic ring can lead to the formation of a radical cation in the phenyl ring along with a radical anion at C-Cl bond (Structure-A, Scheme-17). Involvement of **A** in the reactions of **3a** and **3b** helps in understanding the formation of **10a** and

10b. It can be visualised that the chloride ion arising from **A** can attack the electron deficient aromatic ring in a nucleophilic manner furnishing an intermediate **B** which can on hydrogen abstraction and aromatization lead to the observed product.

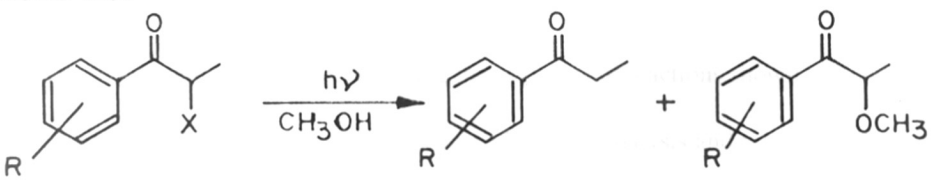
At this stage, we are not sure whether solvolysis and 1,2-aryl migration products from the photolysis of other substrates could involve such an electron transfer mechanism.

In this context, it is relevant to point out that single electron transfer (SET) occurring in photolysis has been documented in chloroacetamide photocyclization and other aromatic alkylations.[24] In fact, most important synthetic application of SET has been in the direct formation of lactams, particularly those involving medium sized rings. Further, synthetic application of this class of reactions have been recently reviewed.[25]

Section D: Photochemical study of phenylsubstituted-α-methoxy-propiophenones

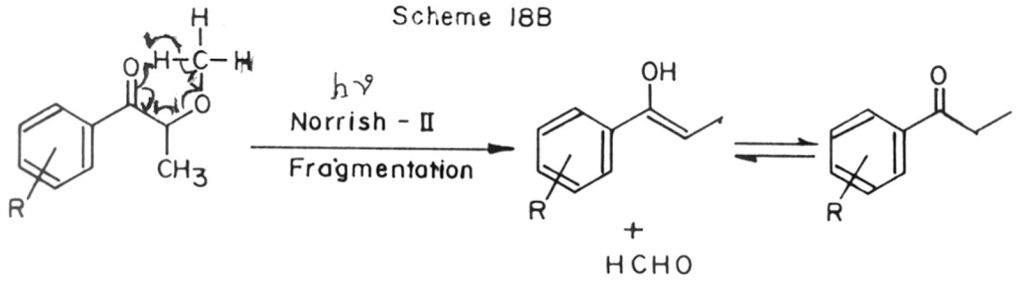
It can be recalled that in the photolysis of various α-substituted propiophenones, the loss of α-substituent by reductive process was commonly observed. Such a reduction was understood in a classical manner by the formation of a radical pair and subsequent interception by hydrogen atom. It is to be noted that photolyses were carried out in methanol and in many cases photosolvolysis was observed (Scheme-18A).

Scheme 18A

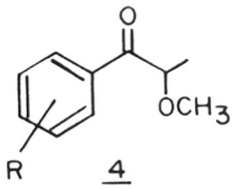


There was a distinct possibility that the observed reduction product could have arisen from a secondary photoprocess (Norrish type II fragmentation) of the methonolysis product (Scheme-18B).

Scheme 18B



To check this surmise, it was decided to investigate the photochemical behaviour of α-methoxy phenyl substituted propiophenones **4a** to **4e**.



4

4a: α-methoxypropiophenone

4b: *p*-methyl-α-methoxypropiophenone

4c: *m*-methyl-α-methoxypropiophenone

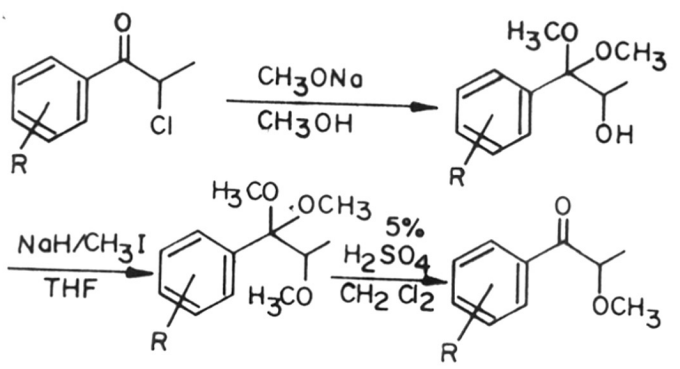
4d: *p*-methoxy-α-methoxypropiophenone

4e: *p*-isobutylα-methoxypropiophenone

The substrates were prepared by following the sequence of reactions shown in Scheme-19.

The compounds **4a** to **e** displayed satisfactory elemental analysis and proton NMR spectral data (Experimental).

Scheme 19



Results and Discussion

Photolysis of **4a-e** were performed in a manner described previously. The products were generally isolated by column chromatography, after 6-8 hours of irradiation. The results from this study have been shown in Table-7 and Scheme-20.

Products from *p*-methoxy-α-methoxypropiophenone 4d

The IR spectrum of one of the products from photolysis of **4d** showed an intense band at 1690 cm^{-1} strongly suggestive of the carbonyl function in it; perhaps an occurrence of reductive cleavage of C-OMe bond of the starting material. The PMR spectrum of the product (Fig.18) was totally suggestive of a photoreduction, it displayed a 3H triplet at 1.20 δ and a corresponding 2H quartet at 2.80 δ, besides showing a 3H singlet at 3.80 δ and a typical well-separated multiplets centered at 6.80 and 7.80 of *p*-disubstituted aromatic system, integrating for four protons. These spectral features coupled with our expectation of Norrish type II fragmentation enabled the characterization of the product as **13d**. The IR spectrum (Fig.19) of the second product showed a broad -OH stretching bond at 3400 cm^{-1} and a corresponding band at 1130 cm^{-1} suggesting of a tertiary hydroxyl function. The PMR spectrum (Fig.20) helped in readily identifying the product. A downfield secondary methyl doublet at 1.44 δ (J=7Hz), a 1H quartet at 5.10 δ (J=7Hz) and a clean 3H singlet at 3.77δ

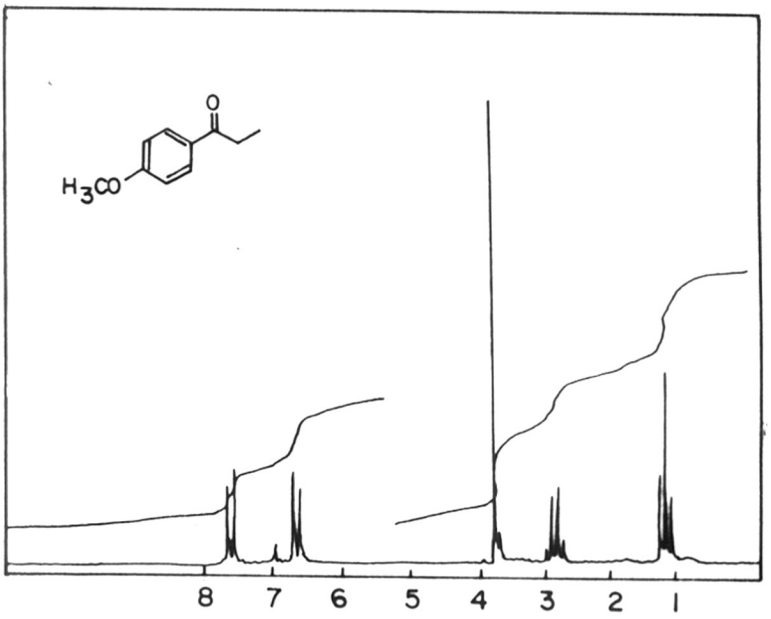


FIG.18 ^{1}HNMR SPECTRUM OF 13a

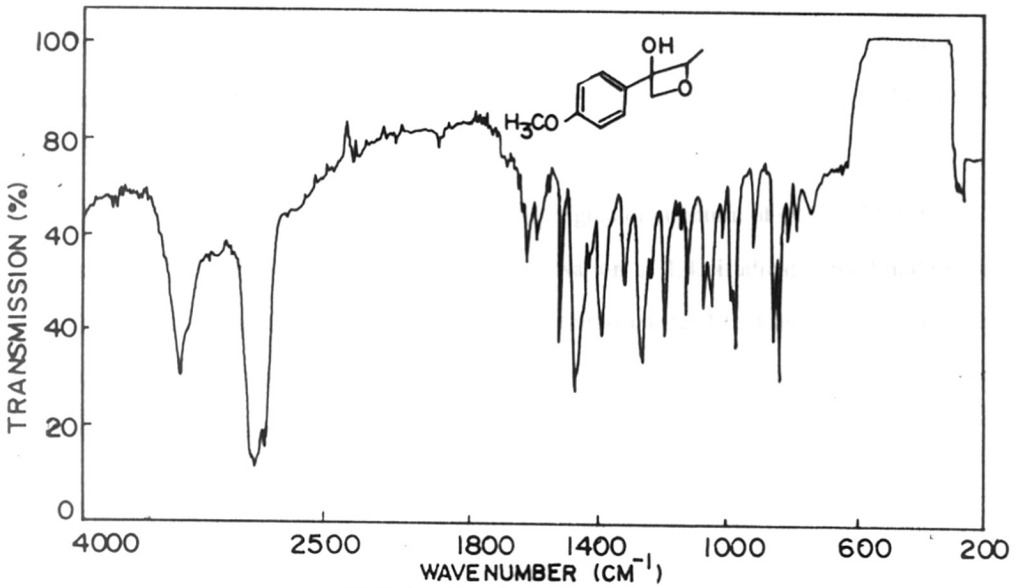


FIG.19 IR SPECTRUM OF 14d

were the main features. Other important aspects of the spectrum were a typical AB doublet of doublets at 4.62 and 4.84, a broad 1H signal at 2.56 besides the usual *p*-disubstituted pattern of multiplets for four protons. These NMR data and our expectation of a possible NII cyclization readily enabled the characterization of the product as **14d**. Further support for this structural assignment was derived from its mass spectrum (Fig.21) which, although did not show the molecular ion peak, displayed a peak at m/z 150 arising from a loss of acetaldehyde molecule, followed by the base peak at m/z, 135 accounting for $[CH_3O.Ph.CO]^+$ moiety. An alternate mode of the genesis of the base peak could be the initial loss of a formaldehyde molecule leading to *p*-methoxypropiophenone (m/z, 164), followed by a loss of the ethyl group.

Similar photolysis of 4a, 4b, 4c and 4e in methanol afforded a similar set of substituted propiophenones and corresponding tertiary alcohols arising from NII photoprocesses. The characterization of products was similarly based on their IR, PMR and Mass spectral data (Experimental). The results from all these substrates are shown in Scheme-20, Table-7.

A general feature about the results from these substrates was the clean formation of two products, well separated in GLC and also separable by column chromatography (Silica gel - 5% ethylacetate in pet.ether).

It should be mentioned here that there has been a greater quantum of oxetanol formation than the fragmentation product. Such a tendency for cyclisation of 1,4 biradical is well understood in terms of the polar nature of the solvent.[26] At the outset, the structures **14a-14e** indicate the possibility of mixture of stereoisomers. Nevertheless, owing to our different interest, the separation of stereoisomers was not attempted.

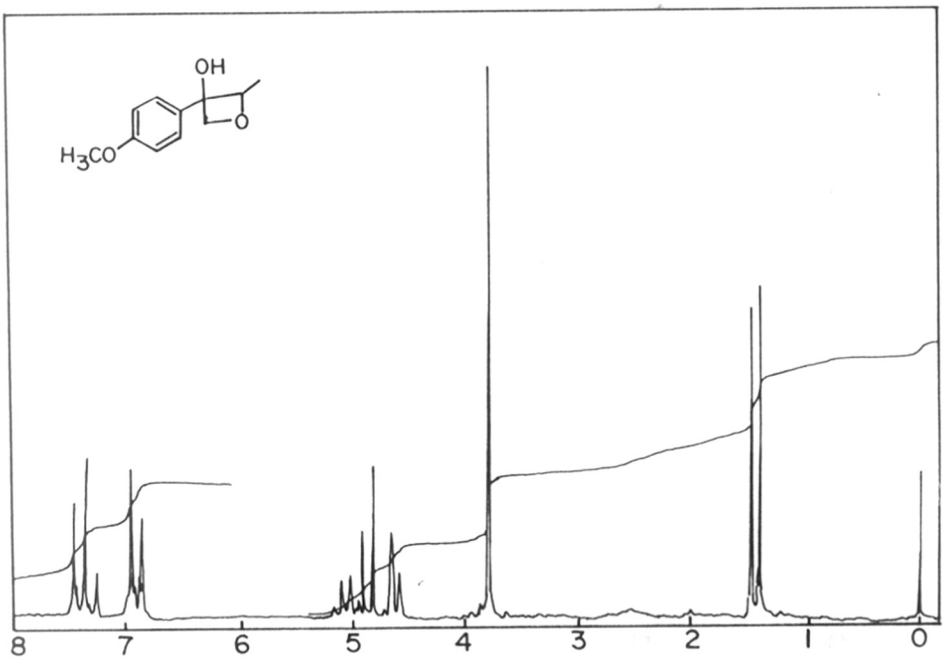


FIG.20 ^{1}H NMR (90 MHz) SPECTRA OF 14d

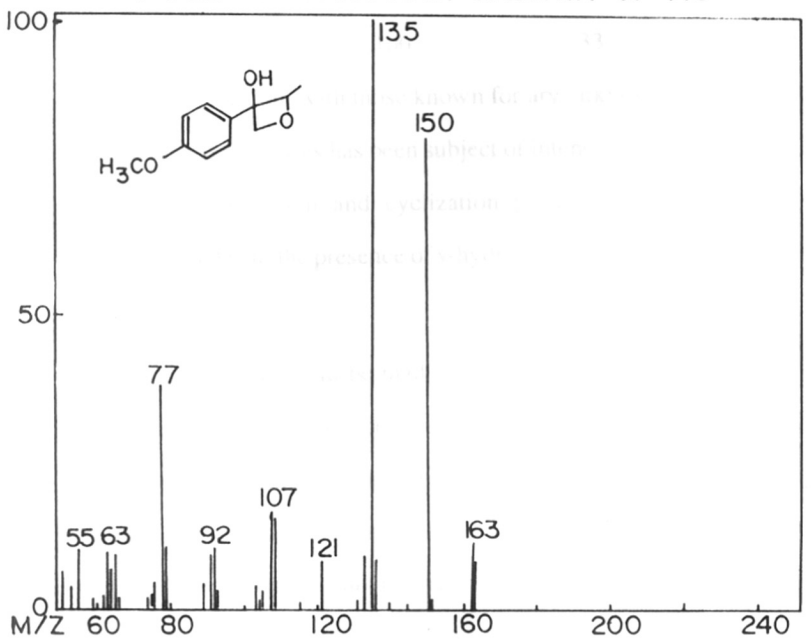
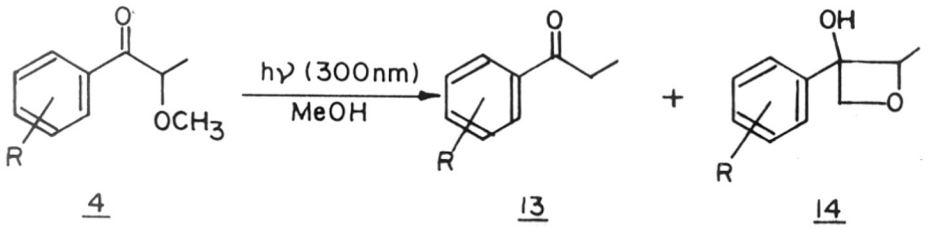


FIG.21 MASS SPECTRUM OF 14d

Scheme 20



4 13 14

Table-7: Product distribution from the photolysis of 4a-e

Substrate	R	Conversion %	Composition %	
			13	**14**
4a	H	95	35	65
4b	p-CH_3	100	44	56
4c	m-CH_3	100	32	68
4d	p-OCH_3	65	50	50
4e	p-isobutyl	100	33	66

These results are well in accord with those known for aryl alkyl ketones.[27] The effect of ring substituents on Norrish type II processes has been subject of intense study. The trend in the present result of furnishing of fragmentation and cyclization products is highly suggestive of the overwhelming NII processes due to the presence of γ-hydrogen. There has not been any α-cleavage observed.

An important observation needs to be made here is the formation of oxetanols from these α-methoxy propiophenones along with reduced amounts of fragmentation products. This result can help us to deduce that ring substituted propiophenones observed in the photolysis of different α-substituted propiophenones and other previous substrates did not arise from the secondary photoprocesses of solvolysis products. This is evident from the fact that oxetanol formation was conspicuously absent in the photolysis of the previous substrates.

Summary

The present study on the photochemistry of α-substituted (*p*-isobutyl) propiophenones, α-chloro (*m*-substituted) propiophenones and α-methoxy ring substituted propiophenones has generated an extremely useful picture about their photobehaviour. It has made a significant contribution in advancing the understanding of the photobehaviour of this class of alkyl aryl ketones.

Section A:

A pronounced α-substituted effect has been observed; there has been an exclusive selectivity for the reduction of C-X bond in the case of α-tosyl, α-acetoxy and α-N,N-dimethyl amino propiophenones. The importance of this result can be readily appreciated since α-deoxygenation and α-deamination of ketone are of synthetic value and are not easily attainable by non-photochemical methods.

Section B:

The dihalopropiophenones have shown an altogether different type of photobehaviour. The present study on the photochemistry of α,α-dihalo aryl alkyl ketones is the first of its kind. The solvolysis of α,α-dichloropropiophenone to α,α-dimethoxy propiophenone is unique in generating the stabilized α-keto carbenium ion[28a,b] for the first time. These results assume special significance in view of the current interest in the chemistry of carbocations bearing electron withdrawing group. In addition, the formation of methyl benzoate arising from α-cleavage has been a special feature with these substrates.

Section C:

The results from the photolysis *m*-substituted-α-chloropropiophenones have been remarkably different from those of corresponding para derivatives. An unusual feature of the results from

m-methoxy and *m*-phenoxy ketones is the formation of 2-chloro-5-methoxy (phenoxy) propiophenones, incorporating chlorine into the aromatic nucleus. An electron transfer from the phenyl ring to the C-Cl bond resulting in Zwitter radical ionic pair is invoked to understand this result, followed by intramolecular nucleophilic attack by the chloride ion on the radical-cation of aromatic ring. Another feature of the result is the preferred occurrence of 1,2-aryl migration in *m*-methyl-α-chloropropiophenone similar to that of *p*-methyl-α-chloropropiophenone. As expected, the *m*-nitroketone has shown a sluggish photoreaction leading to only photoreduction.

Section D:

The entire course of photoreactivity towards reduction, 1,2 aryl migration and solvolysis observed in the previous substrates has been remarkably changed by virtue of a α-methoxy substituent, providing a γ-hydrogen for abstraction by the carbonyl group. These substrates have undergone essentially Norrish type II photoprocesses of β-fragmentation and 1,4 cyclization. There has been a greater quantum of cyclization compared to the NI process. The process of hydrogen abstraction and the further reactions of the ensuing 1,4 biradical is so overwhelming that the minor substituent effects are not perceivable. More significantly, these results mostly rule out the possibility of the occurrence of photoinduced reductive dehalogenation products *via* the alternative pathway viz. methanolysis, followed by Norrish type II fragmentation.

Experimental

General procedure for the photochemical reactions of substituted propiophenones

A 3% solution of the substrate in dry methanol (0.60g. in 20 ml) was degassed by passing N_2 gas for 15 minutes, followed by addition of propylene oxide (1-2 ml, wherever indicated) and irradiated in a Rayonet photochemical reactor with 254/300 nm light. The progress of the reaction was monitored by periodic Thin Layer Chromatography of aliquotes at different intervals of time. Generally, after an irradiation for six hours, the solvent was evaporated and the residue distilled under reduced pressure. The products were separated either by column chromatography on silica gel or preparative TLC. As most of the products were well known compounds, their identification could be easily done by a direct comparison of their spectral data. In many instances, the products could be characterised by peak accentuation technique in GLC with authentic samples.

Section A: Photochemical investigation of *p*-isobutyl-α-substituted-propiophenones

Preparation of the substrates 1b-1d

***p*-Isobutyl-α-tosylpropiophenone (1b)**

This substrate was prepared by following a reported procedure.[29] A solution of (1.96g, 0.007M) of silver *p*-toluenesulfonate and *p*-isobutyl-α-bromopropiophenone[11] (1.345g, 0.005M) in 20 ml of acetonitrile was heated under reflux for 40 hours. The solution was filtered and the solvent was stripped off in vacuuo. The residue obtained was purified by crystallization from ethanol. Yield 1.26g. (70%), m.p. 64-65°C. **IR** (CCl_4) : 2960, 1700, 1600, 1380, 1235, 1180, 1020, 930 and 820 cm^{-1}. ^{1}**H-NMR** 0.90 (d, 6H), 1.60 (d, 3H), 1.68-2.10 (m, 1H), 2.40 (s, 3H), 2.52 (d, 2H), 5.70 (q, 1H), 7.10 (d, 2H), 7.20 (d, 2H), 7.60 (d, 2H), 7.70 (d, 2H). **Anal. Calcd. for** $C_{20}H_{24}O_4S$: C, 66.66; H, 6.66; Found: C, 66.30; H, 6.75.

***p*-Isobutyl-α-acetoxypropiophenone (1c)**

This compound was prepared by acetylation of *p*-isobutyl-α-hydroxypropiophenone.

***p*-isobutyl-α-hydroxypropiophenone:**[11,11a]

To a stirred solution of sodium methoxide (4.32g, 0.08M) in 25 ml of dry methanol was added a solution of *p*-isobutyl-α-chloropropiophenone (11.225g, 0.05M) in 10 ml dry methanol in a dropwise manner under dry condition. After complete addition, the reaction mixture was stirred for 12 hr. Solvent was evaporated and 100 ml water was added and extracted with ether (3x25 ml). The total organic extract was dried over anhydrous K_2CO_3 and solvent removed. To the residue taken in 25 ml CH_2Cl_2, 5% H_2SO_4 (25 ml) was added and stirred for 6 hr. Organic layer was separated and aqueous layer was washed with dichloromethane (3x25 ml). The combined organic extract was washed by saturated sodium bicarbonate solution and dried over anhydrous sodium sulphate. After the evaporation of solvent, the residue was distilled. **b.p.** 146-47°C/7mm. Yield: 7.60g. (74%). **IR** (Neat): 3480, 2980, 1685, 1610, 1460, 1360, 1280, 1140, 1080, 1030, 970, 850 cm^{-1}. **^{1}H-NMR**: 0.88 (d, 6H), 1.44 (d, 3H), 1.71-2.04 (m, 1H), 2.48 (d, 2H), 3.77 (d, 1H exchangeable with D_2O), 5.11 (q, 1H), 7.22 (d, 2H), 7.77 (d, 2H). **Anal. calcd. for** $C_{13}H_{18}O_2$: C, 75.72; H, 8.73; **Found**: C, 75.45; H, 9.05.

The above α-hydroxyketone (2.06g, 0.01M) and dry pyridine (1.185g, 0.015M) were taken in 10 ml dry CH_2Cl_2 followed by addition of acetyl chloride (1.17g, 0.015M) in 10 ml dry CH_2Cl_2 with continuous stirring for 3 hr. A standard work-up yielded a product. **b.p.** 175-180 (bath)/3mm. Yield: 1.92g. (77%). **IR** (Neat): 2940, 1740, 1690, 1600, 1370, 1230, 1130, 1090, 1040, 980 and 860 cm^{-1}. **^{1}H-NMR**: 0.90 (d, 6H), 1.50 (d, 3H), 1.60-2.10 (m, 1H), 2.05 (s, 3H), 2.50 (d, 2H), 5.90 (q, 1H), 7.20 (d, 2H), 7.80 (d, 2H). **Anal. calcd. for** $C_{15}H_{20}O_3$: C, 72.58; H, 8.06. **Found**: C, 72.76; H, 8.41.

***p*-isobutyl-α-N,N-dimethylaminopropiophenone (1d)**

A mixture of α-bromo(*p*-isobutyl)propiophenone (2.69g, 0.01M), dimethylammonium chloride (1.25g, .015M), anhydrous K_2CO_3 (2.76g, 0.02M) and tributyl ammonium hydrogen sulphate (30 mg) was taken in 30 ml CH_2Cl_2 and stirred overnight under anhydrous condition. The reaction was quenched by adding 50 ml water. Organic layer was separated. A normal work-up gave a product. **b.p.** 107-8°C/1.5mm, Yield 1.51g. (65%). **IR** (Neat): 2960, 1680, 1605, 1440, 1370, 1230, 1180, 1100, 1040 and 830 cm^{-1}. **^{1}H-NMR**: 0.90 (d, 6H), 1.28 (d, 3H), 1.68-2.08 (m, 1H), 2.32 (s, 6H), 2.52 (d, 2H), 4.08 (q, 1H), 7.28 (d, 2H), 7.95 (d, 2H). **Anal. calcd. for** $C_{15}H_{23}NO$: C, 77.25; H, 9.87; N, 6.00. **Found**: C, 77.42; H, 9.98; N, 5.70.

Photoproducts from 1a to 1d:

The photolysis was carried out as described in the general procedure with the addition of propylene oxide as an acid scavanger. However, in the case of **1d**, the propylene oxide was not added. The products were separated by preparative TLC (silicagel-benzene). GLC of the total photoproduct was done. The details about the GLC conditions and % of various photoproducts are shown in the following Table:

Compound	Weight of the distillable material (mg) B.P. (bath)/mm	GLC conditions Temperature/ Column	RRT (% of the photo-products)	
			5	**6**
1a	435 140-45°C/5mm	190°C/carbowax	5.22(25)	4.58(75)
*1b	535	--	(99)	--
1c	280 190-200°C/7mm	200°C/carbowax	1.95(99)	--
1d	433 140-50°C/5mm	180°C/carbowax	5.33(99)	--

*After removing solvent in vacuuo, the residue was not distilled as it showed a tendency for decomposition. The starting material and the product were separated by preparative TLC.

Photoproductsof (1a)

***p*-isobutylpropiophenone (5)**: **IR** (Neat): 1690 cm^{-1}; **^{1}H-NMR**: 0.91 (d, 3H), 1.22 (t, 3H), 1.60-2.10 (m, 1H), 2.53 (d, 2H), 2.98 (q, 2H), 7.20 (d, 2H), 7.90 (d, 2H).

Methyl α(*p*-isobutylphenyl)propionate (6): **IR** (Neat): 1745 cm^{-1}; **^{1}H-NMR**: 0.88 (d, 6H), 1.43 (d, 3H), 1.60-2.05 (m, 1H), 2.4 (d, 2H), 3.56 (s, 3H), 3.60 (q, 1H), 7.10 (m, 4H). **MS** m/z (%): 220 (M^+, 38), 177(43), 162(49), 145(21), 131(19), 118(100), 105(25), 91(34), 77(17).

Photoproductsof **1b-1d** is *p*-isobutyl propiophenone **5** only. The spectral data is given above.

Section B: Photolysis of α,α-dihaloketones 2a, 2b

Preparation of *p*-isobutyl-α,α-dichloropropiophenone (2a)

This compound was prepared by a known[16] procedure. A solution of (5.61g, .025M) of α-chloro *p*-isobutylpropiophenone in 50 ml of dimethyl formamide was heated to 80°C and Cl_2 was slowly bubbled for 45 minutes. The reaction mixture was poured into 2N HCl (100 ml) and extracted repeatedly with CCl_4. The organic layer was washed by water followed by brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and residue was distilled. **b.p.** 160-61°C/15mm. Yield 5.93g. (92%). **IR** (Neat): 2950, 1690, 1610, 1380, 1265, 1190, 1080, 970 and 870 cm^{-1}. **^{1}H-NMR**: 0.90 (d, 6H), 1.60-2.05 (m, 1H), 2.25 (s, 3H), 2.50 (d, 2H), 7.20 (d, 2H), 8.20 (d, 2H). **Anal. calcd. for** $C_{13}H_{16}Cl_2O$: C, 60.23; H, 6.17; Cl, 27.41. **Found**: C, 60.56; H, 6.44; Cl, 27.02.

***p*-isobutyl-α,α-dibromopropiophenone (2b)**

Bromine (32.2g, 0.20M) was added dropwise over a period of 1 hr. into a solution of *p*-isobutylpropiophenone[10] (19g, 0.10M) in CCl_4 (50 ml). After stirring for 3h, the reaction mixture was poured into cooled 10% sodium meta bisulphite solution (100 ml). The organic layer was separated and washed successively with saturated $NaHCO_3$, water and brine. The usual work-up

afforded **2b**. **b.p.** 111-12°C/2mm, Yield 29.30g. (84%). **IR** (Neat): 2980, 1690, 1610, 1430, 1380, 1250, 1140, 1070, 960 and 860 cm^{-1}. **^{1}H-NMR**: 0.90 (d, 6H), 1.60-2.05 (m, 1H), 2.50 (d, 2H), 2.65 (s, 3H), 7.10 (d, 2H), 8.20 (d, 2H). **Anal. calcd. for** $C_{13}H_{16}Br_2O$: C, 44.82; H, 4.59; Br, 45.97. **Found**: C, 44.95; H, 5.05, Br, 45.64.

Photoproducts from 2a and 2b:

The photolysis was carried out as described in the general procedure with the addition of propylene oxide as acid scavenger. The products were separated by preparative TLC (silica gel-benzene).

The details about the GLC conditions and % of various photoproducts from **2a** and **2b** are shown in the Table -

Compound	Distillable material b.p.(bath)/mm	GLC condition	RRT (% of photoproduct) 5	6	7	8
2a	280 mg 180-90°C/3.5	200°C/ Carbowax	3.10 (14)	2.60 (23)	2.34 (23)	6.74 (40)
2b	235 mg 180-90°C/2	130-80°C/ HP-1	2.70 (34)	--	2.12 (66)	--

***p*-isobutylpropiophenone (5)**: Spectral data given.

Methyl-α(*p*-isobutylphenyl)propionate (6): Spectral data given.

Methyl(*p*-isobutylphenyl)benzoate (7): **IR** (Neat) 1735 cm^{-1}; **^{1}H-NMR**: 0.90 (d, 6H), 1.60-2.05 (m, 1H), 2.50 (d, 2H), 3.80 (s, 3H), 7.20 (d, 2H), 7.90 (d, 2H). When this compound was hydrolysed, *p*-isobutyl benzoic acid was obtained and its spectral data comparable with reported.[11] **Mass** m/z (%): 250 (M^+, 2), 219(20), 207(7), 161(40), 118(22), 89(100).

***p*-isobutylbenzoic acid**[11]: The above ester was hydrolysed to get *p*-isobutylbenzoic acid. m.p. 105°C. **IR** (neat): 3300-2500, 1700 cm^{-1}. **^{1}H-NMR**: 0.90 δ (d, 6H), 1.60-2.00 (m, 1H), 2.55 (d, 2H), 7.24 (d, 2H), 8.07 (d, 2H), 9.31 (br s, 1H). **MS** m/z (%): 178 (M^+, 24), 133(32), 119(21), 105(100), 91(45), 79(22).

***p*-Isobutyl-α, α-dimethoxypropiophenone (8a)**: **IR** (neat): 1690 cm^{-1}. **^{1}H-NMR**: 0.90 (d, 6H), 1.55 (s, 3H), 1.60-2.05 (m, 1H), 2.50 (d, 2H), 3.30 (s, 6H), 7.10 (d, 2H), 8.00 (d, 2H). **MS** m/z (%): 250 (M^+, 2), 219(20), 207(7), 161(40), 118(22), 89(100).

Section C: Photolysis of *m*-substituted-α-chloropropiophenones 3a-3d

Preparation of 3a to 3d

Treatment of *m*-substituted benzaldehyde (0.05M) with Grignard reagent prepared from ethyl bromide (10.90g, 0.1M) and Mg turnings (2.4g, 0.1M) under standard conditions afforded the secondary alcohol.

Substituent at the meta position	b.p.	Yield %
$-OCH_3$	131-32°C/15mm	90
-OPh	145-46°C/1.5mm	92
$-CH_3$	87-90°C/6mm	88

Oxidation of the secondary alcohols to the corresponding *m*-substituted propiophenones

The above secondary alcohols (0.042M) when subjected to Brown's reagent[30] (prepared by dissolving 5g. of sodium dichromate in 15 ml of water, followed by addition of 4 ml of conc. H_2SO_4 and diluted to 25 ml) were oxidised to afford the corresponding ketones.

Compound R	b.p.	Yield %
$-OCH_3$	135-40°C/15mm	91
-OPh	135-36°C/1mm	90
$-CH_3$	108-109°C/6mm	91

α-Chlorination of the above ketones to 3a-3d

α-chlorination was performed bya reported procedure[31a,b] A mixture of hydrated copper (II) chloride (0.096M), LiCl (0.048M) was taken in 40 ml DMF, the temperature was raised to 80-90°C, and the ketone (0.04M) in 15 ml DMF was added in one lot. Temperature of the reaction mixture was maintained between 80-90°C for specified hours (Table) with constant stirring. The reaction mixture after cooling to room temperature was poured into dilute HCl (200 ml), extracted with ether (3x50 ml). The combined organic layer was washed with dil. HCl, followed by saturated $NaHCO_3$. The pure α-chloro ketone was obtained by column chromatography (Silicagel - Benzene), followed by distillation.

Compound R	Reflux time (Reaction time) hr.	b.p./m.p.	Yield %
$-OCH_3$	6	120-21°C/4mm	74
-OPh	15	156-57°C/1.5mm	58
$-CH_3$	4	185-90°C/40mm	66
$-NO_2$	15	42-45°C	51

m-nitropropiophenone was obtained by nitration of propiophenone following a reported procedure.[32]

Spectral data of α-chloro (*m*-substituted) propiophenones **3a-3d** are as follows:

***m*-Methoxy-α-chloropropiophenone (3a)**

IR (Neat): 2920, 2820, 1695, 1600, 1590, 1490, 1450, 1420, 1270, 1050, 750 cm^{-1}. **^{1}H-NMR**: 1.70 (d, 3H), 3.83 (s, 3H), 5.10 (q, 1H), 6.90-7.60 (m, 4H). **Anal. calcd. for** $C_{10}H_{11}ClO_2$: C, 60.45; H, 5.54, Cl, 17.88. **Found**: C, 60.80; H, 5.36; Cl, 17.51.

***m*-Phenoxy-α-Chloropropiophenone (3b)**

IR (Neat): 3020, 2990, 2920, 1690, 1590, 1490, 1430, 1250, 890, 740 cm^{-1}. **^{1}H-NMR**: 1.70 (d, 2H), 5.10 (q, 1H), 6.90-7.70 (m, 9H). **Anal. calcd. for** $C_{15}H_{13}ClO_2$: C, 69.27; H, 4.99; Cl, 13.62. **Found**: C, 69.27; H, 5.17; Cl, 13.75.

***m*-Methyl-α-chloropropiophenone (3c)**

IR (Neat): 2920, 2980, 1690, 1600, 1580, 1490, 1250, 1160, 750 cm^{-1}. **^{1}H-NMR**: 1.73 (d, 3H), 2.40 (s, 3H), 5.22 (q, 1H), 7.22-7.95 (m, 4H). **Anal. calcd. for** $C_{10}H_{11}ClO$: C, 65.75; H, 6.02; Cl, 19.45. **Found**: C, 65.38; H, 6.12; Cl, 19.21.

***m*-Nitro-α-chloropropiophenone (3d)**

IR (Nujol): 3100, 2920, 1690, 1600, 1520, 1440, 1360, 1240, 1190, 1070, 810, 710 cm^{-1}. **^{1}H-NMR**: 1.70 (d, 3H), 5.15 (q, 1H), 7.50-8.90 (m, 4H). **Anal. calcd. for** $C_9H_8ClNO_3$: C, 50.58; H, 3.74; Cl, 16.62; N, 6.55. **Found**: C, 50.13; H, 3.61; Cl, 16.90; N, 6.25.

Photoproducts

Photolysis of **3a-3d** were carried out as described previously with the addition of 1,2 ml of propylene oxide and the products were isolated by preparative TLC (silicagel-benzene). The details about GLC conditions and % of various photoproducts from **3a-3d** are shown in Table.

Compound	Weight of the Distillable material in mg, b.p.(bath)/mm	GLC conditions	RRT (% of photoproducts)			
			9	**10**	**11**	**12**
3a	280 180-90°C/5mm	180°C/ Carbowax	5.99 (13)	10.62 (68)	--	9.19 (19)
3b	272 190-200°C/3mm	130-80°C/ 5°C/min HP-1	9.41 (70)	7.29 (21)	7.64 (8)	--
3c	443 120-60°C/3mm	150°C/ Carbowax	3.8 (33)	--	4.20 (66)	--
3d	250 180-85°C/4mm	150°C/ HP-1	3.24 (100)	--	--	--

Products from *m*-methoxy-α-chloropropiophenone (3a)

m-methoxy propiophenone (9a)

IR (Neat): 1695 cm^{-1}; ^{1}**H-NMR**: 1.16 (t, 3H), 2.86 (q, 2H), 3.76 (s, 3H), 6.76-7.56 (m, 4H).

2-chloro, 5-methoxypropiophenone (10a)

IR (neat): 1690 cm^{-1}; ^{1}**H-NMR**: 1.15 (t, 3H), 2.85 (q, 2H), 370 (s, 3H), 6.70-7.25 (m, 3H); **MS** m/z (%): 198 (M^+, 44), 200 (M^{+2}, 14), 169(100), 171(34), 141(41), 143(12), 126(38), 128(12).

***m*-methoxy-α-methoxypropiophenone (12a)**

IR (neat) 1700 cm^{-1}; ^{1}**H-NMR**: 1.46 (d, 3H), 3.33 (s, 3H), 3.82 (s, 3H), 4.57 (q, 1H), 7.00-7.66 (m, 4H). Identity of this compound was further confirmed by peak accentuation technique with the authentic sample prepared by following the procedure described in Section-D (Experimental).

Photoproducts of m-phenoxy-α-chloropropiophenone (3b)

m-phenoxy propiophenone (9b)

IR (Neat): 1690 cm^{-1}; ^{1}**H-NMR**: 1.20 (t, 3H), 2.92 (q, 2H), 6.12-7.44 (m, 9H).

2-chloro, 5-phenoxypropiophenone (10b)

IR (neat): 1690 cm^{-1}; ^{1}**H-NMR**: 1.22 (t, 3H), 2.97 (q, 2H), 6.82-7.73 (m, 8H). **MS** m/z (%): (M^+), 260(60), M^{+2}, 262(20), 231(100), 233(33), 203(50), 205(17), 77(54).

Methyl-α-(m-phenoxyphenyl)propionate (11b)

IR (Neat): 1740 cm^{-1}; ^{1}**H-NMR**: 1.40 (d, 3H), 3.68 (s, 3H), 3.88 (q, 1H), 6.88-7.56 (m, 9H); **MS**: m/z (%): 256 (M^+, 60), 197(100), 119(25), 104(45), 91(68), 77(62). **MS** m/z (%): 164 (M^+, 3%), 119(100), 105(15), 91(60), 77(32).

Photoproduct of *m*-methyl-α-chloropropiophenone (3c)

***m*-Methylpropiophenone (9c)**

IR (Neat): 1690 cm^{-1}; **^{1}H-NMR**: 1.16 (t, 3H), 2.40 (s, 3H), 2.86 (q, 2H), 7.13-7.73 (m, 4H).

Methyl-α(*m*-methylphenyl)propionate (11c)

IR (neat): 1735 cm^{-1}; **^{1}H-NMR**: 1.48 (d, 3H), 2.32 (s, 3H), 3.68 (s, 3H), 3.72 (q, 1H), 7.08-7.88 (m, 4H). **MS** m/z (%): 178 (M^+, 3%), 119(100), 1.5(15), 91(60), 77(32).

Photoproduct of *m*-nitroα-chloropropiophenone (3d)

***m*-nitro propiophenone (9d)**

IR (nujol): 1690 cm^{-1}; **^{1}H-NMR**: 1.23 (t, 3H), 3.03 (q, 2H), 7.40-8.60 (m, 4H).

Section D: Photolysis of phenylsubstituted-α-methoxypropiophenones 4a-e

Preparation of 4a-e

General Procedure: The α-hydroxy ketals were prepared as described in the preparation of α-acetoxy *p*-isobutyl propiophenone **1c** (Section-A). (0.02M) of the α-hydroxy ketal in THF (15 ml) was added dropwise to a suspension of NaH (0.025M) in THF (25 ml) at 0°C. After 10 minutes, CH_3I (0.025M) in THF (10 ml) was added slowly over a period of 15 minutes. Stirring was continued for 3 hr. The reaction was quenched by adding ice cold water (50 ml) and extracted repeatedly with ether (3x25 ml). The residue obtained after the removal of solvent was taken in CH_2Cl_2 and treated with 5% H_2SO_4 to get the required deprotected α-methoxy ketones. The crude product obtained was purified by distillation under diminished pressure. b.ps and yields are mentioned below.

Compound	R	b.p.	Yield %
4a	-H	118-20°C(bath)/6mm	80
4b	*p*-CH_3-	138-40°C(bath)/8mm	82
4c	*m*-CH_3-	110-12°C/6mm	86
4d	*p*-OCH_3-	128-30°C(bath)/1mm	72
4e	*p*-isobutyl-	175-78°C/6mm	80

α-methoxy propiophenone (4a)

IR (Neat): 2990, 2940, 1700, 1600, 1460, 1250, 1220, 1140, 980, 720 cm^{-1}; **^{1}H-NMR**: 1.45 (d, 3H), 3.30 (s, 3H), 4.50 (q, 1H), 7.20-8.10 (m, 5H). **Anal. calcd. for** $C_{10}H_{12}O_2$: C, 73.10; H, 7.31. **Found**: C, 72.71; H, 6.96.

***p*-methyl-α-methoxypropiophenone (4b)**

IR (Neat): 2990, 2940, 1700, 1610, 1450, 1240, 1220, 1140, 980, 850 and 780 cm^{-1}. **^{1}H-NMR**: 1.40 (d, 3H), 2.36 (s, 3H), 3.26 (s, 3H), 4.33 (q, 1H), 7.13 (d, 2H), 7.90 (d, 2H). **Anal. calcd. for** $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. **Found**: C, 74.53; H, 7.87.

***m*-methyl-α-methoxypropiophenone (4c)**

IR (Neat): 3000, 2980, 1710, 1620, 1600, 1480, 1280, 1150, 1000, 790 cm^{-1}. **^{1}H-NMR**: 1.36 (d, 3H), 2.36 (s, 3H), 3.23 (s, 3H), 4.33 (q, 1H), 7.10-7.90 (m, 4H). **Anal. calcd. for** $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. **Found**: C, 73.73; H, 7.78.

***p*-methoxy-α-methoxypropiophenone (4d)**

IR (Neat): 2990, 2940, 1700, 1610, 1520, 1470, 1320, 1270, 1050, 980, 860 and 770 cm^{-1}. **^{1}H-NMR**: 1.37 (d, 3H), 3.24 (s, 3H), 3.75 (s, 3H), 4.48 (q, 1H), 7.46 (d, 2H), 7.91 (d, 2H). **Anal. calcd. for** $C_{11}H_{14}O_3$: C, 68.41; H, 7.21. **Found**: C, 67.72; H, 7.31.

***p*-isobutyl-α-methoxypropiophenone (4e)**

IR (Neat): 2990, 1710, 1640, 1490, 1440, 1390, 1260, 1210, 1150, 1000, 890 and 790 cm^{-1}. **^{1}H-NMR**: 0.93 (d, 3H), 1.46 (d, 3H), 1.73-1.85 (m, 1H), 2.04 (d, 2H), 3.35 (s, 3H), 4.60 (q, 1H), 7.20 (d, 2H), 7.88 (d, 2H). **Anal. calcd for** $C_{14}H_{20}O_2$: C, 76.36; H, 9.09. **Found**: C, 76.59; H, 9.40.

Photolyses of **4a-e** were carried out as described before, without adding propylene oxide. Photoproducts were separated by column chromatography (silica gel. 5% ethyl acetate in pet.ether). The details about GLC conditions and various photoproducts (%) from **4a-4e** are shown in the Table.

Product composition from the photolysis of 4a-e

Compound	Distillable material b.p. (bath)/mm	GLC condition Temp./Column	Photoproducts **13** RRT (%)	**14** RRT (%)
4a	330 mg 140-70°C/5mm	150°C/OV-101	1.69 (35)	4.00 (65)
4b	425 mg 120-60°C/4mm	150°C/OV-101	2.72 (44)	6.54 (56)
4c	400 mg 120-60°C/4mm	150°C/OV-101	3.23 (32)	7.64 (68)
4d	405 mg 140-80°C/OV-101	180°C/OV-101	3.60 (50)	7.34 (50)
4e	335 mg 120-80°C/4mm	180°C/OV-101	2.11 (33)	5.91 (66)

The identity of products **13a**, **13b**, **13c**, **13d**, **13e** was established by peak accentuation technique with authentic samples and also by their spectral data comparison with reported[33a,b] spectral data of the compounds **14a-e** is as follows:

1-phenyl oxetanol-3 (14a)

IR (neat): 3400 cm^{-1}. **^{1}H-NMR**: 1.45 (d, 3H), 2.55 (s, 1H exchangeable with D_2O), 4.60 (d, 1H), 4.85 (d, 1H), 5.15 (q, 1H), 7.10-7.65 (m, 5H). **Mass** m/z (%): 134(64), 133(79), 120(100), 105(45), 77(13).

1-(*p*-methylphenyl)oxetanol-3 (2-methyl) (14b) .

IR (neat): 3400 cm^{-1}. **^{1}H-NMR**: 1.45 (d, 3H), 2.35 (s, 3H), 2.55 (br s, 1H, exchangeable with D_2O), 4.60 (d, 1H), 4.80 (d, 1H), 5.00 (q, 1H), 7.10 (d, 2H), 7.50 (d, 2H), **Mass** m/z (%): 148(21), 134(100), 119(88), 91(48).

1-(*m*-methylphenyl)oxetanol-3 (2-methyl) (14c)

IR (Neat): 3400 cm^{-1}. **^{1}H-NMR**: 1.44 (d, 3H), 2.32 (s, 3H), 2.56 (s, 1H, exchangeable with D_2O), 4.64 (d, 1H), 4.92 (d, 1H), 5.12 (q, 1H), 7.07-7.52 (m, 4H). **Mass**: m/z, 148(21), 134(100), 119(79), 92(70).

1-(*p*-methoxyphenyl)oxetanol-3 (2-methyl) (14 d)

Solid **m.p.** 80-81° (recrystallised by ethanol). **IR** (Nujol): 3400 cm^{-1}. **^{1}H-NMR**: 1.44 (d, 3H), 2.56 (broad s, 1H, exchangeable with D_2O), 3.77 (s, 3H), 4.62 (d, 1H), 4.84 (d, 1H), 5.04 (q, 1H), 6.88 (d, 2H), 7.37 (d, 2H). **Mass** m/z (%): 163(11), 164(8), 150(79), 135(100), 107(16), 77(38).

1-(*p*-isobutylphenyl)oxetanol-3 (2-methyl) (14e) .

IR (Neat): 3400 cm^{-1}. **^{1}H-NMR**: 0.88 (d, 6H), 1.46 (d, 2H), 1.64-2.00 (m, 1H) and also **^{1}H** broad singlet merged here), 4.60 (d, 1H), 4.86 (d, 1H), 5.02 (q, 1H), 7.04 (d, 2H), 7.15 (d, 2H). **Mass** m/z (%): 190(7), 176(47), 161(17), 147(26), 133(100), 91(12).

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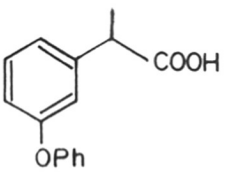
CHAPTER IV

Synthesis of (±) Fenoprofen, an important antiinflammatory agent

Objective: To achieve a simple and practical synthesis of (±) fenoprofen, 5 a well-known non-steroidal antiinflammatory agent, from commercially available m-phenoxybenzaldehyde.

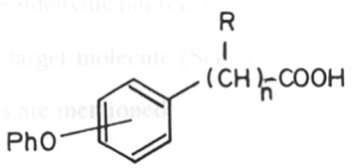


5

Introduction

The compound **5**, chemically known as α-methyl,3-phenoxybenzeneacetic acid belongs to the well-known class of α-arylpropionic acids; the latter class of compounds with their general methods of preparation have been already presented in the previous Chapter. Nonetheless, a few special features of phenoxy substituted α-arylpropionic acids need to be briefly mentioned.

Fenoprofen belongs to a class that may be represented by a general structure shown below:



From the biological activity point of view, the optimal separation of the carboxyl group from the aromatic ring was determined to be one methylene group (n=1). α-substitution indicated by R with small alkyl groups led to compounds with enhanced activity (with the methyl group being the most potent), whereas α-substitution with a branched alkyl group had a detrimental effect on the activity. Changing the substitution pattern of the phenoxy group from para to meta enhanced the biological activity, while moving it to the ortho position considerably diminished it.[1]

Fenoprofen was introduced essentially as an analgesic by the trade name "*Nalgesic*" by Lilly Laboratories, USA, in 1974. Despite its antiinflammatory, antipyretic and analgesic activities, its use has been mainly in the area of rheumatic disorders as an analgesic agent.

Compared to the tremendous inputs made for the development of methodologies for Ibuprofen, Neproxen and Ketoprofen, there are very few strategies specially devised for Fenoprofen. This situation may be due to the fact that the general methods employed for α-arylpropionic acids can as well be used to prepare this product. As a prelude to the work described in this chapter, it is pertinent to give a brief outline of the methods reported in literature for this drug.

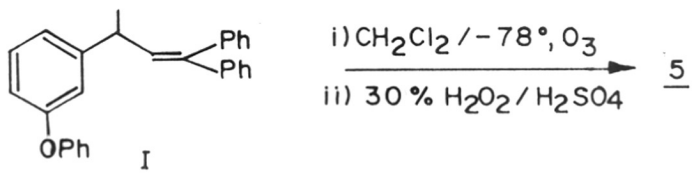
Literature Survey

Although the available literature about the methods of preparation of **5** is scanty, most of them are in patent form owing to the commercial importance of the compound and published papers are isolated.

A Japanese patent[2] indicates the synthesis of **5** by ozonolysis of the diphenyl substituted alkene I leading to the aldehydic intermediate which could be oxidized with hydrogen peroxide and sulphuric acid to the target molecule (Scheme-1). However, neither the preparation of I nor the yields of the reactions are mentioned.

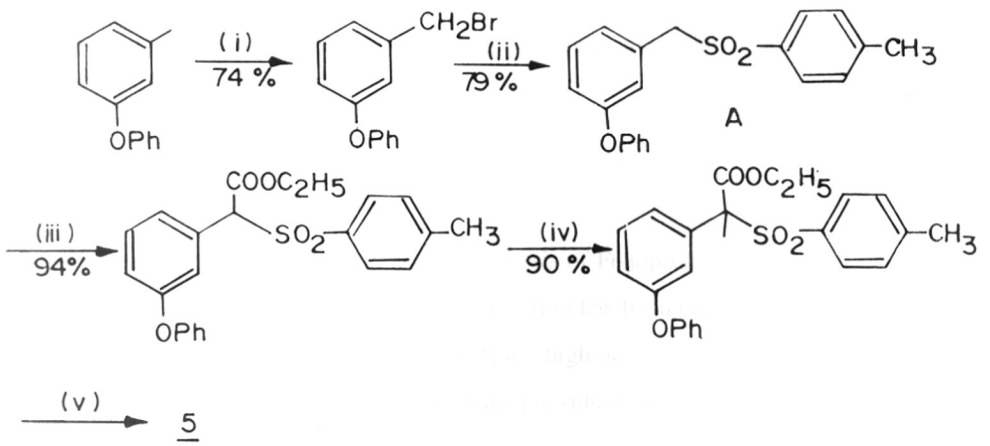
The activation of an α-carbon for methylation and ethoxy carbonylation by a sulphonyl group and susceptibility of a C-S bond for cleavage under hydrogenation condition, as in Structure **A**, is utilised in another Japanese patent.[3] It may be mentioned that the target molecule could be realised in five steps starting from m-phenoxy toluene (Scheme-2).

Scheme I



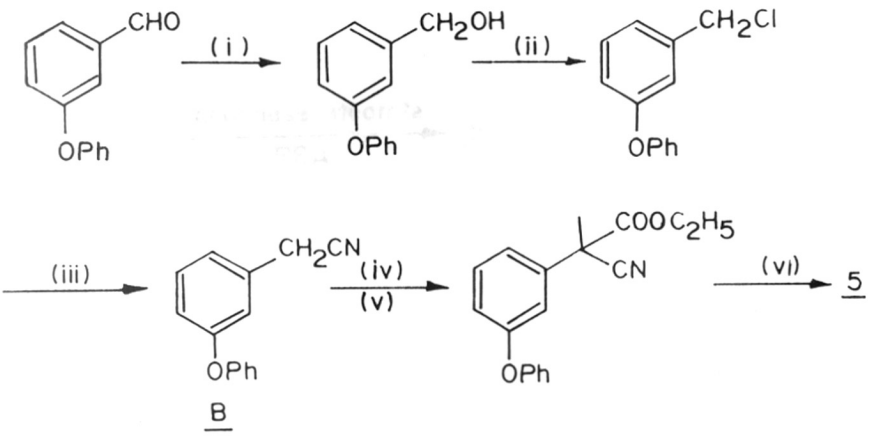
I

Scheme 2



(i) N-bromosuccinimide, CCl_4, reflux 15 hr (ii) Sodium p-toluenesulfinate-dihydrate, N,N-dimethyl formamide; 13 hr, 100°C (iii) C_2H_5ONa, $(C_2H_5O)_2CO$ Δ (with the removal ethanol) (iv) CH_3I/C_2H_5ONa (v) 5% Sodium Amalgam in ethanol / 7 hr / aq. NaOH

Scheme : 3



i) Reduction ; (ii) $SOCl_2$; (iii) NaCN ; (iv) $(C_2H_5O)_2CO$;

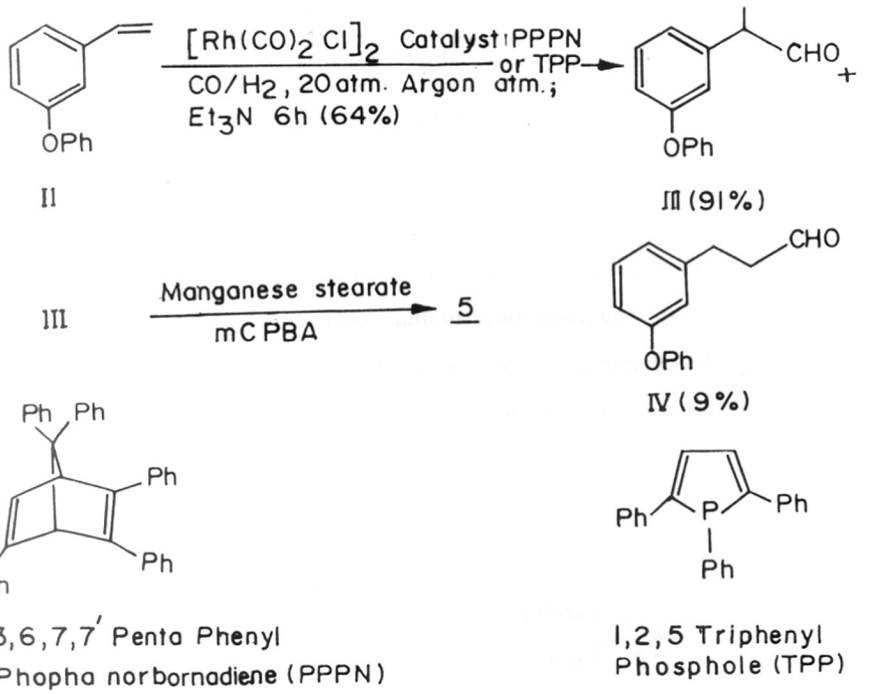
v) $(CH_3)_2SO_4$, (vi) NaOH, Ethanol

A comparable sequence of reactions can be seen in the method described in a German patent.[4] (Scheme-3). Ethoxy carbonylation and methylation are effected utilising the activation by a cyano group (see Structure **B**). The final step involving hydrolysis and a partial decarboxylation led to the desired product.

It can be seen that the reactions at the benzylic site of a m-phenoxy phenyl compound constitute the common theme in the above methods.

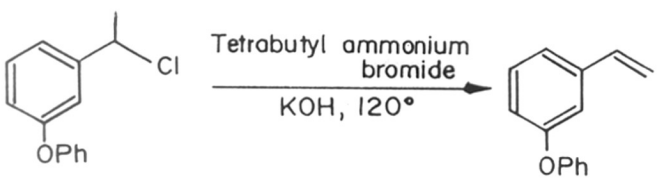
A recently published report about the synthesis of Fenoprofen utilizes hydroformylation of vinyl arenes,[5] as a key reaction. Although this reaction has been carried out by employing Ruthenium,[6] Cobalt,[7] Rhodium[8] and Platinum[9] catalysts, high activities and the required selectivity to branched aldehydes are realised with Rhodium phosphane system only.[10] A typical procedure followed is outlined in Scheme-4.

Scheme. 4



Among the various catalysts tried, PPPN and TPP were found to be effective leading to a high regioselectivity. It can be noticed that the reaction requires the use of complex catalytic systems besides involving high pressure operations. The required vinyl arenes II were prepared by the hydrolysis of the corresponding 1-aryl, 1-chloroethane followed by an elimination reaction (Scheme-4A).

Scheme 4A



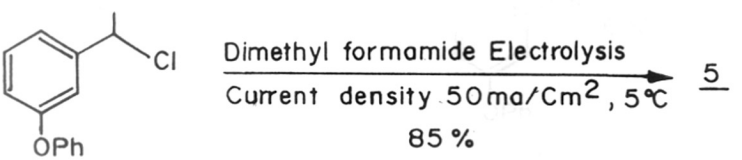
II

The authors proposed to realise the target molecule by oxidation of III with manganese stearate[6] along with m-chloroperbenzoic acid as a catalyst initiator.

Despite the high regioselectivity offered by the hydroformylation reaction, the use of sophisticated catalysts and high pressures make this reaction academic in nature, rather than leading to a practical method.

An elegant method reported by Sock et al.[11] for the electrolytic carboxylation of organic halides deserves a mention here. These authors synthesised various aliphatic and aromatic acids by the electrolysis of corresponding halides in presence of carbon dioxide. The utility of this method in synthesising pharmaceutically important compounds is exemplified by the preparation of Fenoprofen and Neproxen (Scheme-5).

Scheme 5



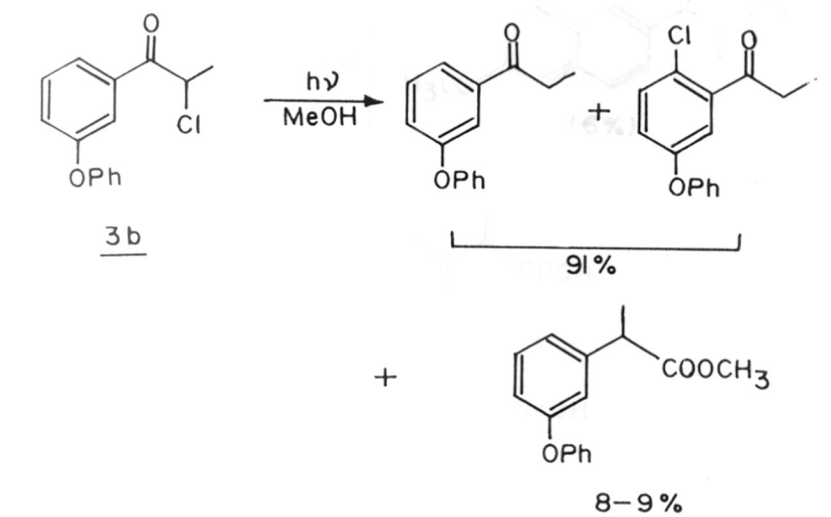
The method comprises in electrolysing a 0.4M solution of the halide in an aprotic solvent such as acetonitrile, acetone or dimethylformamide in a glass cell equipped with a magnesium anode and a cathode of nickel, stainless steel or graphite. A small amount of a supporting electrolyte such as tetrabutyl ammonium bromide or lithium perchlorate was used to accelerate the reaction; carbon dioxide was slowly bubbled through the electrolyte by low over-pressure in the cell.

The main difficulty that may be encountered in this method is the preparation of the corresponding halide and the need of practical technology for an electrochemical process.

Present Work

The foregoing literature survey reveals that there has not been a direct method for fenoprofen, involving a 1,2-aryl migration reaction. In this context, it can be recalled that the effect of different m-substituents in the phenyl ring on the photo behaviour of α-chloropropiophenones was investigated in a previous Chapter. One of the substrates deliberately chosen was α-chloro(m-phenoxy)propiophenone (**3b**) which was expected to lead to fenoprofen ester on 1,2 aryl migration. However, the observed major process was a photo reduction with a concomitant 1,2 shift occurring in a minor way (Scheme-6).

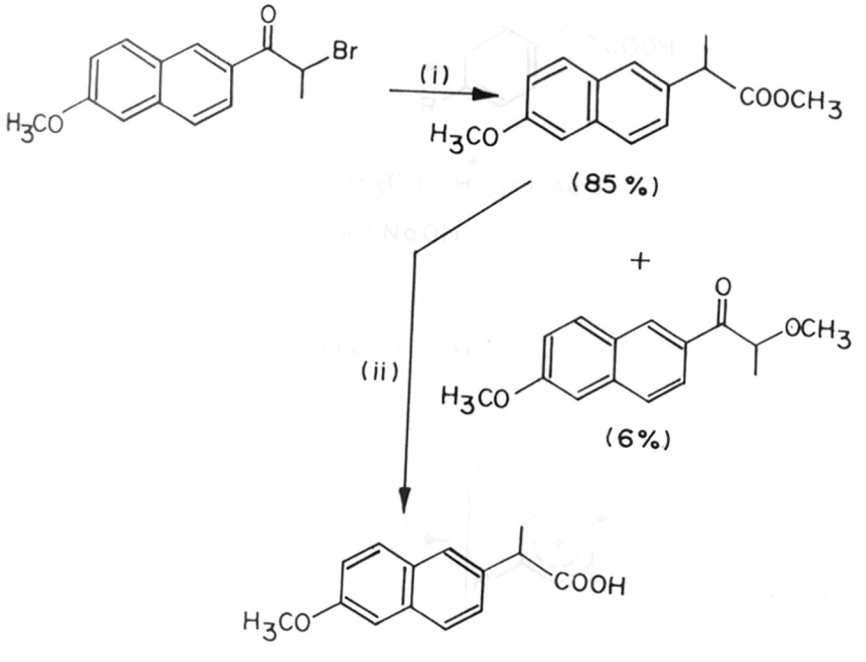
Scheme 6



The above result prompted us to devise a convenient and efficient thermal method to synthesize **5**. It may be mentioned that among various methods developed for α-aryl propionic acids, the one involving 1,2-aryl migration seems to be specially convenient, offering practical processes for many drugs of this class[12]. Various α-leaving groups have been probed for their efficacy in leading to the required rearrangement.

To realise an efficient 1,2 aryl migration, two prerequisites have been well recognised. The primary requirement is the masking of the carbonyl group as a ketal. For example, Giardano et al.[13] in their reactions of α-bromo propiophenones with silver salts observed the formation of both the substitution and the rearrangement products (Scheme-7).

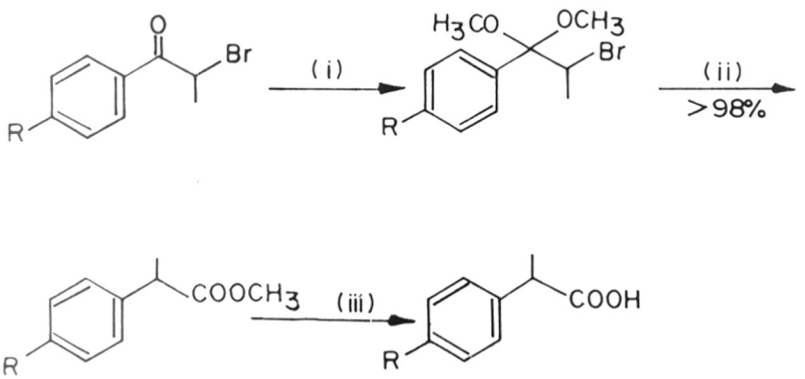
Scheme 7



(i) Ag_2CO_3 , $BF_3 . 2CH_3OH$; (ii) NaOH

These authors envisaged that ketalization of the carbonyl group would alter its electronic property and would promote the rearrangement reaction at the α-carbon. Thus, when dimethyl ketals of α-bromo propiophenones, were treated with $AgBF_4$ or other silver salts, these authors essentially obtained the rearrangement products (Scheme-8).

Scheme 8

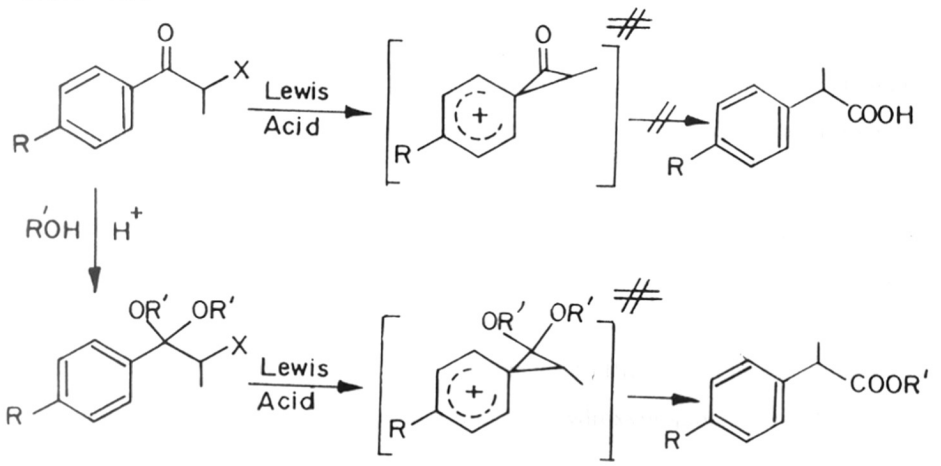


(i) $HC(OCH_3)_3$; CH_3OH, H^+ ; (ii) $AgBF_4$; CH_3OH

(iii) NaOH

Such a requirement of ketalization for rearrangement has been further supported by the mechanistic studies reported by Castaldi et al.[14] (Scheme-8A).

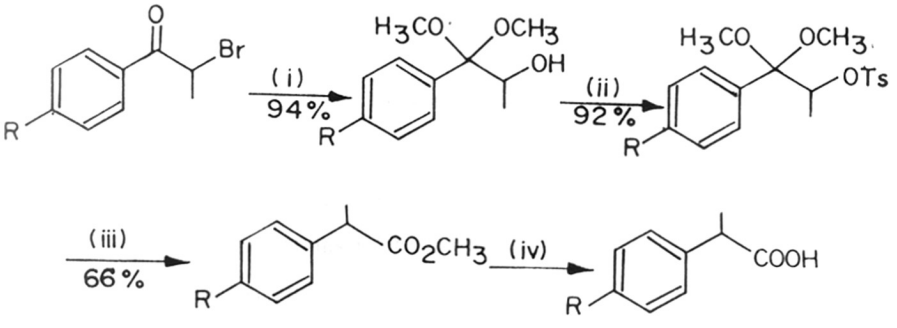
Scheme 8A



It is obvious from the Scheme-8A that the spirocyclic intermediate from the α-haloketone is highly strained and does not lead to rearrangement, while the corresponding intermediate from the dimethyl ketal is less strained and has yielded the rearrangement.

The second major requirement for an efficient 1,2-aryl migration appears to be the presence of a facile leaving group at the α position. Various leaving groups such as bromo, chloro, sulfonyl and tosyl have been studied. For example, Tsuchihashi et al.[15] demonstrated the efficacy of α-tosyloxy group in leading to the rearrangement reaction (Scheme-9).

Scheme 9



(i) CH_3ONa, CH_3OH, (ii) Ts.Cl, Pyridine, (iii) $CaCO_3$, $CH_3OH - H_2O$ (7:3), reflux, (iv) NaOH

A major breakthrough in terms of generating a practical method for α-aryl propionic acids was the use of Lewis acids in the reactions. Castaldi et al.[16] demonstrated that soft and borderline Lewis acids like $ZnCl_2$ activated the Carbon-halogen bond and could substitute the expensive silver salt previously used.

In this context, it should be pointed out that the rearrangement reaction discussed above has not been reported so far in the synthesis of fenoprofen. Thus, development of such a strategy looked promising. We came across a recent report[12] in which a few α-aryl propionates were prepared from the corresponding dimethyl ketals, taking advantage of efficacy of chlorosulphonyl group as a leaving moiety; these authors treated *p*-substituted α-hydroxypropiophenonedimethyl ketals with

sulfuryl chloride in presence of a weak base at -50°C and obtained the corresponding methyl propionates in 55-86% yields. They observed that electron-releasing substituents such as the alkyl and methoxy groups favoured the rearrangement while the electron withdrawing groups deterred it. It is remarkable that the effect of m-substituents on the rearrangement was left unprobed. Similar electronic effects have been observed by us[17] in a photoreaction. Nevertheless, a photochemical reactivity pattern may not be expected to be observed in a thermal reaction. In this context, we planned to study the thermal reaction of m-phenoxy α-hydroxy propiophenone dimethyl ketal with sulfuryl chloride leading to Fenoprofen.

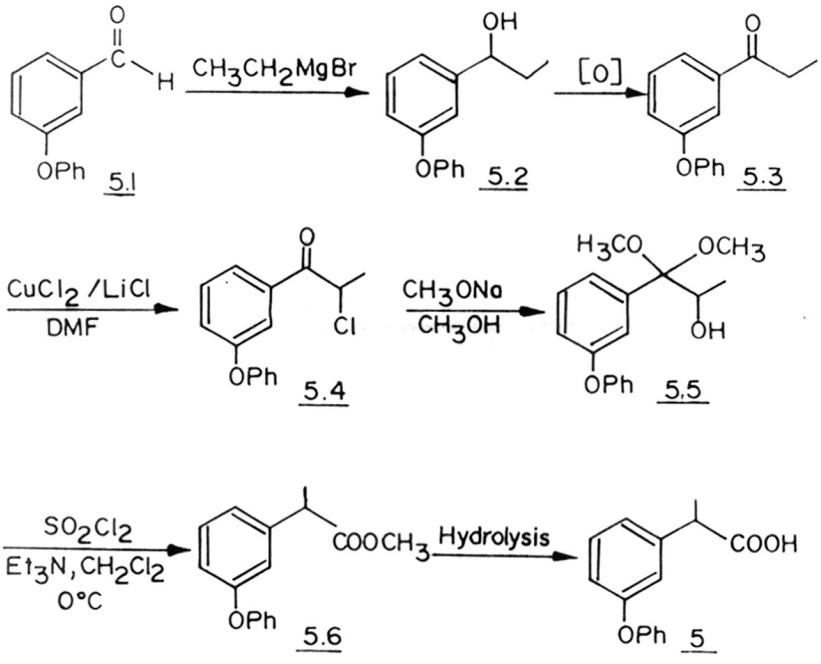
Results and Discussion

In view of the above discussion, we planned to prepare α-hydroxy(m-phenoxy)propiophenonedimethyl ketal and transform into its chlorosulfonyl ester and examine its rearrangement to **5**. Commercially available m-phenoxybenzaldehyde appeared suitable as a starting material. Grignard reaction of this aldehyde with ethyl bromide readily afforded the corresponding carbinol; the latter on oxidation with Brown's[18] reagent furnished m-phenoxypropiophenone. An examination of literature methods for the preparation of the hydroxy ketal revealed that both α-bromo and α-chloroketones have been employed. Nonetheless, we chose to prepare the chloro derivative. Various methods are known for α-chlorination of ketones. The problem with most of the reagents appears to be the inability to stop the chlorination at the mono stage, as the monochlorinated ketone is more reactive towards further chlorination. In this respect, use of Cu^{II} chloride and lithium chloride in an aprotic dipolar solvent such as DMF has been found to be effective.[19a,b] Thus, treatment of m-phenoxy propiophenone with 2 equivalents of CuII chloride ($CuCl_2$) and 1.5 equivalent of lithium chloride in DMF at around 80°C afforded the required α-chloroketone in about 60% yield. The product was found to be homogeneous on two GLC columns and it displayed the following spectral data. **IR**: 3020, 2990, 2920, 1690, 1590, 1490, 1430, 1250, 890, 740 cm^{-1}. **^{1}H NMR** (Fig.1): 1.70 (d, 3H), 5.10 (q, 1H), 6.90-7.70 (m, 9H). **Mass** m/e (%): 262 (M^{+2}, 20%), 260 (M^+, 60%), 197(100), 169(57), 141(71), 115(59), 77(54).

Besides the right spectral resonances, the compounds analyzed well for its elemental composition (Experimental).

The treatment of the chloroketone with sodium methoxide[20] in methanol furnished the corresponding α-hydroxy ketal in high yield. The compound thus obtained was well characterised by its ^{1}H-NMR. The prominent features of the NMR spectrum (Fig.2) of the hydroxyketal were a secondary methyl doublet at 0.90 δ, two 3H singlet at 3.16 and 3.33 δ and a broad 1H multiplet between 3.86 and 4.03 δ. Another significant feature was a broad 1H signal at 2.13 which exchanged with D_2O. The protocol that we planned to examine for the synthesis of **5** is given in Scheme-10.

Scheme 10



It must be mentioned that such a rearrangement was carried out by the authors referred[12] to above at a low temperature (-50°C). This suggests the requirement of a low temperature for a clean rearrangement. Nevertheless, with our objective of devising a practical synthesis for fenoprofen, we decided to perform the reaction at around 0°C.

Rearrangement reaction: A mixture of α-hydroxydimethylketal **5.5** (5 mmol) and triethylamine (10 mmol) taken in dry CH_2Cl_2 was cooled to -5°C to -0°C and sulfuryl chloride (7.5 mmol) in dry

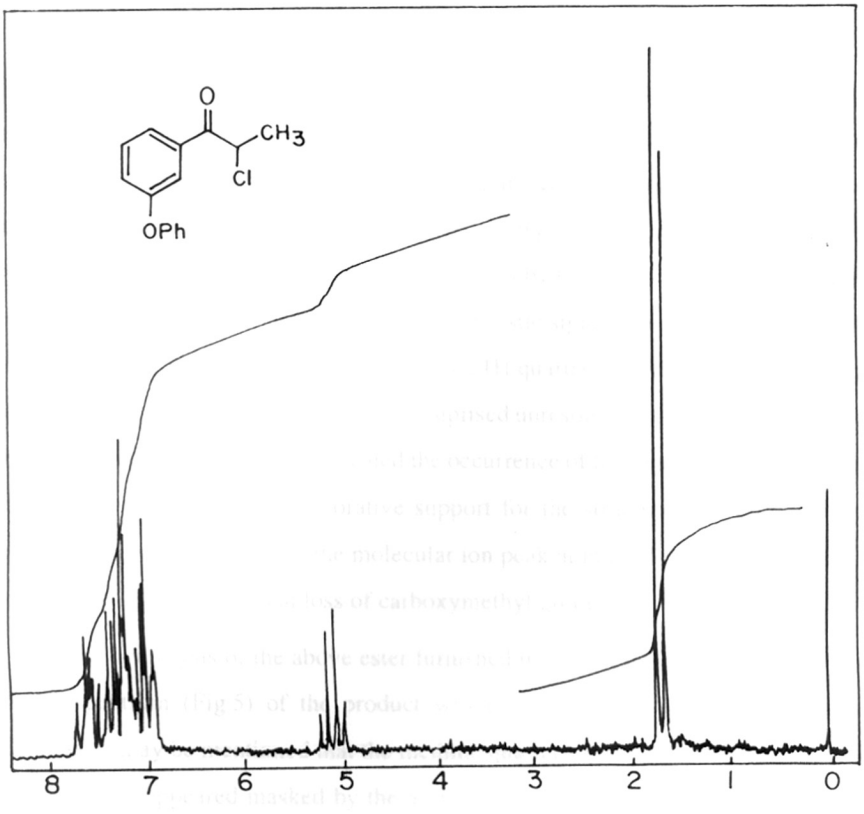


FIG. 1 : ^{1}H NMR (80 MHZ) SPECTRUM OF 5.4

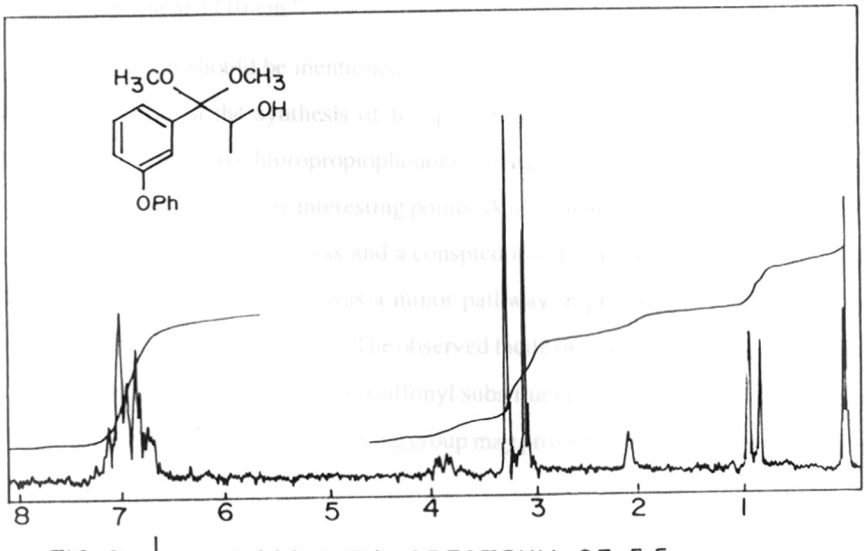


FIG. 2 : ^{1}H NMR (60 MHZ) SPECTRUM OF 5.5

CH_2Cl_2 was slowly introduced into it. The reaction was monitored by TLC and when the ketal reacted completely, the reaction mixture was allowed to rise to room temperature and subjected to standard work up (Experimental). The product was purified by passage through a column of silica gel, followed by distillation under diminished pressure. b.p. 190-95° (bath)/5mm, Yield (65%). The NMR spectrum of the product (Fig.3) was conspicuous by the absence of two 3H singlets initially observed for the α-hydroxyketal. The other characteristic signals were a 3H doublet at 1.40 δ and 3H singlet at 3.68 δ. The spectrum also displayed a 1H quartet centered at 3.88 δ overlapping with the ester methyl signal. The aromatic region comprised unresolvable multiplets accounting for nine protons. Thus, the spectrum clearly revealed the occurrence of the expected rearrangement leading to the desired ester. Further, corroborative support for the structure was provided by its mass spectrum (Fig.4), which displayed the molecular ion peak at m/z, 256 besides showing base peak at m/z, 197, arising by the typical loss of carboxymethyl group.

Alkaline hydrolysis of the above ester furnished the target molecule **5** in a very good yield. The NMR spectrum (Fig.5) of the product was too simple to need any further elaboration. Nevertheless, it may be mentioned that the methine quartet stood well defined at 3.71 δ, while the carboxylic proton appeared masked by the aromatic protons. The IR spectrum showed (Fig.6) a broad OH signal at 3000 cm^{-1} with the typical shoulder of a carboxylic group in addition to a sharp carbonyl absorption at 1710 cm^{-1}.

At the outset, it should be mentioned that 1,2 aryl migration reaction described here has not been reported so far in the synthesis of fenoprofen. A comparison between the photochemical reaction of *m*-phenoxy-α-chloropropiophenone (Chapter-III) and the thermal rearrangement described here brings forth some interesting points. A notable feature is the occurrence of reduction of the C-X bond in the photo process and a conspicuous absence of such a process in the thermal reaction. While the rearrangement was a minor pathway in photolysis, it becomes the exclusive process in the present thermal reaction. The observed facile thermal rearrangement may be attributed to the leaving group ability of the chlorosulfonyl substituent. The presence of two methoxy groups adjacent to the carbon containing the leaving group may provide considerable anchimeric assistance.

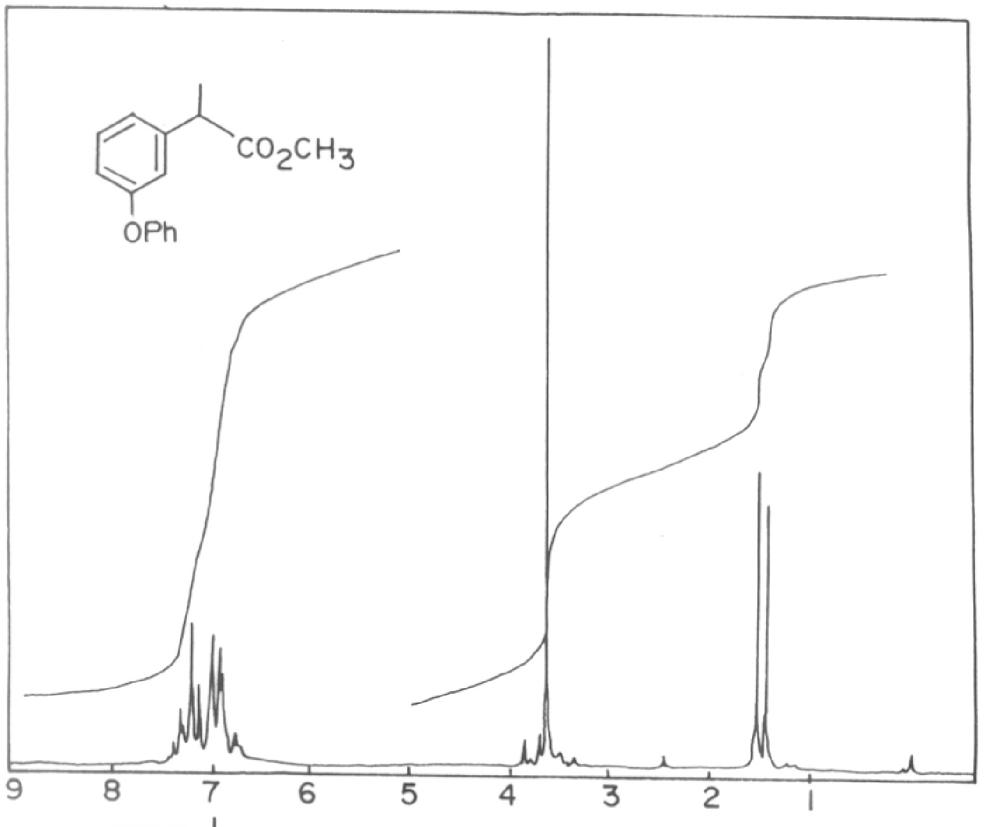


FIG. 3 : ^{1}H NMR (80 MHZ) SPECTRUM OF 5.6

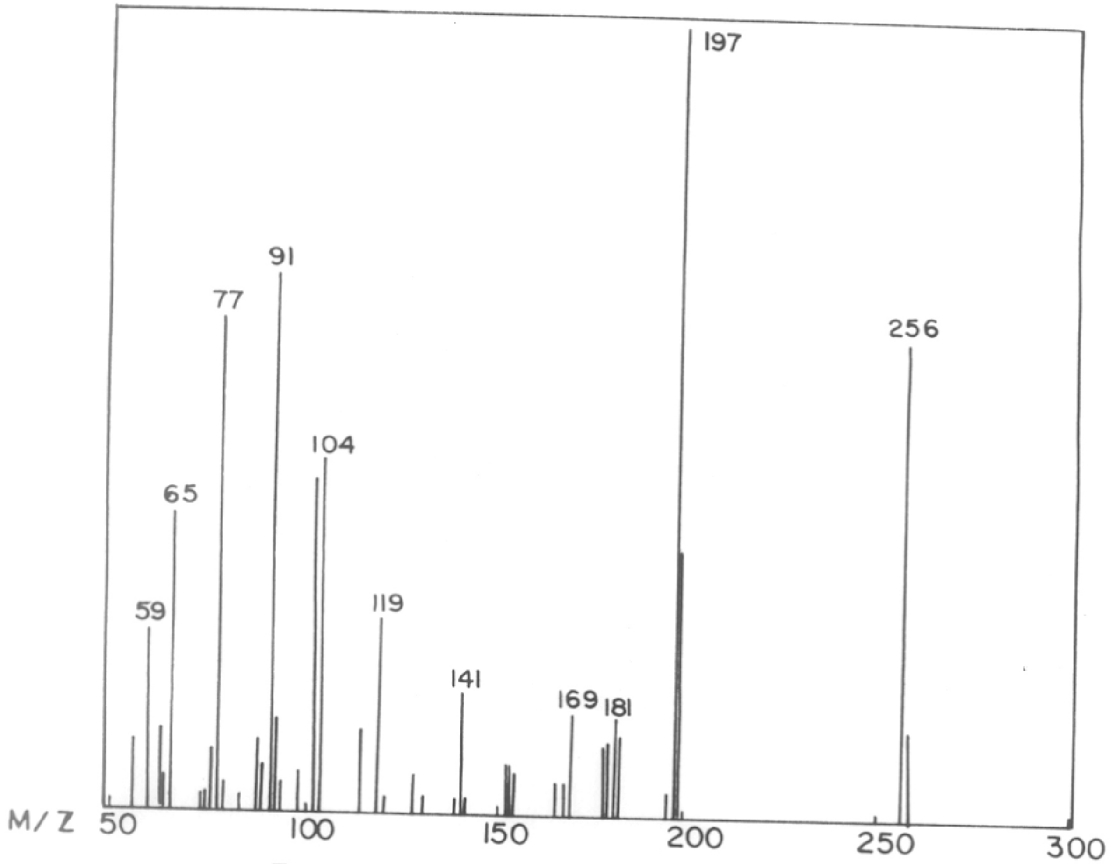


FIG. 4 : MASS SPECTRUM OF 5.6

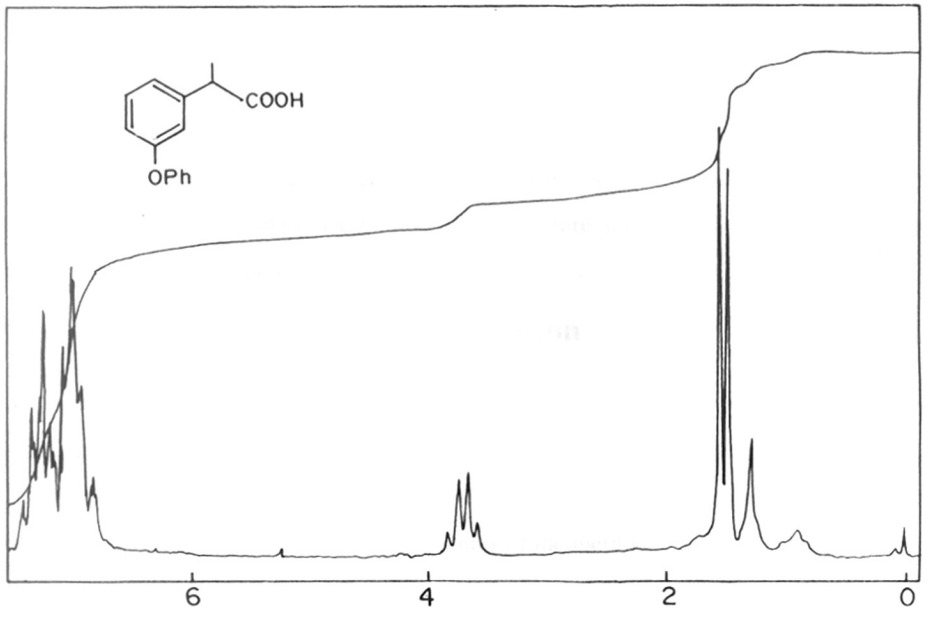


FIG. 5: ^{1}H NMR (90 MHZ) SPECTRUM OF 5

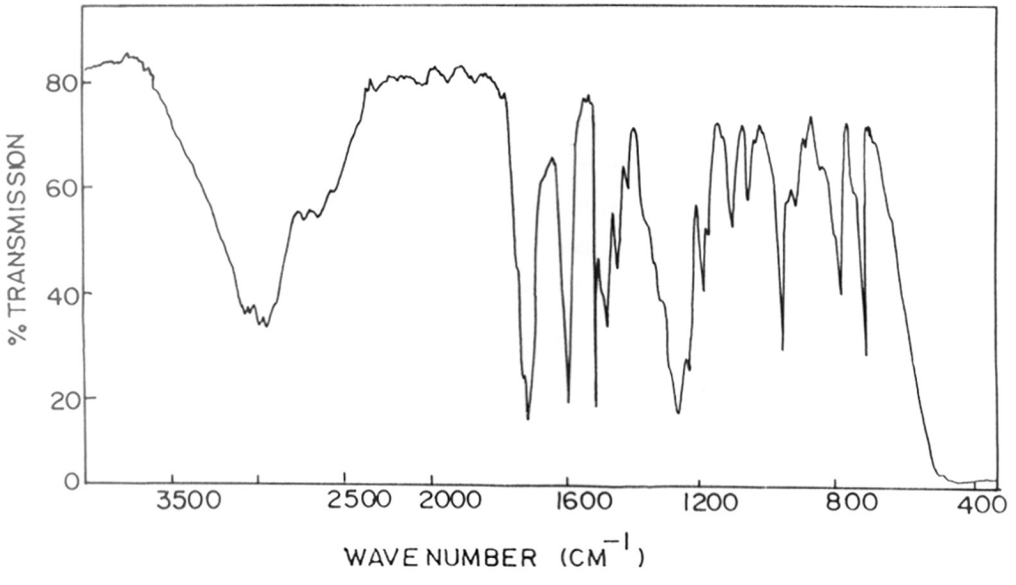


FIG. 6: IR SPECTRUM OF 5

Another point of practical significance to be noted here is that the rearrangement reaction was carried out at 0°C instead of doing at -50°C, as reported previously. This makes a valuable contribution in terms of reducing the cost of the process. At the same time, it must be emphasised that the rearrangement conditions in terms of temperature, duration of the reaction, etc. are yet to be optimised and thus, there is scope for further improvement.

Conclusion

In a nutshell, the work described in this chapter offers the first example of 1,2 aryl migration in the synthesis of fenoprofen. The drawbacks of a few isolated reported methods have already been indicated previously. The ready accessibility of m-phenoxy benzaldehyde and the attractive yields in the reactions constitute the promising features of the method.

Experimental

For general remarks, see Chapter 1

Preparation of *m*-phenoxy-α-hydroxypropiophenone dimethylketal (5.5)

(A) **1-(*m*-Phenoxyphenyl)propanol-1 (5.2)**: To the Grignard reagent prepared from 4.8g. of Mg turnings (0.2g. atom) and ethyl bromide (21.8g, 0.2M) in anhydrous ether (75 ml), and in an atmosphere of nitrogen was added commercially available m-phenoxy benzaldehyde (19.80g, 0.1M). The reaction mixture was stirred and the rate of addition of the aldehyde was so adjusted as to maintain a gentle reflux. When the reaction was complete (2 hours), the reaction mixture was slowly treated with a saturated aqueous solution of NH_4Cl. The aqueous and organic layers were separated and the aqueous layer was repeatedly extracted with ether (3x50 ml). The combined organic extract was washed with saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of solvent was distilled under reduced pressure, b.p. 145-146°C/1.5mm, Yield 21g. (92%).

(B) ***m*-Phenoxypropiophenone (5.3)**: Brown's oxidation[18] reagent (prepared by dissolving 10g. of $Na_2Cr_2O_7$ in 30 ml of water and 7.6 ml of conc. H_2SO_4 and further diluted to 50 ml) was added dropwise to a stirred solution of the above alcohol (19.38g, 0.085M) taken in ether (75 ml) at ambient temperature. As the reaction proceeded, cold water circulation through the reflux condenser was required to maintain a gentle reflux. The reaction was monitored by TLC and when the reaction was complete (6 hr.), a standard work-up was adopted to realize the product, b.p. 135-36°/1mm, Yield 17.2g. (90%). **IR** (neat): 3040, 2980, 1690, 1590, 1480, 1430, 1250, 1160, 880, 770, 700 cm^{-1}. **^{1}H-NMR**: 1.20 (t, 3H), 2.96 (q, 2H), 6.95-7.89 (m, 9H).

(C) ***m*-Phenoxy-α-chloropropiophenone (5.4)**: A mixture of $CuCl_2$ $2H_2O$ (16g, 0.096M) and LiCl (2g, 0.048M), dimethyl formamide (40 ml) were taken in 250 ml flask fitted with a reflux condenser. The above ketone (9g, 0.04M) taken in 15 ml DMF was introduced in one lot and the reaction mixture was heated to 80-90°C and maintained at that temperature for 15 hr. The reaction mixture was slowly added into cooled 0.5N HCl (200 ml) and repeatedly extracted with ether (3x100 ml). The crude product obtained on removal of solvent was initially passed through a column of silica gel using benzene as an eluent and distilled under diminished pressure. b.p. 156-57°C/1.5mm, Yield 6g. (58%). **IR** (neat): 3020, 2990, 2920, 1690, 1590, 1490, 1430, 1250, 890, 740 cm^{-1}.

^{1}H NMR: 1.70 (d, 3H), 5.10 (q, 1H), 6.90-7.70 (m, 9H). **Mass** m/z (%): 262 (M^{+2}, 20), 260 (M^+, 60%), 197(100), 169(57), 141(71), 115(59), 77(54). **Anal. Calcd. for** $C_{15}H_{13}ClO_2$: C, 69.27; H, 4.99, Cl, 13.62. **Found**: C, 69.27, H, 5.17; Cl, 13.75.:

(D) ***m*-Phenoxy-α-hydroxypropiophenone dimethylketal (5.5)**: Into a stirred solution of sodium methoxide in methanol (prepared by careful addition of 0.46g, 0.02g. atom of sodium into 25 ml of dry methanol) was added the α-haloketone - (2.61g, .01M) taken in 15 ml of methanol, in a dropwise manner. The reaction mixture was stirred till the disappearance of the starting ketone (TLC). The residue obtained after removal of methanol was poured into ice cold water and repeatedly extracted with ether (3x50ml). The product was isolated as usual. Yield 2.2g. (90%). **IR** (neat): 3480, 2980, 2940, 1590, 1490, 1430, 1350, 1260, 1220, 1100, 1050, 870, 760, 700 cm^{-1}. **^{1}H-NMR**: 0.9 (d, 3H), 2.13 (broad s, 1H), 3.16 (s, 3H), 3.33 (s, 3H), 3.86-4.03 (m, 1H), 6.73-7.26 (m, 9H).

(E) **Methyl α(*m*-phenoxyphenyl)propionate (5.6)**: A stirred solution of the hydroxy ketal (1.3g, 0.0045M) and triethylamine (0.726g, 0.09M) in anhydrous CH_2Cl_2 (10 ml) was cooled to 0°C to -5°C. Into it was introduced a solution of freshly distilled sulfuryl chloride (0.54 ml, .007M) in methylene chloride (10 ml) in a dropwise manner. The temperature was maintained in the range -5°C to 0°C during the addition. After the addition, the reaction mixture was allowed to rise to room temperature and kept overnight. The reaction mixture was quenched with saturated $NaHCO_3$ solution (25 ml). Usual workup yielded the product which was purified by passage through a column of silica gel/eluting with 10% ethyl acetate in pet.ether. Yield 0.75g. (65%). **IR** (neat): 2980, 2940, 1740, 1590, 1500, 1460, 1250, 1170, 1080, 930, 700 cm^{-1}. **^{1}H-NMR**: 1.40 (d, 3H), 3.68 (s, 3H), 3.88 (q, 1H), 6.80-7.56 (m, 9H). **Mass** m/z (%): 256 (M^+, 60), 197(100), 119(25), 104(45), 91(68), 77(62). **Anal. calcd. for** $C_{16}H_{16}O_3$: C, 75.00; H, 6.21. **Found**: C, 74.87; H, 6.21.

α-Methyl-*m*-phenoxybenzeneacetic acid (Fenoprofen) (5)

A mixture of above ester (0.512g, .002M) and 2N NaOH (30 ml) was stirred at 80°C for two hours. The reaction mixture was cooled to room temperature and made acidic by the addition of conc. HCl. Extraction with ethyl acetate followed by drying and removal of solvent afforded a viscous liquid, Yield 0.430g. (88%). **IR** (neat): 3000 (broad), 2640, 1710, 1590, 1500, 1450, 1250, 950, 780, 700 cm^{-1}. **^{1}H-NMR**: 1.51 (d, 3H), 3.17 (q, 1H), 6.66-7.48 (m, 10H). **MS**, m/z (%): 242 (M^+, 78), 197(100), 104(31), 91(67), 77(58). **Anal. calcd. for** $C_{15}H_{14}O_3$: C, 74.38; H, 5.78. **Found**: C, 74.33; H, 6.18.

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Publications based on the work presented in this thesis:

1. On the construction of Bicyclo [m.3.0] Bridged Alkenes: Thermal Rearrangement of Spirocyclic Vinylcyclopropanes.
   H.R.Sonawane, B.S.Nanjundiah and G.M.Nazeruddin
   Tetrahedron Lett. (**1992**), *33*, 1645.

2. An efficient synthesis of fenoprofen, an important antiinflammatory agents
   H.R.Sonawane, B.S.Nanjundiah and G.M.Nazeruddin
   Indian Journal of Chem. (**1994**), *33B*, 705.

3. Photochemistry substituted propiophenones: An interesting α- and Aryl substituents effect on their photobehaviour
   H.R.Sonawane, B.S.Nanjundiah and G.M.Nazeruddin
   Communicated to *Tetrahedron*.

Tetrahedron Letters, Vol. 33, No. 12, pp. 1645-1646, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
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On the Construction of Bicyclo [m.3.0] Bridged Alkenes: Thermal Rearrangement of Spirocyclic Vinylcyclopropanes§

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Abstract: A facile transformation of spirocyclic vinylcyclopropanes to titled bridged-alkenes is presented; this approach finds an application in the synthesis of natural product carbon framework of diverse nature such as that of precapnelladiene and muscone.

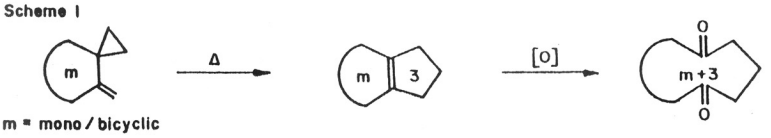
A large number of terpenoid natural products of carbon framework incorporating cyclopentane moiety fused to medium-sized rings have come to focus recently as synthetic targets.[1] This may be exemplified by precapnelladiene[2] [5-8] and the sesterterpene ophiobolin F[3] [5-8-5]. In this context, we perceived that devising a simple and efficient method to build a cyclopentane ring onto a given medium/large ring that would generate a class of bicyclo [m.3.0] bridged-alkenes, would be of immense synthetic value.

Our approach towards this objective primarily rests upon the well-known vinylcyclopropane-cyclopentene rearrangement, a versatile and widely-used cyclopentane annulation strategy.[4] Surprisingly, we find that the thermal transformation of spirocyclic vinylcyclopropanes has remained practically unexplored.[4,5] (Scheme-1).

We wish to report herein our preliminary results from such a reaction that generated bicyclic and tricyclic bridged-alkenes and their oxidative scission to the corresponding medium and large-sized 1,5-diones, a class of potentially useful synthetic intermediates (Schemes 2 and 3).

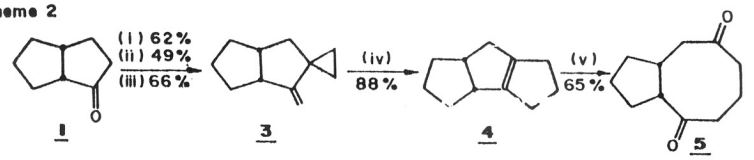
The results arising from the substrates **1**[6,7] and **2** are noteworthy and illustrate the efficacy of the approach. The first example provides a short and efficient synthesis of triquinane **4**[7] and the bicyclic dione **5** in high yields. Interestingly, **5** constitutes a well-recognised entry point to the synthesis of precapnelladiene,[8] a biologically active sesquiterpenoid of marine origin. Especially, the facile transformation of **6** into **7** demonstrates the high degree of flexibility associated with the approach; that is, the highly mobile conformation of the C-12 carbocycle compared to that of the relatively rigid **3**[9] does not deter the rearrangement. From the synthetic point of view, the suitability of the dione **8** as a key intermediate leading to muscone[10] is well recognised. It is significant to note that the transformations **3**→**5** and **6**→**8** represent three-carbon ring expansion process, an exercise of active current interest.[11] The generality of this approach and its potential in natural product synthesis, especially the framework of Taxol, a complex diterpene of current chemo-therapeutic interest, are being explored.

Scheme 1



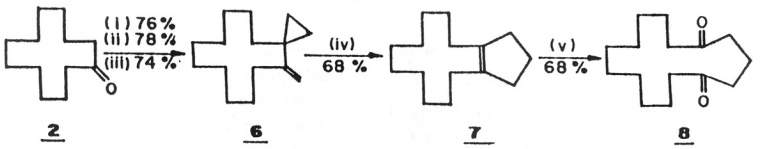
m = mono / bicyclic

Scheme 2



1 3 4 5

Scheme 3



2 6 7 8

(i) Mannich / CH_3I ; (ii) $\overset{+}{\underset{|}{S}}=O\bar{I}$ / NaH ; (iii) Zn / $TiCl_4$ / CH_2Br_2 ; (iv) Δ, 500°
(v) $RuCl_3$ — $NaIO_4$, CCl_4 / MeCN / H_2O

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§NCL Communication No.: 5253

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(Received in UK 28 August 1991)

Indian Journal of Chemistry
Vol. 33B, July 1994, pp. 705-706

An efficient synthesis of fenoprofen, an important antiinflammatory agent†

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Received 5 October 1993; accepted 3 February 1994

A simple and practical synthesis of (±)-fenoprofen, a well-known non-steroidal antiinflammatory agent, from the commercially available *m*-phenoxybenzaldehyde has been described.

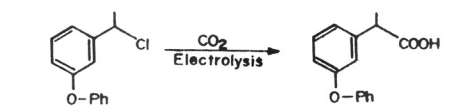
α-Arylpropanoic acids have emerged as an important class of nonsteroidal anti-inflammatory agents during the last two decades.[1] The therapeutic efficacy of this class of drugs is well attested by the introduction and extensive use of more than a dozen compounds exemplified by ibuprofen, neproxene, ketoprofen and fenoprofen (**1**). While numerous approaches have been developed for the synthesis of the first three compounds[2] mentioned above, there has not been, surprisingly, any convenient synthesis of **1** but for two isolated reports[3,4] and a few patents[5]. The first report desribed electrochemical carboxylation of benzyl halide into **1** (Scheme I).

The other report involved hydroformylation of *m*-phenoxystyrene utilizing rhodium phospholes and rhodium phosphonorbornadiene as catalysts (Scheme II).

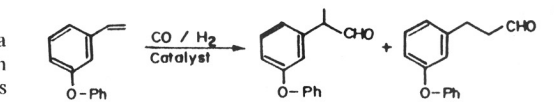
Although these methods appear attractive, the difficulty in acquiring starting materials as well as the use of special techniques become the limiting factors. We wish to report herein a simple and convenient method for the synthesis of **1**. The sequence of reactions employed is depicted in Scheme III.

The key step in the synthesis is the transformation of α-hydroxyacetal **3**[6] into its chlorosulfonyl ester *in situ* and its concomitant rearrangement[7] to the methyl ester **4** in high yields. The required **2** could be readily prepared from *m*-phenoxybenzaldehyde by the routine sequence of reactions: Grignard reaction with ethyl bromide, Brown's oxidation[8] and finally α-chlorination[9a,b] with $CuCl_2$-LiCl/DMF.

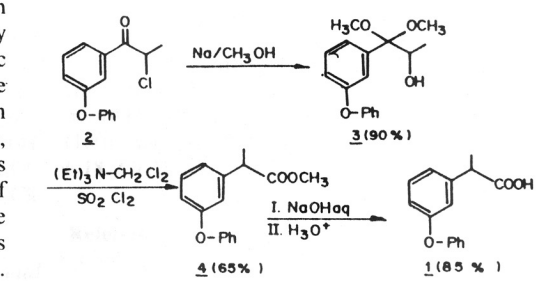
In summary, this communication offers a practical and efficient synthesis of (±)-fenoprofen (**1**) using commercially available *m*-phenoxybenzaldehyde as the starting material. In addition, this procedure has



Scheme I



Scheme II



Scheme III

the inherent potential to lead to chiral **1**, by virtue of the 1, 2-aryl migration reaction being stereospecific[10].

Experimental

All b.ps are uncorrected, IR spectra were recorded as smears on a Perkin-Elmer infracord Model 137E. PMR spectra were taken in $CDCl_3$ solutions on a Varian FT-80A or a Bruker WH-90 instrument using TMS as internal standard. Mass spectra were recorded on a CEC mass spectrometer, Model 21-1108, using an ionization potential of 70 eV.

1-(3-*phenoxyphenyl*)*propanol*-1

Treatment of *m*-phenoxybenzaldehyde (9.90 g, 0.05 mole) with Grignard reagent prepared from ethyl bromide (10.90, g, 0.10 mole) and Mg turnings (2.4 g, 0.10 g atom) under standard conditions afforded the secondary alcohol, yield 10.50 g (92%), b.p. 145-46°/1 mm.

3-*phenoxypropiophenone*

The above secondary alcohol (9.69 g; 0.042 mole) when subjected to oxidation under Brown's conditi-

† NCL Communication No. 5604

on[8] furnished the corresponding ketone, yield 8.61 g 9.61 g (90%), b.p. 135-36°/1 mm.

α-Chloro-3-phenoxypropiophenone (**2**)

α-Chlorination was effected by following the reported method.[100a,b] A mixture of hydrated copper chloride (8 g, 0.048 mole) and LiCl (1 g, 0.024 mole) was taken in 20 ml DMF. The reaction mixture was heated to 80-90° for 15 hr with constant stirring. The reaction mixture was cooled, poured into HCl (0.5 *N*, 100 ml) and extracted with ether (30 ml × 3). The combined organic extract was successively washed with aq. HCl (0.5 *N*), saturated aq. $NaHCO_3$, water and brine. The organic extract was dried over anhyd. Na_2SO_4 and solvent removed to get a residue which was purified by column chromatography over SiO_2 (benzene), yield 3.00 g (58%), b.p. 156-57°/1.5 mm; IR: 1685 cm^{-1} ^1H NMR: δ 1.70 (d, 3H), 5.10 (q, 1H), 6.90-7.70 (m, 9H); MS: m/z (relative intensity) 262 $(M+2)^+$ (20), 260 (M^+) (60), 197 (100), 169 (57), 141 (71), 115 (59), 77 (54) (Found: C, 69.27; H, 5.17; Cl, 13.75. $C_{15}H_{13}O_2Cl$ requires C, 69.27; H, 4.99; Cl, 13.62%).

α-Hydroxy-3-phenoxypropiophenone dimethyl acetal (**3**)

The α-chloroketone **2** (1.307 g, 0.005 mole) on treatment with Na/CH_3OH under standard conditions[6] furnished the corresponding acetal (**3**), yield 1.30 g (90%).

Methyl α(3-phenoxyphenyl)propionate (**4**)

A mixture of dimethyl acetal **3** (1.307 g, 0.005 mole) and triethylamine (0.90 g, 0.009 mole) taken in 10 ml dry CH_2Cl_2 was cooled to − 5° to 0°C, and sulphuryl chloride (0.945g, 0.001 mole) in 10 ml dry CH_2Cl_2 was added to it dropwise by maintaining the temperature of reaction mixture between − 5° and 0°C under, dry conditions, with constant stirring. After the complete addition of sulphuryl chloride, the reaction mixture was allowed to attain room temperature, stirred overnight, and saturated aq. $NaHCO_3$ (25 ml) added to it. The aq. layer was extracted with CH_2Cl_2 (25 × 3 ml). The combined organic extract was washed with water and brine, dried over anhyd. Na_2SO_4, and solvent removed. The product was purified by column chromatography over SiO_2 (10% ethyl acetate in pet. ether), yield 0.750 g (65%), b.p. 190-195° (bath)/5 mm; IR 1740 cm^{-1}; ^1H NMR: δ 1.40 (d, 3H); 3.68 (s, 3H); 3.88 (q, 1H); 6.80-7.56 (m, 9H); MS: m/z (relative intensity): 256 M^+ (60), 197 (100), 119 (25), 104 (45), 91 (68), 77 (62) (Found: C, 74.87; H, 6.21. $C_{16}H_{16}O_3$ requires C, 75; H, 6.21%).

Fenoprofen, α-(3-phenoxyphenyl)propionic acid (**1**)

The ester **4** (0.256 g, 0.001 mole) when subjected to alkaline hydrolysis[7] furnished **1**, yield 0.215 g (89%), b.p. 180-85 (bath)/0.1 mm; IR, 3200, 1710, 1600 cm^{-1}; ^1H NMR: δ 1.51 (d, 3H); 3.17 (q, 1H); 6.66-7.48 (m, 10 H); MS: m/z (relative intensity): 242 M^+ (78), 197 (100), 104 (31), 91 (67), 77 (58) (Found: C, 74.33; H, 6.18. $C_{15}H_{14}O_3$ requires C, 74.38; H, 5.78%).

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