NOVEL CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES AND RELATED CHEMISTRY

THESIS SUBMITTED TO
COCHIN UNIVERSITY OF SCIENCE AND TECHNOLOGY
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BY

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FEBRUARY, 2001

Dedicated to Jesus Christ on the occasion
of The Great Jubilee (2000) of his birth
and the Advent of the Third Millennium

DECLARATION

I hereby declare that the thesis entitled **"NOVEL CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES AND RELATED CHEMISTRY"** embodies the results of investigations carried out by me at the Organic Chemistry Division of the Regional Research Laboratory [CSIR], Trivandrum under the supervision of **Dr. G. Vijay Nair** and the same has not been submitted elsewhere for any other degree.

Sr. P. M. Treesa

February, 2001
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CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"NOVEL CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES AND RELATED CHEMISTRY"** has been carried out by Sr. P. M. Treesa under my supervision at the Organic Chemistry Division of the Regional Research Laboratory [CSIR], Trivandrum and the same has not been submitted elsewhere for any other degree.

G. Vijay Nair
(Thesis Supervisor)

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Sr. P. M. Treesa

Trivandrum
February, 2001

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PREFACE

Quinone methides play an important role as intermediates in biogenesis and biomimetic synthesis of a variety of natural products and therefore have attracted considerable attention in recent years. In organic synthesis, they serve as building blocks for biologically active natural products and their synthetic analogues. However, the synthetic potential of these reactive species has not been tapped adequately. This is particularly true in the case of heterocyclic quinone methides.

Prompted by the enormous synthetic potential of quinone methides - heterocyclic as well as carbocyclic - in heterocyclic construction, we have investigated the dipolar cycloaddition reactions of oxoindolinylidenes and the Diels-Alder trapping of quinolinone quinone methide and a carbocyclic quinone methide. The results of these investigations are embodied in the thesis.

The thesis is divided into four chapters and the relevant references are given at the end of each chapter.

The first chapter presents a brief overview of the chemistry of *o*-quinone methides with special emphasis on their cycloaddition reactions. The chemistry of heterocyclic quinone methides and oxoindolinylidenes are dealt with under separate subheadings. A definition of the problem is provided at the end of the chapter.

The results of our investigations on the dipolar cycloaddition reactions of carbonyl ylides to oxoindolinylidenes are disclosed in the second chapter. General information on experimental procedure is given in this chapter.

The third chapter gives an account of the *in situ* generation and Diels-Alder trapping of quinolinone quinone methide.

The generation and hetero Diels-Alder reactions of a carbocyclic quinone methide from 2-hydroxy naphthoquinone and the CAN mediated radical reactions of the latter forms the subject matter of the final chapter.

It may be mentioned that each chapter of the thesis is presented as a separate unit and therefore the structural formulae, schemes and figures are numbered chapterwise.

A summary of the work is given towards the end of the thesis.

LIST OF ABBREVIATIONS

AM1	: Austin Method 1
brs	: broad singlet
CAN	: cerium(IV) ammonium nitrate
COSY	: correlation spectroscopy
d	: doublet
D	: dimensional
dd	: double doublet
ddd	: doublet of double doublet
DDQ	: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	: dimethyl sulfoxide
DEPT	: distortionless enhancement by polarization transfer
EIMS	: electron impact mass spectrum
h	: hour
HOMO	: highest occupied molecular orbital
HRMS	: high resolution mass spectrum
LUMO	: lowest unoccupied molecular orbital
m	: multiplet
M^+	: molecular ion
m/z	: mass charge ratio
min	: minutes
nOe	: nuclear Overhauser effect
NOESY	: nuclear Overhauser and exchange spectroscopy
PM3	: Parameterization Method 3
RT	: room temperature
s	: singlet
t	: triplet
q	: quartet
TLC	: thin layer chromatography
TMS	: tetramethylsilane

CHAPTER 1

CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES: AN INTRODUCTION

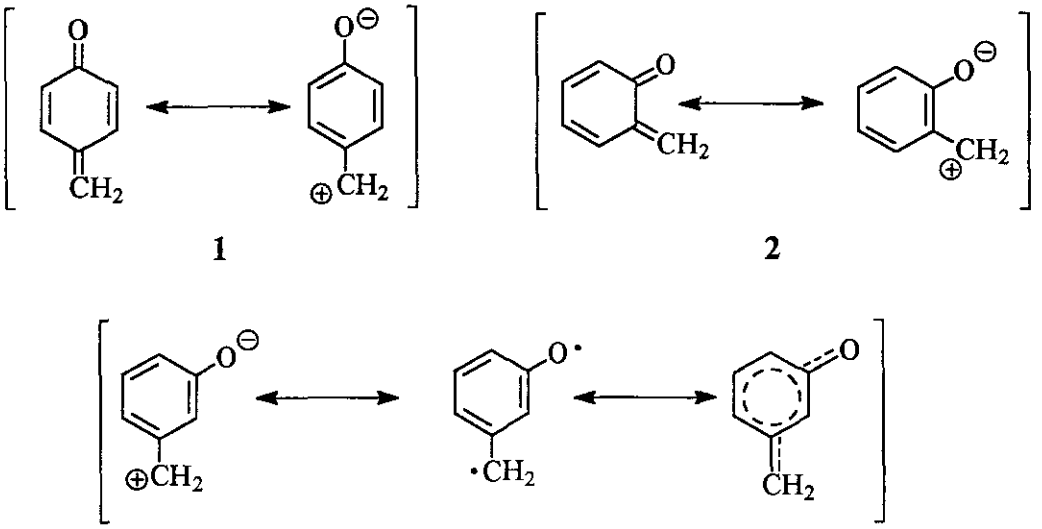
1.1. GENERAL INTRODUCTION

The focal theme of the thesis is the cycloaddition reactions of certain heterocyclic and carbocyclic *o*-quinone methides. Therefore, to put things in perspective, a brief overview of the chemistry of *o*-quinone methides, with special emphasis on their cycloaddition reactions, is given in the following sections. Mechanistic aspects of cycloaddition reactions, particularly relating to orbital interactions, are also included. Of necessity, the literature coverage is selective and is not intended to be comprehensive.

It may be noted that various methods of generating *o*-quinone methides *in situ* and their subsequent participation in cycloaddition reactions have been extensively reviewed.[1-3]

1.2. QUINONE METHIDES

Quinone methides are interesting compounds that have been proposed to be intermediates in a large number of chemical and biological transformations. As in the case of quinones, these also can be classified as *p*-quinone methides, *o*-quinone methides and *m*-quinone methides (Figure 1).



1 **2**

3

Figure 1

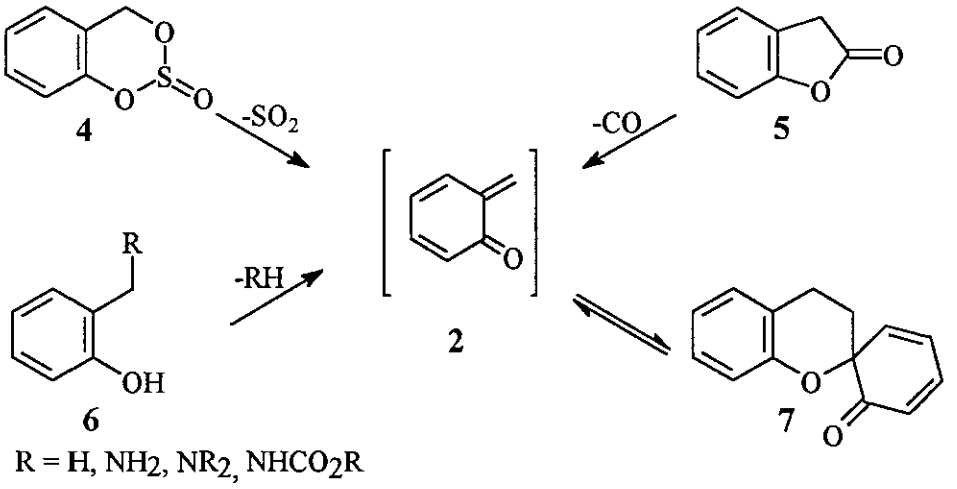
The *o*-and *p*-quinone methides are believed to play an important role in a variety of biochemical transformations. They are known to be powerful electrophiles due to the asymmetry introduced by two electronically different substituents, carbonyl and methylidene, as shown in the resonance structures in Figure 1.[4] However, *m*-quinone methides, for which several structures including the non-Kekule form may be envisioned, are less widely known.[5]

1.3. *o*-QUINONE METHIDES

o-Quinone methides are widely utilized in organic syntheses, in particular for carrying out inverse electron demand Diels-Alder reactions with electron rich alkenes to give chroman derivatives.[2] In addition, *o*-quinone methides have been proposed to play an important role in the chemistry and mode of action of several classes of antitumour agents. For example, the action of dynemicin A, a potent antitumour antibiotic, involves the intermediacy of a semiquinone methide.[6]

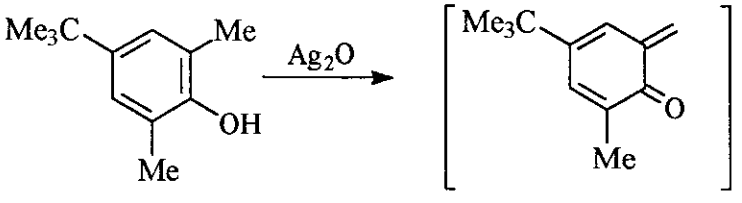
1.3.1. GENERAL METHODS OF PREPARATION

The common protocol employed for the *in situ* generation of *o*-quinone methides relies on the Lewis acid catalyzed thermal, or photoinduced elimination of water, or secondary amine from an *o*-hydroxybenzyl alcohol or phenol Mannich base. The thermal dissociation of the corresponding spirochromane dimer, the oxidation of substituted *o*-alkyl phenols and the thermal or photochemically induced cheletropic extrusion of carbon monoxide, or sulfur dioxide are some of the other methods of generation of *o*-quinone methides (Scheme 1).[3]



Scheme 1

2,6-Dimethyl phenol blocked in the *para* position with a group lacking α-hydrogen **8**, when oxidized with silver oxide, forms the *o*-quinone methide **9** (Scheme 2).[7]

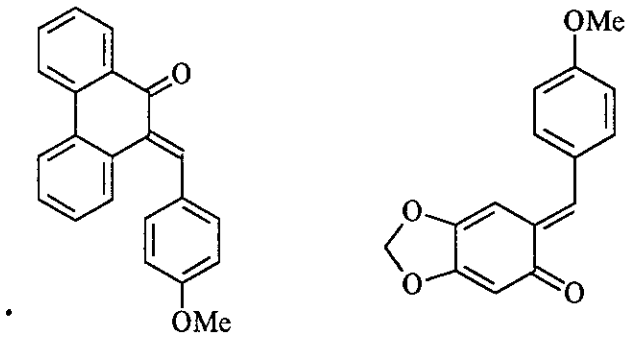


8 **9**

Scheme 2

1.3.2. REACTIVITY OF *o*-QUINONE METHIDES

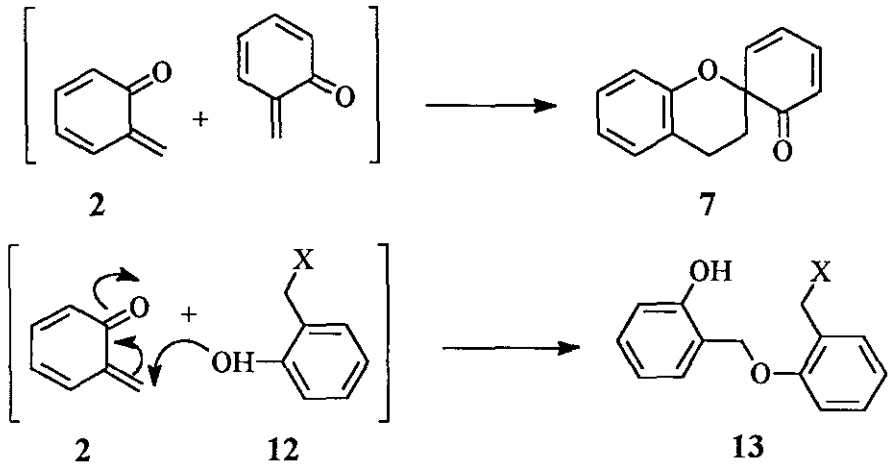
The quinone methides are usually highly reactive and they are generated *in situ* and trapped with suitable dienophiles. 10-(*p*-Methoxybenzilidene)-9(10H)phenanthrone[8] **10** and 6-(*p*-methoxybenzilidene)-3,4-methylene dioxy-2,4-cyclohexadien-1-one[9,10] **11** are examples of stable *o*-quinone methides (Figure 2).



10 **11**

Figure 2

The higher reactivity of *o*-quinone methides *vis a vis* α,β-unsaturated carbonyl compounds may be attributed, at least in part, to the regeneration of aromaticity as a consequence of the cycloaddition process. This behavior is apparent from the ease with which *o*-quinone methides undergo dimerization or Michael addition with the quinone methide precursor especially in the absence of an external dienophile (Scheme 3).[11-13]



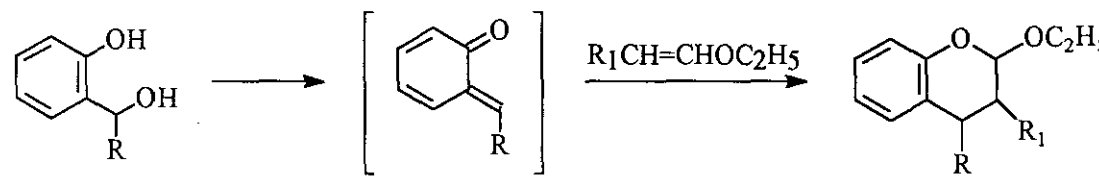
Scheme 3

1.3.3. CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES

The most important and well-studied reactions of *o*-quinone methides are [4+2] cycloaddition reactions. The inter and intramolecular cycloaddition reactions of *o*-quinone methides have been exploited in the elegant syntheses of several natural products.

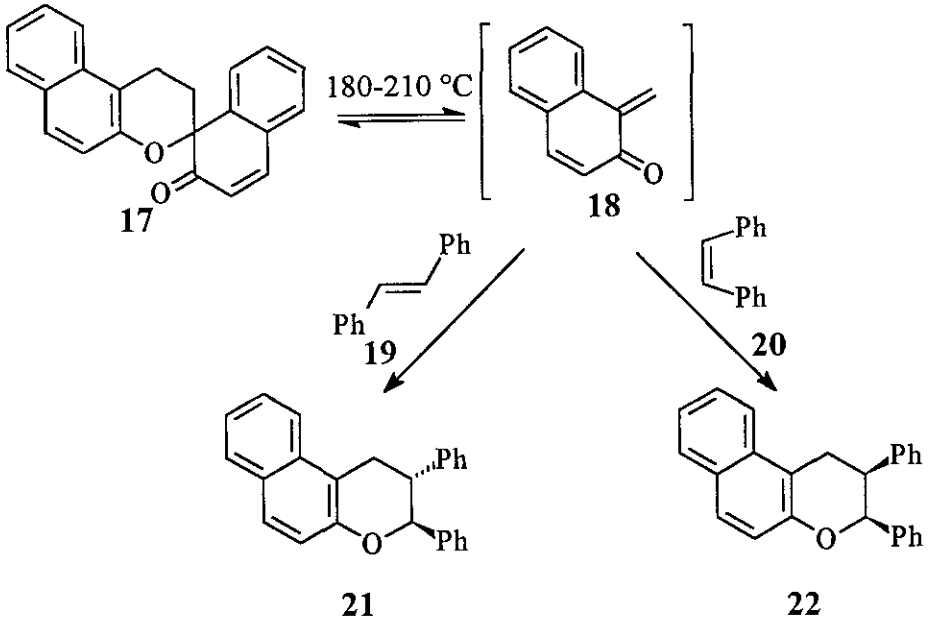
1.3.3.1. INTERMOLECULAR CYCLOADDITION REACTIONS

o-Quinone methides undergo hetero Diels-Alder reaction with alkenes affording a wide variety of chroman skeletons.[1-3] The cycloaddition reactions between vinyl ethers and *o*-quinone methides, thermally generated from 2-hydroxybenzyl alcohols, have been systematically investigated by Pochini *et al.* (Scheme 4).[13]



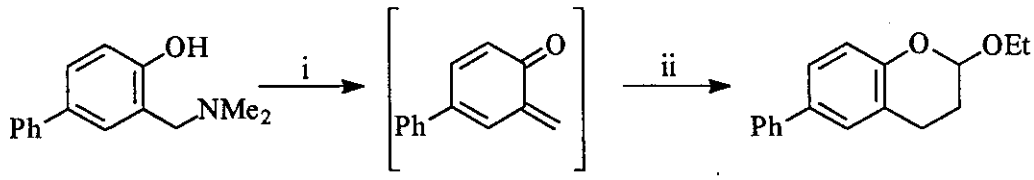
Scheme 4

The naphthoquinone methide, formed by thermal dissociation of spiroannulated chroman, was trapped with *cis* and *trans* stilbene (Scheme 5).[14]



Scheme 5

Most of the methods reported for generating *o*- and *p*-quinone methides involve high temperature thermolysis and/or use of highly derivatised or structurally complex precursors. In 1995, Wan *et al.* reported a simple and general method for generating all three isomers of quinone methide by photolysis of benzyl alcohols in aqueous acetonitrile.[5] Later Saito and co-workers improved this procedure by generating *o*-quinone methides by low energy UV irradiation of Mannich bases of phenol and naphthol derivatives in aqueous solvents. These quinone methides were trapped efficiently by ethyl vinyl ether (Scheme 6).[15]

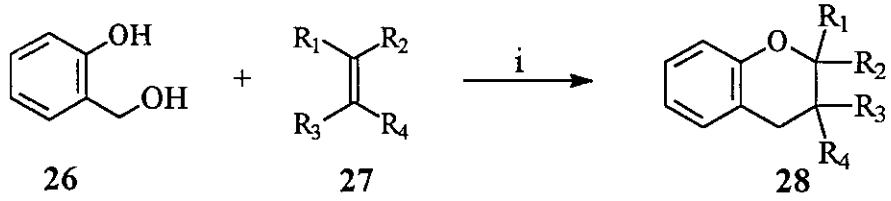


23 **24** **25**

i. *hv* (>300 nm), aq. CH_3CN; ii. CH_2=CHOEt

Scheme 6

Usually quinone methides require the presence of electron rich dienes for cycloaddition reactions. Recently, Chiba and co-workers accomplished the intermolecular hetero Diels-Alder reaction of *in situ* generated *o*-quinone methides and unactivated alkenes through a wet Montmorillonite catalyst in a $LiClO_4$-CH_3NO_2 solution (Scheme 7).[16]



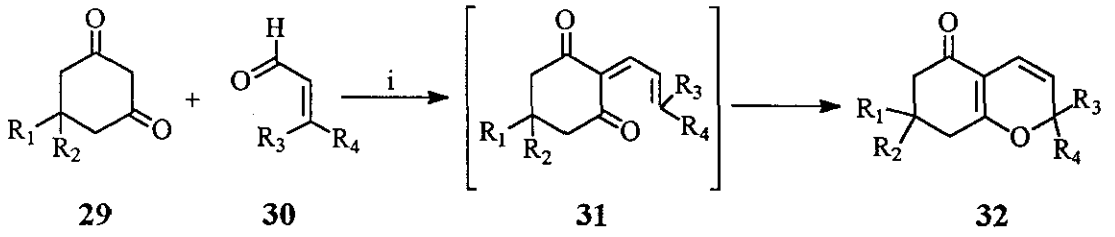
26 **27** **28**

i. $LiClO_4$-CH_3NO_2, K-10, 48 h, 76-79%

Scheme 7

1.3.3.2. INTRAMOLECULAR CYCLOADDITION REACTIONS

The intramolecular hetero Diels-Alder reaction is a powerful tool for the construction of polyheterocycles.[4,17] The simplest example of such a reaction is given in Scheme 8. Here the quinone methide **31** formed by condensation of α,β-unsaturated aldehyde **30** with a 1,3-diketone **29** afforded [2H]-pyran-*cis*-dienone system.[18]

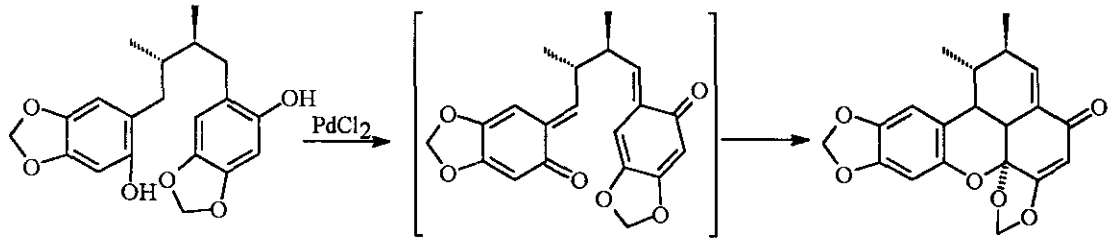


29 **30** **31** **32**

i. Pyridine, reflux, $MgSO_4$

Scheme 8

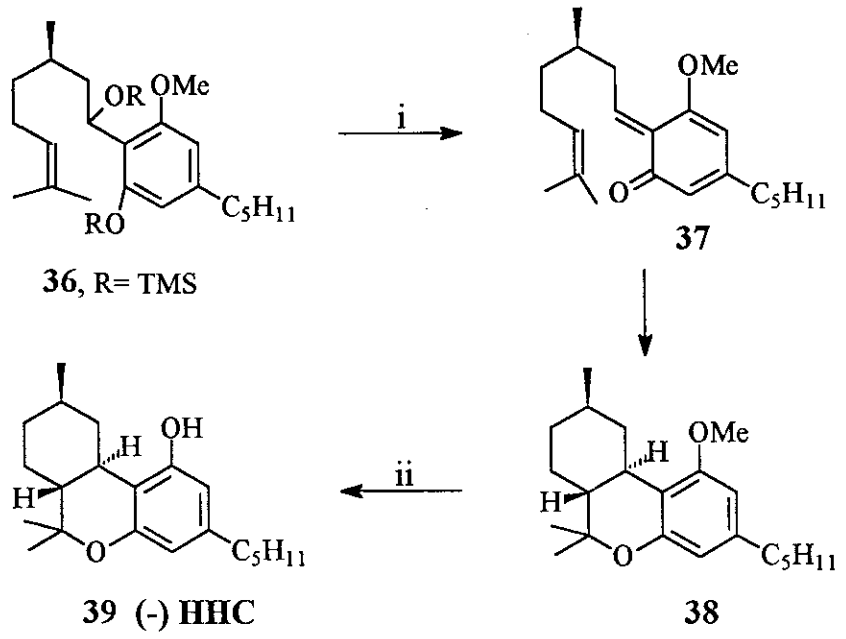
It was the biomimetic synthesis of carpanone **35,** achieved by an intramolecular Diels-Alder reaction of an *o*-quinone methide (Scheme 9), that aroused considerable interest in the intramolecular [4+2] cycloaddition reactions of *o*-quinone methides. The required *o*-quinone methide **34,** was generated by the oxidation of a substituted *o*-alkyl phenol and was trapped intramolecularly to afford carpanone.[19]



33 **34** **35**

Scheme 9

The bis-silylated *o*-hydroxybenzyl alcohol **36** derived from (+)citronellal underwent regiospecific 1,4-desilylation elimination to an incipient *o*-quinone methide **37** which is trapped intramolecularly to yield (-) hexahydrocannabinol (HHC) (Scheme 10).[20]



36, R= TMS

37

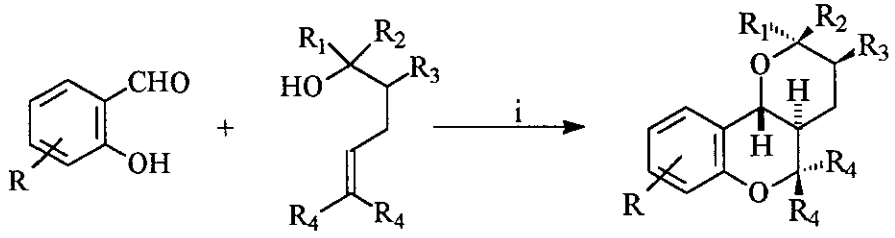
39 (-) HHC

38

i. CsF, CH_3CN; ii. NaSEt/DMF, Δ

Scheme 10

Intramolecular [4+2] cycloaddition reaction of 6-(4-alkoxymethylene)-2,4-cyclohexadien-1-ones generated from the reaction between salicylaldehydes and unsaturated alcohols under mild conditions furnished tricyclic compounds containing the pyranobenzopyran skeleton with *trans* fused B/C ring in very good yields (Scheme 11).[21]

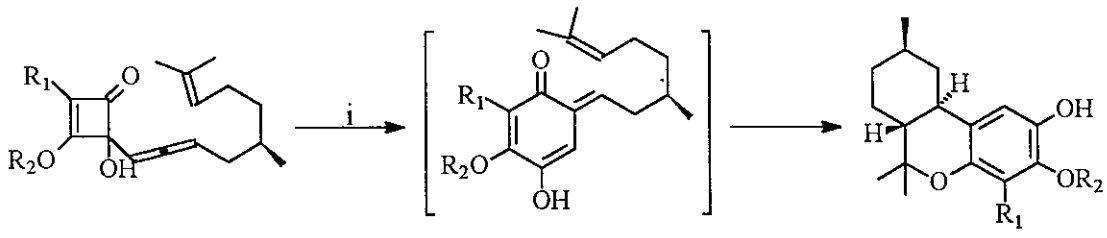


40 **41** **42**

i. $CH(OMe)_3$, *p*-TsOH, C_6H_6, RT

Scheme 11

4-Allenyl cyclobutenone, upon thermolysis in toluene or benzene, undergoes ring expansion giving the corresponding *o*-quinone methide, which is trapped to give stable products. This reaction was utilized in the synthesis of aryl analogs of hexahydrocannabinol (Scheme 12).[22]



43 **44** **45**

i. C_6H_6, 40-50 °C

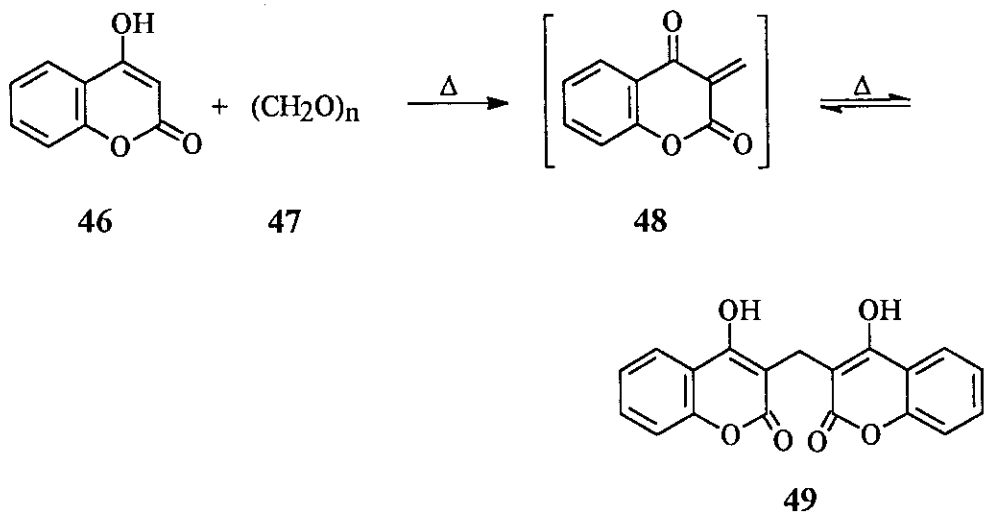
Scheme 12

1.4. HETEROCYCLIC QUINONE METHIDES

α-Methylene ketones derived from heterocyclic compounds are termed heterocyclic quinone methides. The cycloaddition reactions of the latter offer a very convenient route to the synthesis of important natural products and their synthetic derivatives. In comparison to their carbocyclic analogues, heterocyclic quinone methides have received only limited attention.

1.4.1. GENERATION AND REACTIONS OF HETEROCYCLIC QUINONE METHIDES

One of the most widely studied heterocyclic quinone methides is the 3-methylene-2,4-chromandione **48**, generated *in situ* from dicoumarol **49** or its monomer 4-hydroxycoumarin **46** (Scheme 13).[23]

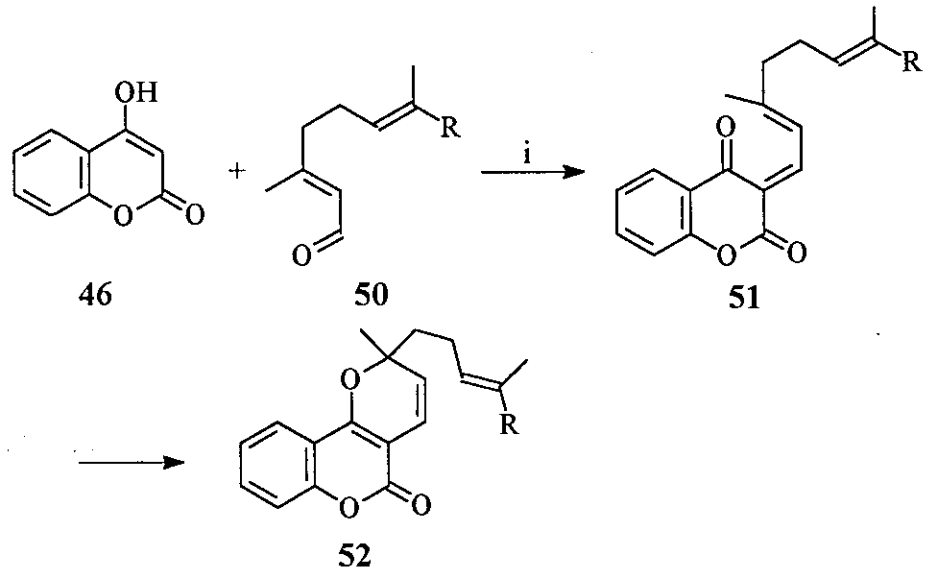


46 **47** **48** **49**

Scheme 13

Extensive investigation on the cycloaddition profile of this methide has shown that it can act as an ambident heterodiene, or dienophile. It can also serve as an ene component in ene reactions.[24]

The synthesis of haemorrhagic 2H-pyrano[3,2-c]coumarin ferprenin is achieved by a tandem Knoevenagel hetero Diels-Alder reaction of 4-hydroxy coumarin (Scheme 14).[25]



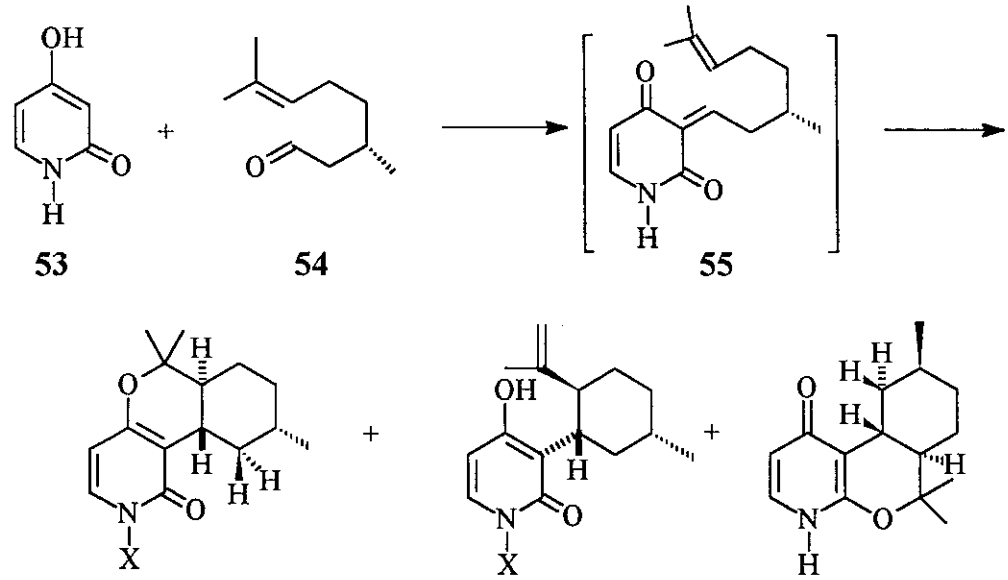
46 **50** **51** **52**

R = $-CH_2CH=C(CH_3)_2$

i. Pyridine, Δ

Scheme 14

The synthesis of pyridoxatin derivatives is achieved through the intramolecular cycloaddition reaction of appropriate quinone methide. The *o*-quinone methide intermediate **55** formed by condensation of 4-hydroxypyridone **53** with citronellal **54** afforded the inverse electron demand Diels-Alder adducts **56** and **58** and the ene adduct **57**. The products **56** and **57** when treated with hexamethyldisilazide and trimethyl silyl chloride afforded the corresponding trimethylsilyloxypyridines, which on further treatment with MoO_5.Pyr.HMPA were converted to pyridoxatin analogues **59** and **60** (Scheme 15).[26]

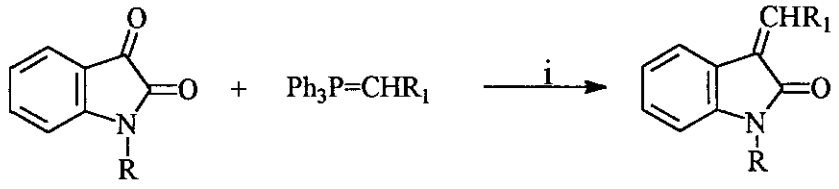


Scheme 15

The aza analogue of 3-methylene chromandione, namely, 3-methylene quinolin-2,4-dione is a versatile intermediate for the construction of pyrano [3,2-c]quinolinones and polycyclic heterocycles.[27] Except for the isolated work by Grundon and co-workers,[28] no effort has been made to study the cycloaddition profile of the above system.

1.5. 3-METHYLENE-2-OXOINDOLINE DERIVATIVES

α-Methylene carbonyl compounds derived from isatins, namely 3-methylene-2-oxoindolines **63**, can be conveniently prepared by Wittig olefination of isatin (Scheme 16).[29]



61 **62** **63**

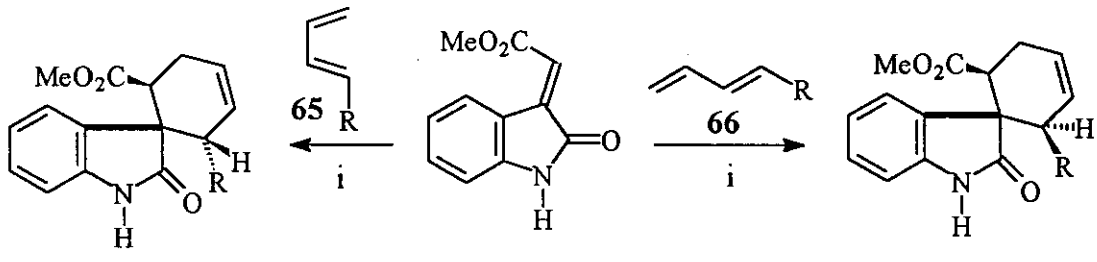
i. CH_3COOH, 70-95 °C, 4 h

Scheme 16

These compounds, also known as oxoindolinylidenes and isatylidenes, possess a reactive 2π-system making them amenable to Diels-Alder and dipolar cycloaddition reactions.

1.5.1. CYCLOADDITION REACTIONS OF 3-METHYLENE-2-OXOINDOLINE DERIVATIVES

The Diels-Alder reactions of this system with various cyclic and acyclic dienes have been studied by different groups.[30-32] *E*-3-Methoxy carbonyl methylene-2-oxoindoline **64** when treated with *cis* and *trans* 1,3-dienes underwent facile Diels-Alder reaction to afford epimeric products **67** and **68**, respectively (Scheme 17).[30]



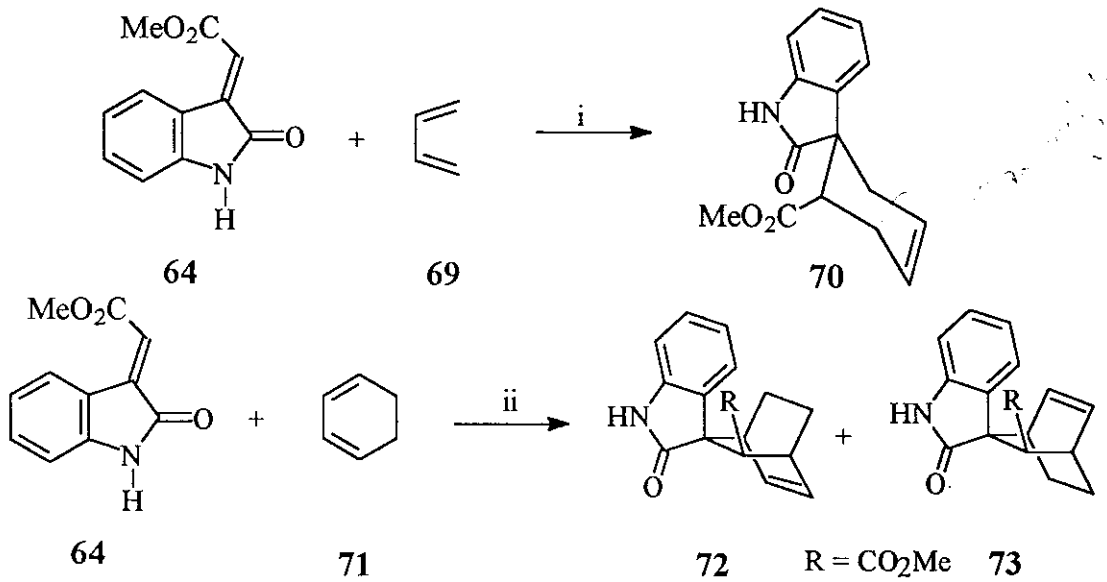
67 **64** **68**

i. Toluene, ST, 120 °C, 5 h

Scheme 17

These adducts are potentially useful intermediates for the synthesis of marine natural products such as surugatoxin, neosurugatoxin and prosurugatoxin.[30,33]

The cycloaddition of oxoindolinylidene with isoprene was studied by Richards *et al.*[31] In the presence of aluminium chloride, 1,3-butadiene and 1,3-cyclohexadiene underwent facile Diels-Alder addition with oxoindolinylidene acetate at 0 °C (Scheme 18).[32]



64 **69** **70**

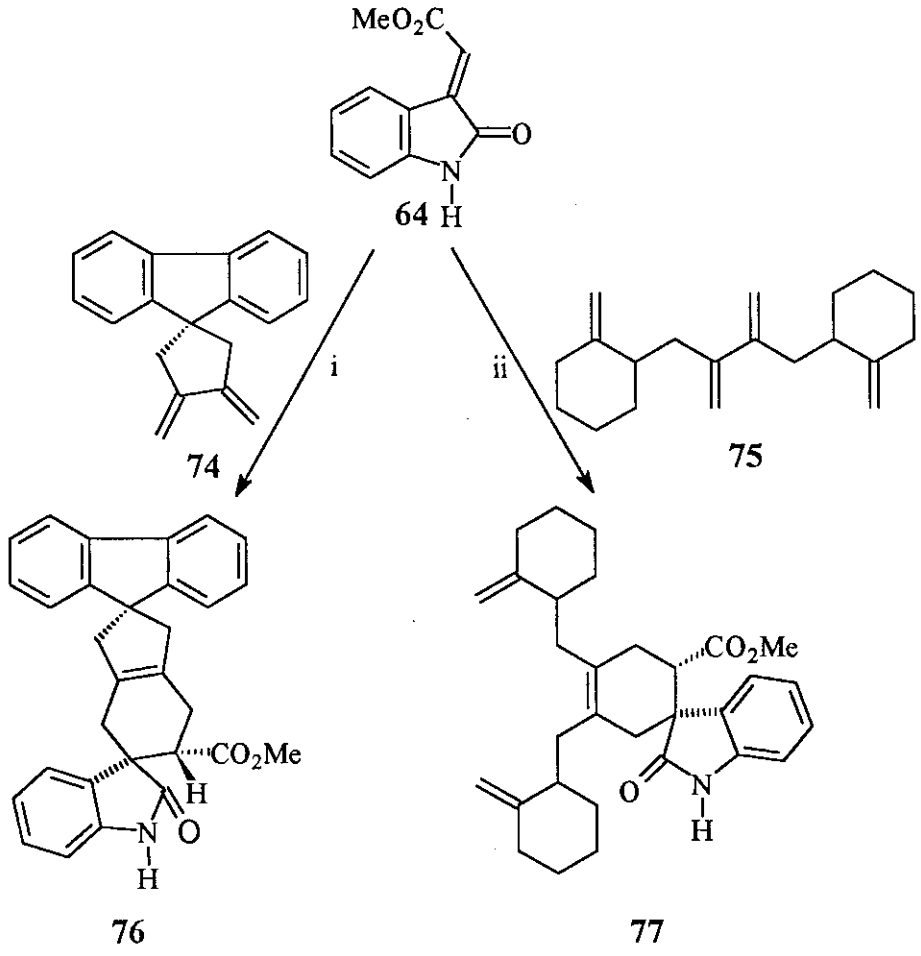
64 **71** **72** R = CO_2Me **73**

i. CH_2Cl_2, $AlCl_3$, 0 °C, 5 h, 92%

ii. CH_2Cl_2, $AlCl_3$, 0 °C, 95% (5.5:1)

Scheme 18

The ability of oxoindolinylidenes to take part in Diels-Alder reactions has been utilized by Grigg *et al.* in the construction of complex molecules.[34] Thus, the dienes **74** and **75** when treated with oxoindolinylidene **64** afforded the Diels-Alder adducts **76** and **77**, in good yields (Scheme 19).



i. $CHCl_3$, 60 °C, 80%; ii. Benzene, 80 °C, 48 h, 84%

Scheme 19

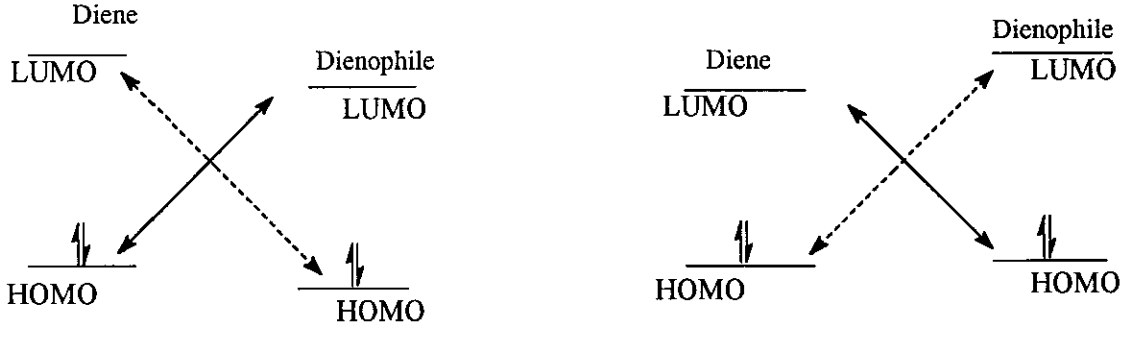
In spite of all the reports on the Diels-Alder cycloaddition reactions of oxoindolinylidenes, dipolar cycloaddition reactions of the latter have received only scant attention. The available data mainly consists of the reactions of diazomethane and azomethine ylides. A detailed account of these reactions is given in Chapter 2.

1.6. THEORETICAL CONSIDERATIONS

In order to gain insight into the mechanism of cycloaddition reactions, Woodward-Hoffman rules have been used.[35-38] The Woodward-Hoffman orbital symmetry rules apply only to concerted reactions and are based on the principle that a reaction takes place in such a way as to maintain maximum bonding throughout the course of the reaction. The postulates of Fukui's Frontier Orbital Theory, regarding the interaction of molecular orbitals in pericyclic reactions offer a simpler way to understand the rate of reaction as well as chemo- and regioselectivities.

1.6.1. [4+2] CYCLOADDITION REACTIONS

As delineated by Fukui, the rate of a Diels-Alder reaction is determined by the degree of interaction between the HOMO of one component with LUMO of the other; smaller the energy gap between the orbitals, more readily the reaction proceeds. In normal Diels-Alder reactions, HOMO of the diene interacts with the LUMO of the dienophile. However, in some other cases, the LUMO of the diene interacts with the HOMO of the dienophile and these reactions are called inverse electron demand Diels-Alder reactions (Figure 3).[36]



Normal Diels-Alder Reaction **Inverse Electron Demand Diels-Alder Reaction**

Figure 3

Diels-Alder reactions usually proceed with high regioselectivity. The regioselectivity can be explained on the basis of the coefficients of the frontier orbitals. The favorable overlap between the orbitals with comparable coefficients determines the regioselectivity of addition. Stereoselectivity of Diels-Alder reactions depends mainly on the secondary orbital overlap in the transition state. The secondary orbital overlap stabilizes *endo* transition state of [4+2] addition and favors the formation of kinetically preferred *endo* isomer.

1.6.2. 1,3-DIPOLAR CYCLOADDITION REACTIONS

The 1,3-dipole is defined as a species that is represented by zwitterionic octet structures and undergoes 1,3-dipolar cycloaddition reactions to a multiple bond system, the dipolarophile.[38]

All 1,3-dipoles have a three atomic π orbital system containing four electrons, analogous to an allyl anion. The 1,3-dipoles contain an onium centre atom 'b' whose charge compensates the negative charge distributed in the two all octet structures over the two termini 'a' and 'c' and the whole system can be considered as a heteroallyl anion, which bears no net charge (Figure 4).

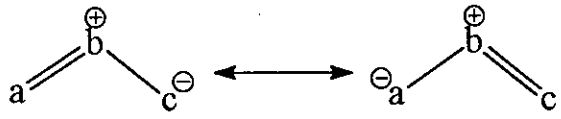
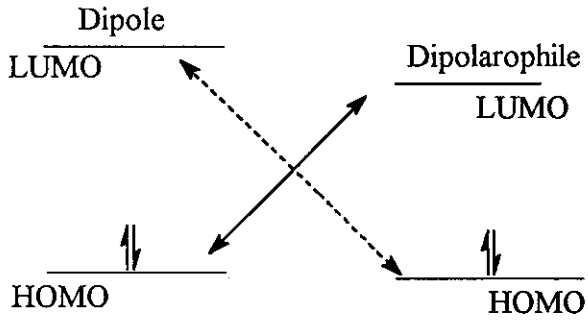


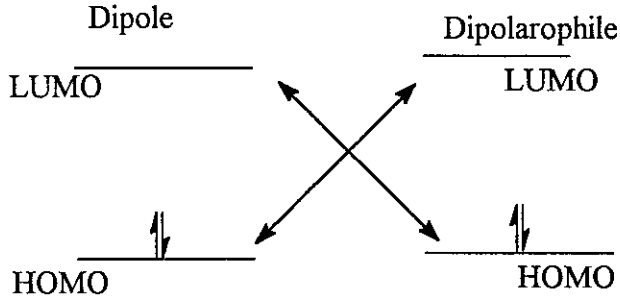
Figure 4

1,3-Dipolar cycloadditions are single step, four centered, concerted reactions, in which two new sigma bonds are formed simultaneously and are susceptible to electronic and steric influences, which affect the nature of the transition state.

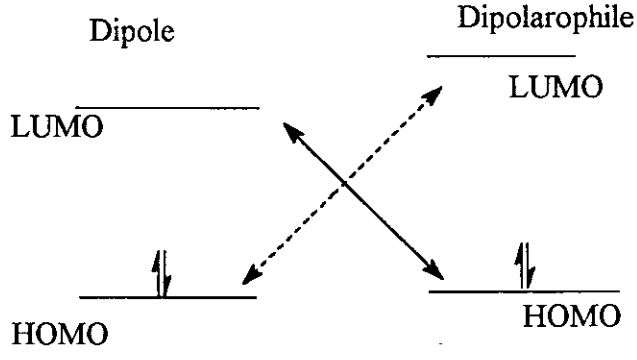
Depending on the relative disposition of the 1,3-dipole and dipolarophile, 1,3-dipolar cycloaddition reactions are classified into three types (Figure 5).



Type 1 (HOMO Controlled)



Type 2 (HOMO-LUMO Controlled)



Type 3 (LUMO Controlled)

Figure 5

1. HOMO controlled, in which the interaction of the dipole HOMO with dipolarophile LUMO is the greatest.

2. Both HOMO and LUMO controlled, which involves large interaction between both frontier orbitals.
3. LUMO controlled, in which the interaction of the dipole LUMO with the dipolarophile HOMO is the greatest.

The substituent that raises the dipole HOMO energy or lowers the dipolarophile LUMO energy will accelerate HOMO-controlled reactions and decelerate LUMO-controlled reactions and *vice versa.* HOMO-LUMO controlled reactions will be accelerated by an increase of either frontier orbital interaction.

1.7. DEFINITION OF THE PROBLEM

The above discussion reveals that inspite of the enormous synthetic potential of dipolar cycloaddition reactions of oxoindolinylidenes, such reactions especially those involving carbonyl ylides to the latter remain practically unexplored. Against the literature backdrop and in the context of our general interest in heterocyclic construction by dipolar cycloaddition reactions, it was decided to explore such reactions of oxoindolinylidenes with carbonyl ylides.

In the second phase of our work, in the context of the synthetic potential of quinolinone quinone methides, it was of interest to study the cycloaddition profile of these methides from practical and theoretical standpoints.

The facile one pot synthesis of dihydronaphthopyrandiones by the hetero Diels-Alder reactions of 3-methylenenaphthalenetrione, a quinone methide accessible *via* Knoevenagel condensation of 2-hydroxynaphthoquinone, formed the subject of investigation in the next phase. As a continuation of these studies, the synthesis of dihydronaphthofurandiones by cerium(IV) ammonium nitrate (CAN) mediated oxidative addition of 2-hydroxy-1,4-naphthoquinone was also explored.

The results of these investigations are presented in the following chapters.

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CHAPTER 2

DIPOLAR CYCLOADDITION REACTIONS OF 2-OXOINDOLIN-3-YLIDENES

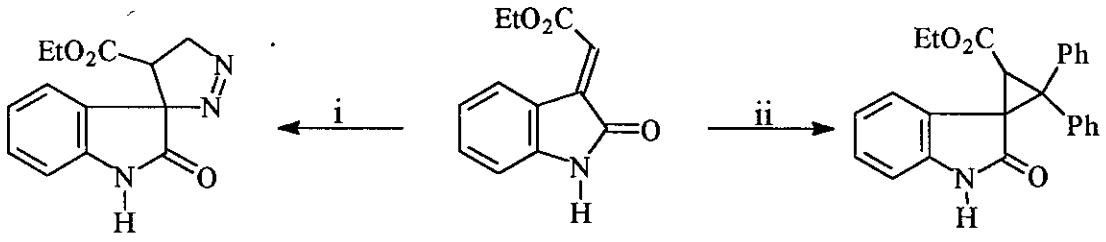
2.1. INTRODUCTION

The 1,3-dipolar cycloaddition reactions constitute one of the most important classes of organic reactions. The ease of generation of various dipoles and the highly regio and stereoselective nature of their addition to π systems have contributed to the universal acceptance of dipolar cycloadditions for the construction of highly complex and valuable heterocycles.[1]

In the context of the general interest of our research group in developing novel heterocyclic synthesis using dipolar cycloadditions,[2] 2-oxoindolin-3-ylidenes (*e.g.* 1) were perceived as excellent dipolarophiles. Although the addition of various dipoles to these systems can potentially lead to novel spiroindolenin framework,[3] not much effort has been made in this direction; the available data is mainly derived from the reactions of diazoalkanes[4] and azomethine ylides.[5-8]

2.1.1. REACTION WITH DIAZOALKANES

The report on the addition of diazoalkanes to 2-oxoindolin-3-ylidenes in 1978 by Franke constitutes the first example of 1,3-dipolar cycloaddition to this system (Scheme 1).[4]



3 **1** **2**

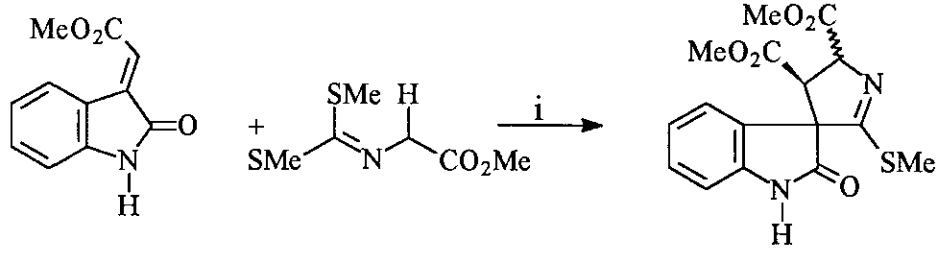
i. CH_2N_2, $(C_2H_5)_2O$, RT; ii. Ph_2CN_2, DMF, RT

Scheme 1

2.1.2. REACTION WITH AZOMETHINE YLIDES

There has been considerable work on the reaction of azomethine ylides with oxoindolinylidene derivatives. Grigg and co-workers have exploited the dipolarophilicity of oxoindolinylidenes in their study of various *in situ* generated dipoles.[5,6,9]

The oxoindolinylidene **4**, when treated with the iminothiocarbonate **5** in the presence of acetic acid in refluxing xylene, afforded a 1:1 mixture of *cis* and *trans* isomers of the cycloadduct **6**, separable by fractional crystallization (Scheme 2).[3a]

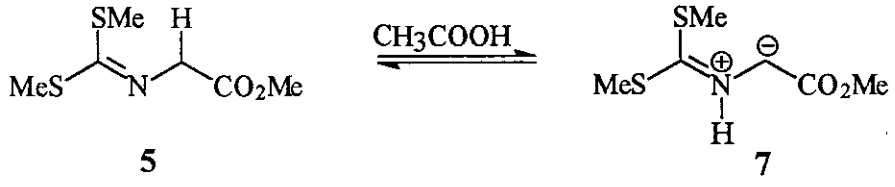


4 **5** **6**

i. Xylene, 144 °C, CH_3COOH, 5 days, 50% (1:1)

Scheme 2

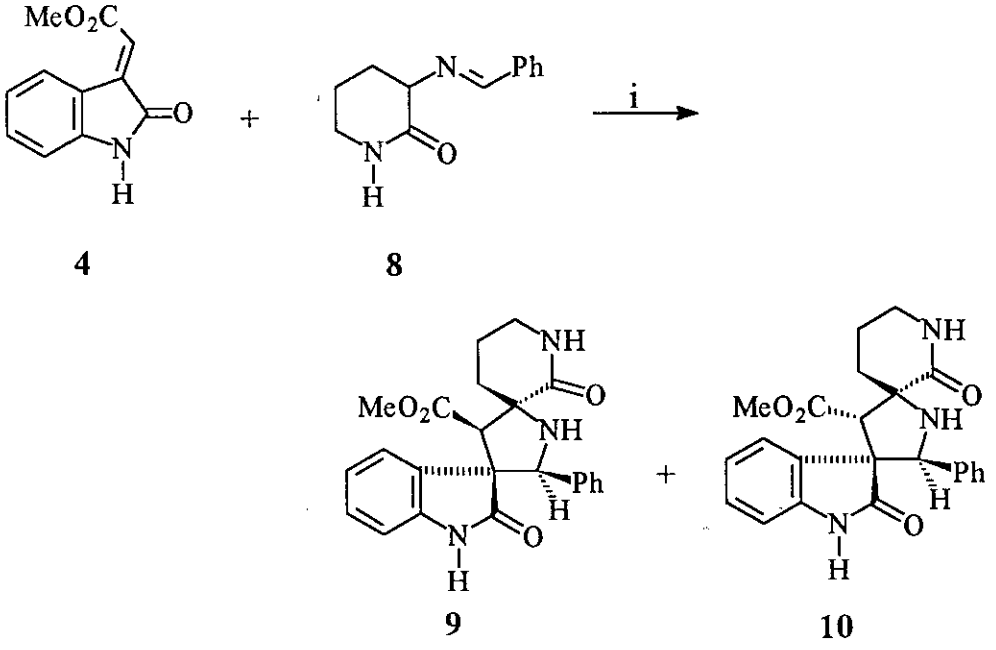
This cycloaddition is proposed to involve tautomeric generation of the azomethine ylide **7** (Scheme 3), followed by cycloaddition and then elimination of methane thiol from the initial cycloadduct.



5 **7**

Scheme 3

The azomethine ylides generated by thermal prototropy of imines undergo cycloaddition reaction with the oxoindolinylidene. Thus, the imine **8**, when refluxed in xylene in the presence of oxoindolinylidene **4**, afforded the cycloadducts **9** and **10** (Scheme 4).[5]



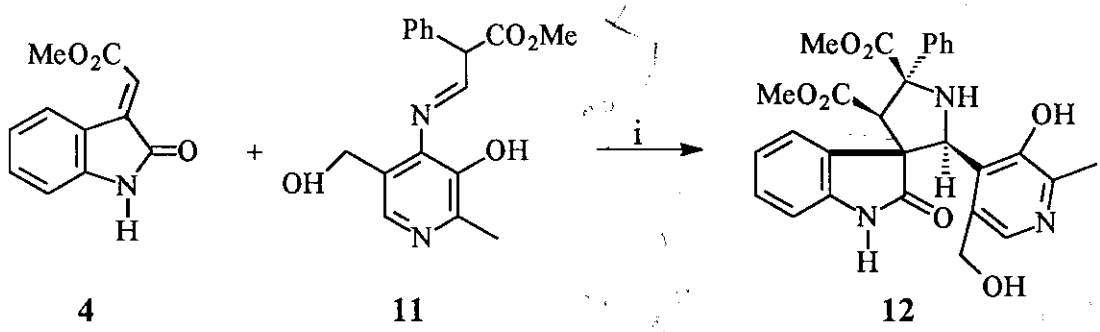
4 **8**

9 **10**

i. Xylene, 130 °C, 36 h, 84% (1.2:1)

Scheme 4

Pyridoxal imine **11** also undergoes similar cycloaddition with 2-oxo-indolinylidene acetate *via* an azomethine ylide (Scheme 5).[6]

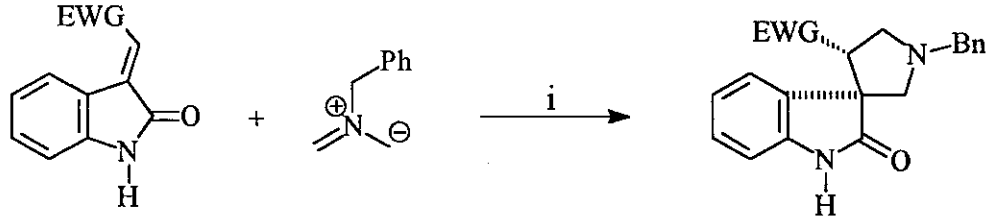


4 **11** **12**

i. Xylene, 130 °C, 5 days, 49%

Scheme 5

The 2-oxoindolin-3-ylidene derivatives **4** and **13** reacted smoothly with nonstabilized azomethine ylide **14**, generated by desilylation route from N-benzyl-N-(methoxymethyl)-N-[(trimethylsilyl)methyl]amine at room temperature, giving rise to cycloadducts **15** and **16**, respectively in good yields (Scheme 6).[7]



4, EWG = CO_2Me **14** **15** (92%)

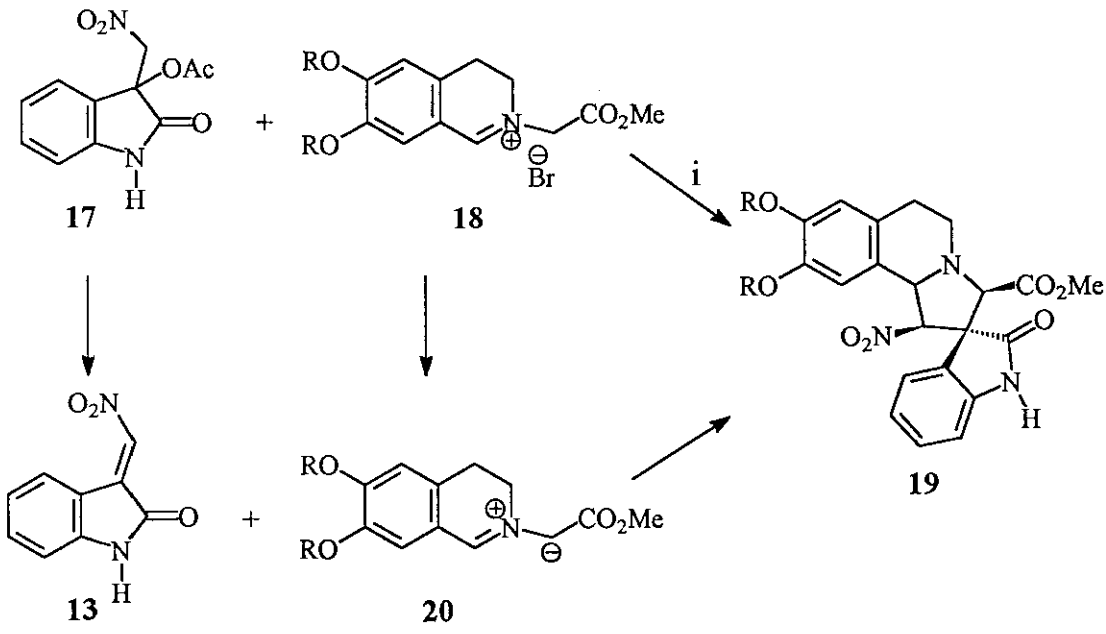
13, EWG = NO_2 **16** (78%)

i. Toluene, RT, 24 h

Scheme 6

Nyerges *et al.* have reported the tandem *in situ* generation and reaction of nitromethylene oxindole and azomethine ylide.[8] When a mixture of oxindole **17**

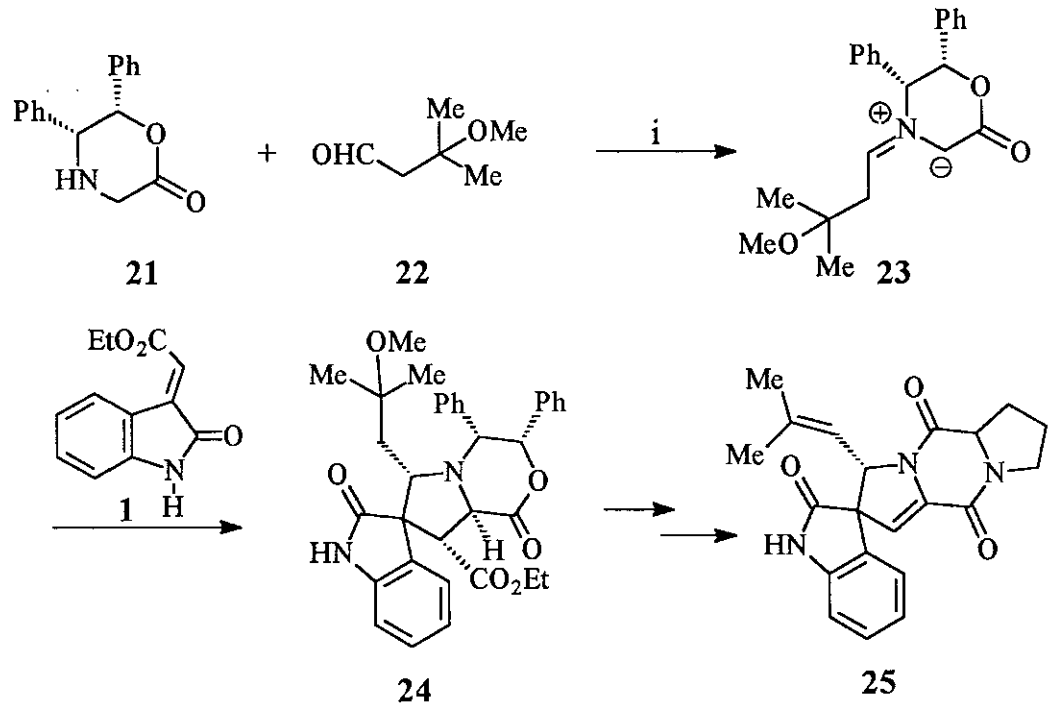
and isoquinolinium salt **18** was treated with 2 equivalents of triethylamine at room temperature, the spiroindolenin system **19** was formed. The actual reacting species are nitromethylene oxindole **13** and azomethine ylide **20** (Scheme 7).



i. Et_3N, Toluene, RT, 1 h, 73-75%

Scheme 7

Recently, the reaction of oxoindolinylidene **1** with azomethine ylide was made use of in the asymmetric synthesis of (+) and (-)spirotryprostatins.[10] The core pyrrolidinone ring of spirotryprostatin B **25** was formed through the reaction of a chiral azomethine ylide **23** with the oxoindolinylidene **1** (Scheme 8).

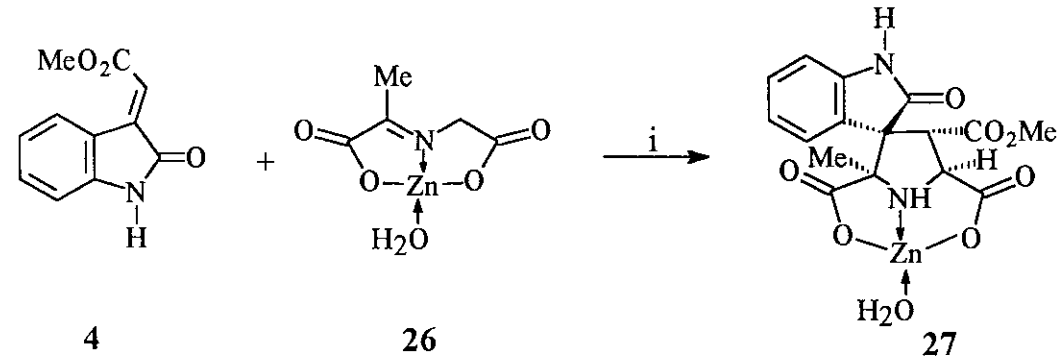


i. Toluene, 3Å Molecular Sieves

Scheme 8

2.1.3. REACTION WITH MISCELLANEOUS SYSTEMS

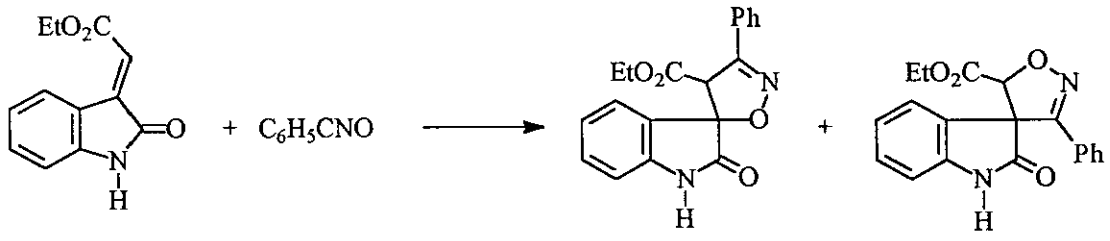
The metallo-1,3-dipoles generated from copper(II) and zinc(II) complexes undergo cycloaddition with oxoindolinylidene acetate to yield the corresponding cycloadducts. The reaction between the zinc complex **26** and the oxoindolinylidene 4 is illustrative (Scheme 9).[9]



i. Et_3N, Pyridine, 12 h, 74%

Scheme 9

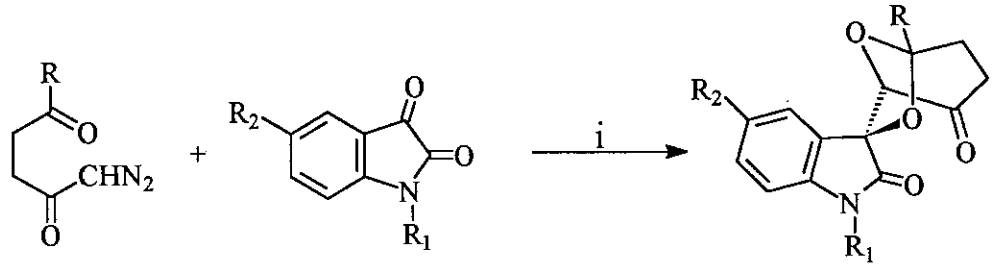
An isolated example of the addition of benzonitrile oxide to oxoindolinylidene acetate is available in the literature (Scheme 10).[4]



1 **28** **29** **30**

Scheme 10

The above discussion reveals that 1,3-dipolar cycloaddition of carbonyl ylides to oxoindolinylidenes has remained unexplored. Conceivably, 1,3-dipolar cycloaddition reactions of carbonyl ylides to π-bonds offer a very convenient strategy for the synthesis of structurally complex oxygen heterocycles.[11] Recent experiments in our laboratory have shown that carbonyl ylides can be added to isatins at room temperature yielding spiroindolenin systems (Scheme 11).[2d]



31 **32** **33**

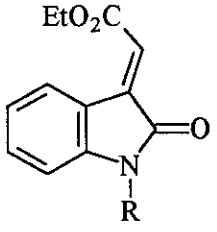
i. $Rh_2(OAc)_4$, Toluene, Argon, RT, 3 h, 60-80%

Scheme 11

Against this background, we have undertaken some investigations on the dipolar cycloaddition of carbonyl ylides to oxoindolinylidenes. The results of these investigations are delineated in the following section.

2.2. RESULTS AND DISCUSSION

The oxoindolinylidene acetates and carbonyl ylides selected for our study are shown in Figures 1 and 2.



1, R = H; **34**, R = Me; **35**, R = Bn

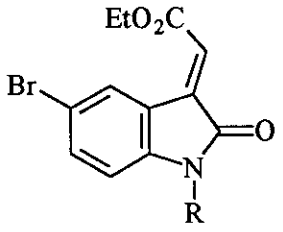


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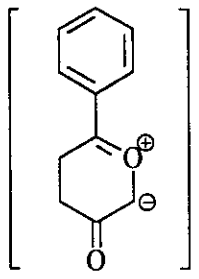
Figure 1



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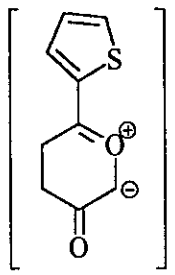

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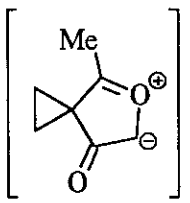
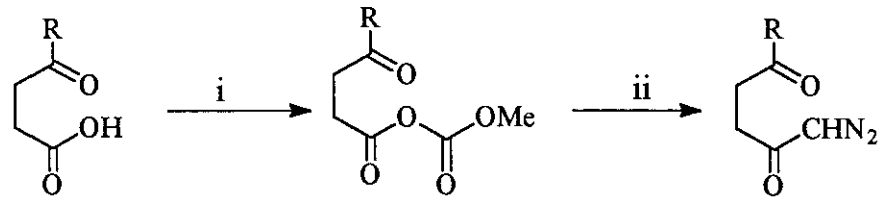


39

Figure 2

The oxoindolinylidene acetates were prepared from the corresponding isatins by Wittig reaction.[12] The diazoketones required for our study were prepared from the appropriate carboxylic acids by known literature procedures (Scheme 12).[13, 14]



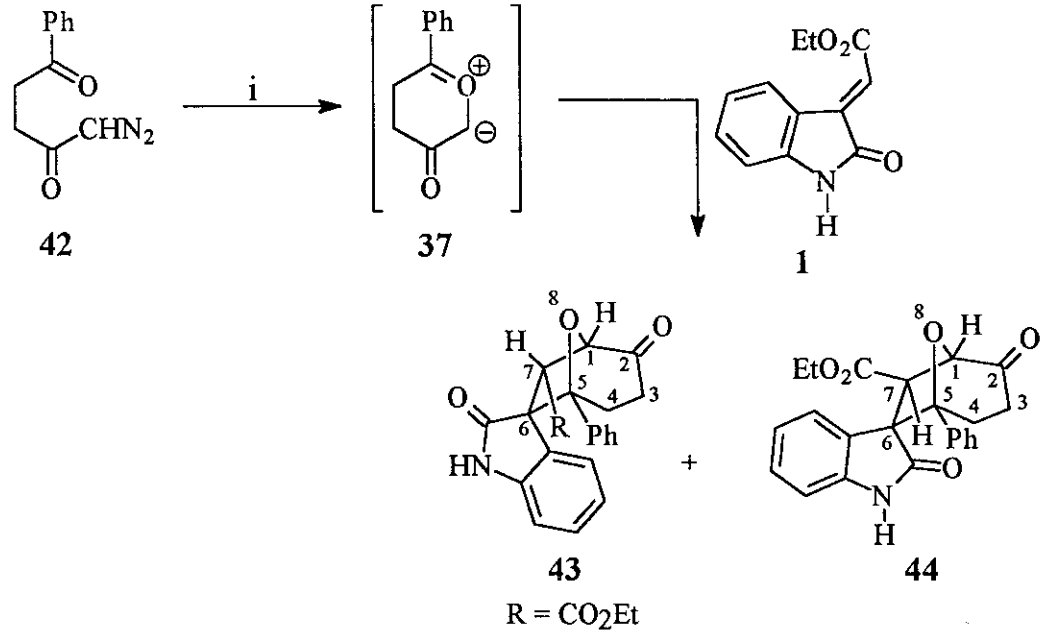
40 **41** **31**

i. $ClCO_2Me$, Et_3N; ii. CH_2N_2

Scheme 12

2.2.1. REACTION WITH SIX MEMBERED CARBONYL YLIDES

Our studies were initiated with the rhodium(II) acetate catalyzed decomposition of 1-diazo-5-phenyl-2,5-pentanedione **42** in the presence of 3-ethoxycarbonylmethylene-2-oxoindole **1**. The reaction proceeded smoothly to afford *endo* and *exo* adducts **43** and **44** in a total yield of 98% (Scheme 13).



i. $Rh_2(OAc)_4$, Toluene, RT, Argon, 45 min, 98% (1.1:1)

Scheme 13

The cycloadducts were separated by column chromatography and characterized on the basis of spectroscopic data. The IR spectrum of the *endo* adduct **43** showed the -NH absorption band at 3225 cm^{-1} and the carbonyl absorption bands were observed at 1734 and 1707 cm^{-1}. The regio and stereochemical assignment of the structure is derived from proton NMR analysis. In the ^1H NMR spectrum, the -NH proton appeared as a singlet at δ 8.18 (exchangeable with D_2O). The bridgehead proton on C-1 appeared as a doublet at δ 4.81 (J = 8.1 Hz) and the proton on C-7 resonated as a doublet at δ 4.11 (J = 8.4 Hz). The possibility of this adduct being the other regioisomer was discarded on the basis of coupling constant of these protons. For the other regioisomer there will be no vicinal coupling for the bridgehead and angular protons. The observed coupling constant indicated that this is the *endo* adduct with the structure **43**. In bicyclic systems, the bridgehead proton is expected to show a vicinal coupling of 4-8 Hz with the *exo* proton and a J value of 0-3 Hz is expected with an *endo* proton. Thus, the J value of 8.6 Hz in this compound indicates that this has the structure **43** with the proton on C-7 in the *exo* position. One of the protons of the methylene moiety (on C-3) displayed a multiplet centered at δ 3.10. The other proton on the same carbon appeared as a multiplet centered at δ 2.71 along with one of the protons of the other methylene group (C-4). The remaining proton on C-4 was visible as a multiplet centered at δ 2.22 integrating for one proton. The methyl protons of the ester group showed a triplet at δ 0.81 (3H, J = 7.1 Hz). In the ^{13}C NMR spectrum, the three carbonyl signals were observed at δ 203.34 (C-2), 179.50 (ester carbonyl) and 168.44 (lactam carbonyl). The bridgehead carbon C-1 appeared at δ 82.25 and the signal due to the other bridgehead carbon C-5 was discernible at δ 87.75. The signal due to the spirocarbon was seen at δ 63.34. These assignments were confirmed by 2D NMR spectrum. The ^{13}C-^1H correlation spectrum was utilized

to assign the signals in the ^{1}H and ^{13}C NMR spectra and is illustrated in Figure 3.

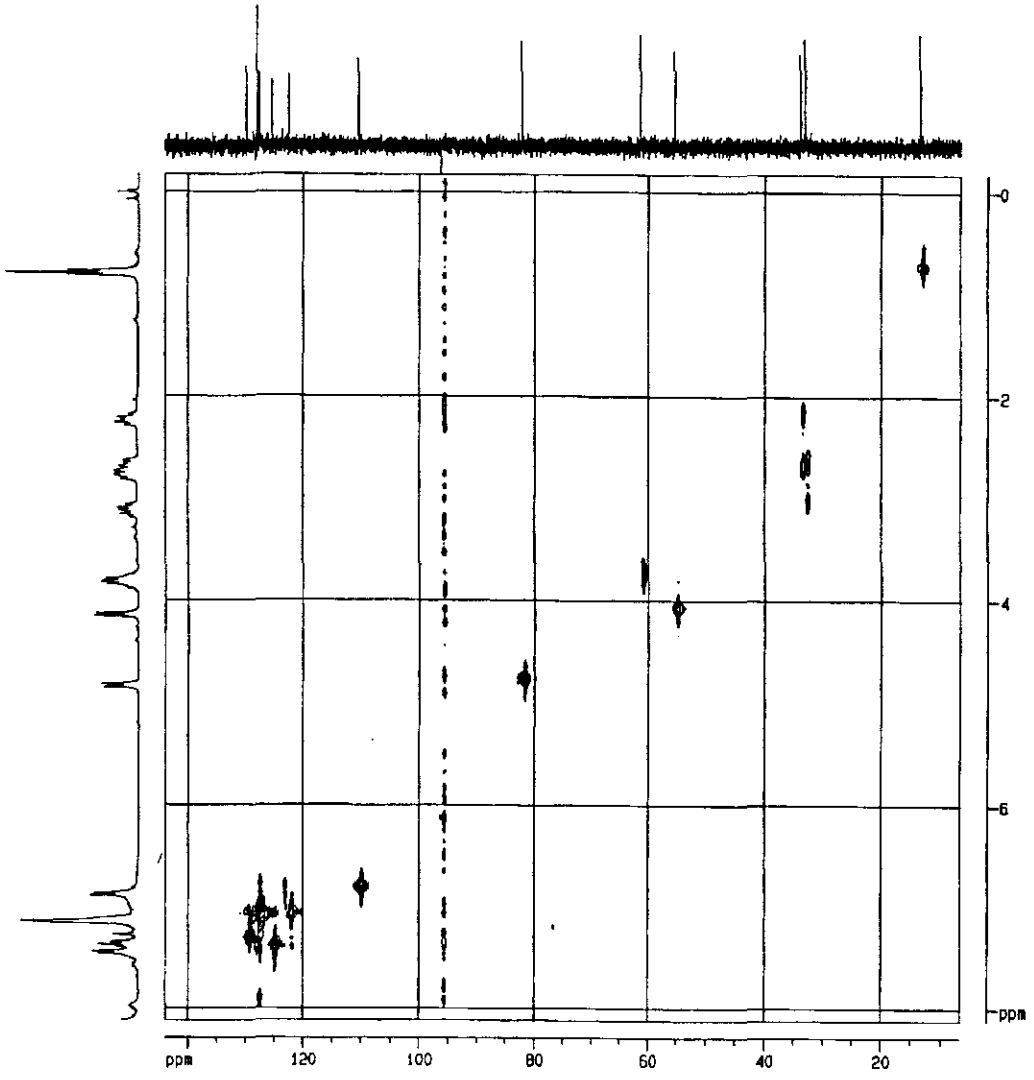


Figure 3. ^{13}C-^{1}H COSY spectrum of **43**

The figure clearly shows all the ^{1}H-^{13}C connectivities. Of these, the most diagnostic are the connections between δ 33.05-2.22 (2.76), 33.83-2.71 (3.07), 55.32-4.11 and 82.25-4.88. All the other signals in ^{1}H and ^{13}C NMR spectra were in good agreement with the assigned structure.

The IR spectrum of the *exo* adduct **44** showed two strong bands at 1735 and 1700 cm^{-1}. The -NH absorption band was observed at 3219 cm^{-1}. In the ^{1}H NMR spectrum, the bridgehead proton on C-1 and the proton on C-7 appeared as doublets at δ 5.18 (J = 3.1 Hz) and 3.82 (J = 3.1 Hz), respectively. The low coupling constant of 2.9 Hz between the bridgehead proton and the angular proton (on C-7) indicated that the carboxylate group is *exo*. The $-OCH_2$ protons were seen as a quartet at δ 3.65 (J = 6.9 Hz). The methylene protons on C-3 displayed a broad multiplet centered at δ 3.16, whereas the protons on the other methylene moiety appeared as two separate multiplets at δ 2.64 and 2.25 integrating for one proton each. The methyl protons of the ester functionality gave a triplet at δ 0.62 (J = 7.1 Hz). The -NH proton was visible at δ 8.35 as a singlet (exchangeable with D_2O). In the ^{13}C NMR spectrum, the signals due to the three carbonyl groups were visible at δ 205.75, 176.85 and 167.91. The bridgehead carbons C-1 and C-5 displayed signals at δ 81.00 and 90.05, respectively. The spiro carbon gave a peak at δ 63.01. Finally, the assigned structure was unequivocally established by single crystal X-ray analysis (Figure 4).

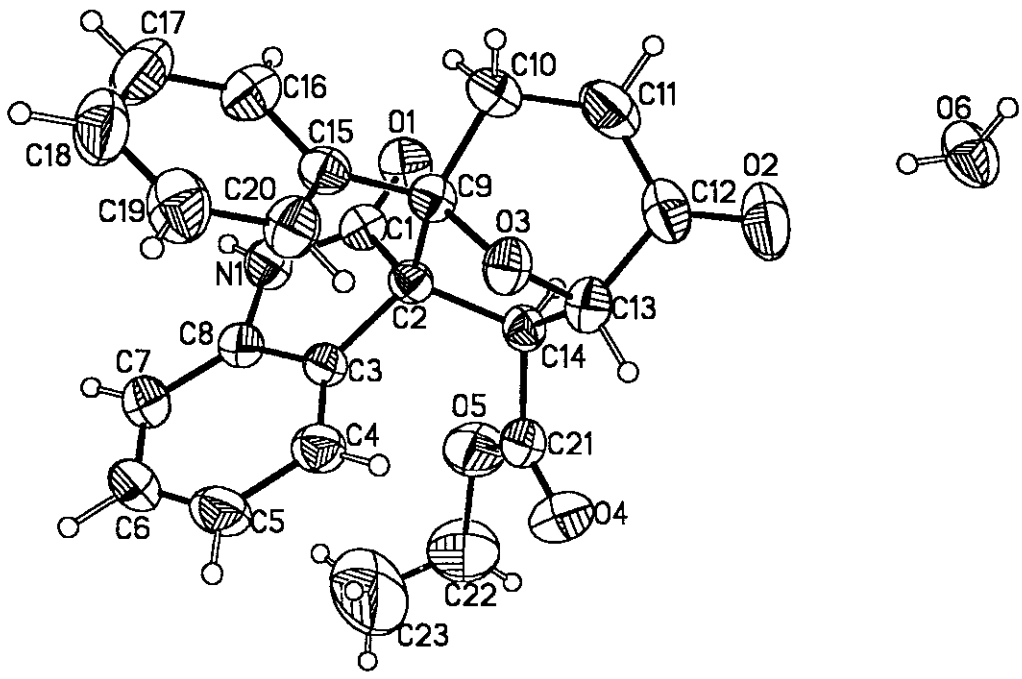
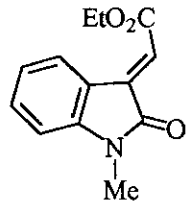
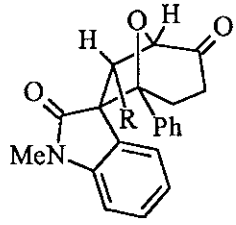
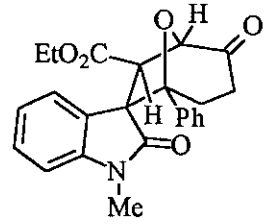
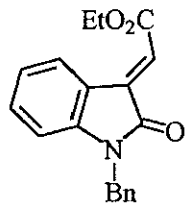
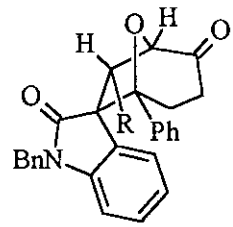
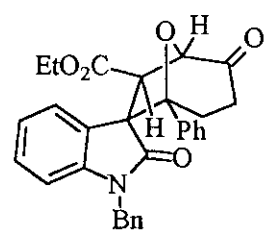
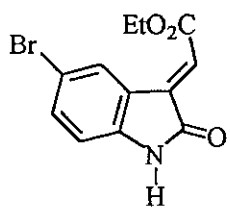
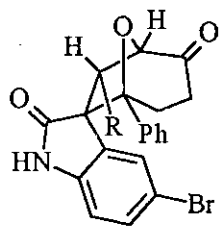
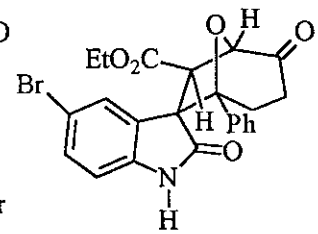


Figure 4. X-ray structure of **44**

Under similar experimental conditions, the reaction of oxoindolinylidene derivatives **34-36** with the diazoketone **42** furnished similar spiro-oxabicyclic compounds. The results are summarized in Table 1.

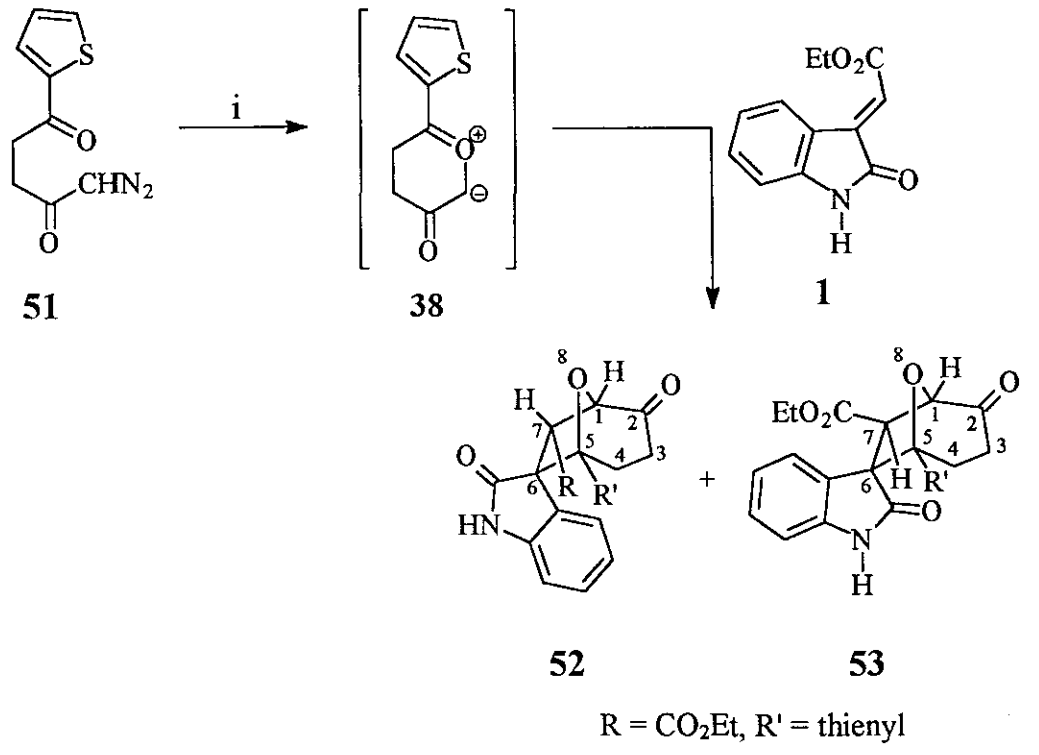
The cycloadducts were separated by column chromatography and characterized by spectroscopic methods. The adducts **49** and **50** were obtained as mixture after column chromatography and were separated by Pasteur style physical separation. All these compounds **45-50** showed characteristic carbonyl absorptions in their IR spectra and typical proton and carbon signals in the NMR spectra.

Table 1. Cycloaddition reactions of diazoketone **42** with oxoindolinylidenes

Entry	Oxoindolin-ylidene	Time (h)	Products	Yield (%)[a] (Ratio)
1	 **34**	2	 **45**  **46**	87 (98)* (2:1)
2	 **35**	1	 **47**  **48**	89 (97)* (2:1)
3	 **36**	0.5	 **49**  **50** R = CO_2Et	97 (2:1)

Reaction Conditions: $Rh_2(OAc)_4$, RT, Argon, [a]Isolated Yield, *Yield based on recovered oxoindolinylidene is given in parantheses.

Subsequent to these investigations, we became interested in the dipolar addition of the thienyl substituted carbonyl ylide **38** with the oxoindolin-ylidenes. The rhodium(II) acetate catalyzed decomposition of 1-diazo-5-(2-thienyl)-2,5-pentanedione **51** in a toluene solution of oxoindolinylidene **1** afforded the cycloadducts **52** and **53** in high yields (Scheme 14).



52 **53**

R = CO_2Et, R' = thienyl

i. $Rh_2(OAc)_4$, Toluene, RT, Argon, 30 min, 95% (2:1)

Scheme 14

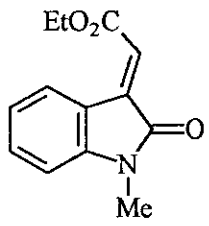
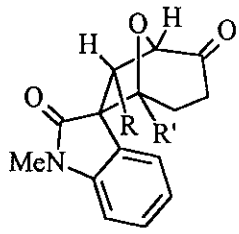
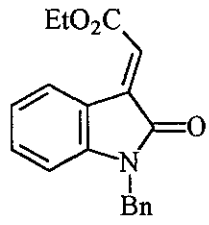
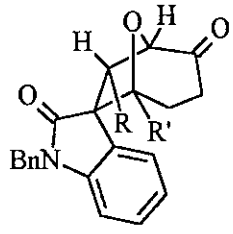
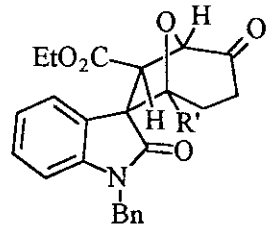
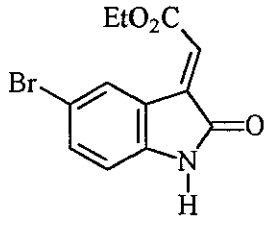
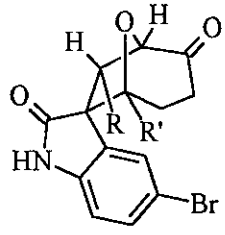
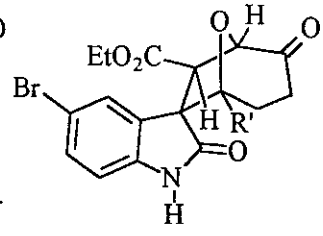
After chromatographic purification, the *exo* and *endo* adducts were obtained as a mixture in 2:1 ratio. These isomers were separated by fractional crystallization. The assignment of the structure is based on spectroscopic analysis. The IR spectrum of the *endo* adduct **52** showed the -NH absorption at 3318 cm^{-1}. The absorption due to the carbonyl groups were seen at 1737 and 1716 cm^{-1}. In the ^1H NMR spectrum, a singlet due to the -NH proton, exchangeable with D_2O, was seen at δ 8.43. The proton on the bridgehead carbon C-1 resonated as a doublet at δ 4.80 (J = 8.3 Hz) and the proton on the adjacent carbon C-7 displayed a doublet at δ 4.17 (J = 8.3 Hz). One of the methylene protons on the carbon α to the carbonyl group (C-3) gave a multiplet

centered at δ 3.10 whereas, the other proton on the same carbon resonated along with one of the protons of the neighbouring methylene group to give a broad multiplet centered at δ 2.70. The other proton on C-4 appeared as a multiplet centered at δ 2.38. In the ^{13}C NMR spectrum, the three carbonyl groups were discernible at δ 202.50, 179.41 and 168.53 corresponding to the keto, ester and lactam moieties, respectively. The signal due to the spirocarbon was observed at δ 63.74. All the other signals were in good agreement with the assigned structure.

The adduct **53** showed the -NH absorption band at 3171 cm^{-1} in IR spectrum and the carbonyl absorption bands were seen at 1740 and 1696 cm^{-1}. The bridgehead proton on C-1 and the proton on the α carbon C-7 appeared as doublets at δ 5.17 (J = 1.3 Hz) and 3.82 (J = 2.8 Hz), respectively. In the ^{13}C NMR spectrum, the signals corresponding to the carbonyl groups were visible at δ 204.96, 176.25 and 167.73 and the spiro carbon displayed the signal at δ 63.55. The two bridgehead carbons C-1 and C-5 gave peaks at δ 81.46 and 89.19, respectively. All the other signals in the ^{1}H and ^{13}C NMR spectra were in good agreement with the assigned structure.

Under similar experimental conditions, oxoindolinylidene acetates **34**, **35** and **36** also underwent facile 1,3-dipolar cycloaddition with the carbonyl ylide **38** formed by the rhodium(II) acetate catalyzed decomposition of the diazoketone **51**. The results of these experiments are summarized in Table 2. As usual, separation of the cycloadducts was effected by column chromatography followed by fractional crystallization. In the case of bromocompounds **57** and **58**, the final separation of the isomers was carried out by Pasteur style physical separation.

Table 2. Reaction of oxoindolinylidenes with the diazocompound **51**

Entry	Oxoindolin-ylidene	Time (h)	Products	Yield (%)[a] (Ratio)
1	 **34**	1.5	 **54**	95 (1:0)
2	 **35**	1	 **55**  **56**	88 (98)* (1.1:1)
3	 **36**	0.5	 **57**  **58**	70 (82)* (2:1)

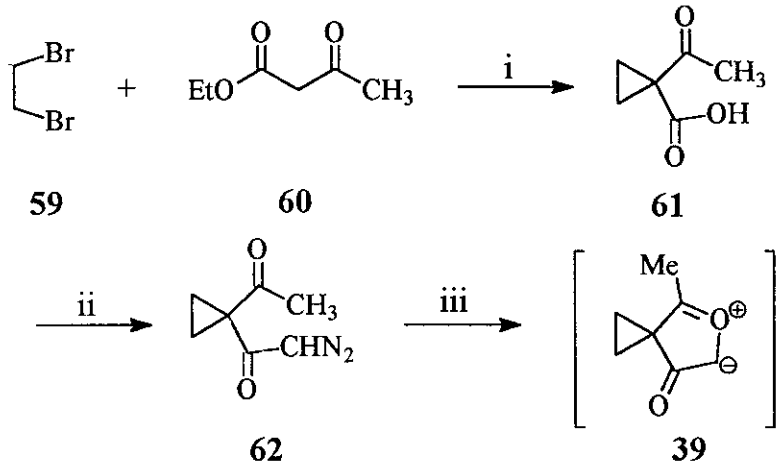
R = CO_2Et, R' = thienyl

Reaction conditions: $Rh_2(OAc)_4$, Toluene, RT, Argon, [a]Isolated yield, *Yield based on recovered oxoindolinylidene is given in parantheses.

2.2.2. REACTION WITH FIVE MEMBERED CARBONYL YLIDE

After having studied the reactivity of oxoindolinylidenes towards six membered carbonyl ylides, we turned our attention to the reaction of oxoindolinylidene acetates towards a five membered carbonyl ylide. The carbonyl ylide precursor **62** was prepared from the corresponding carboxylic

acid which in turn was prepared from ethyl acetoacetate and 1,2-dibromoethane (Scheme 15).[15]

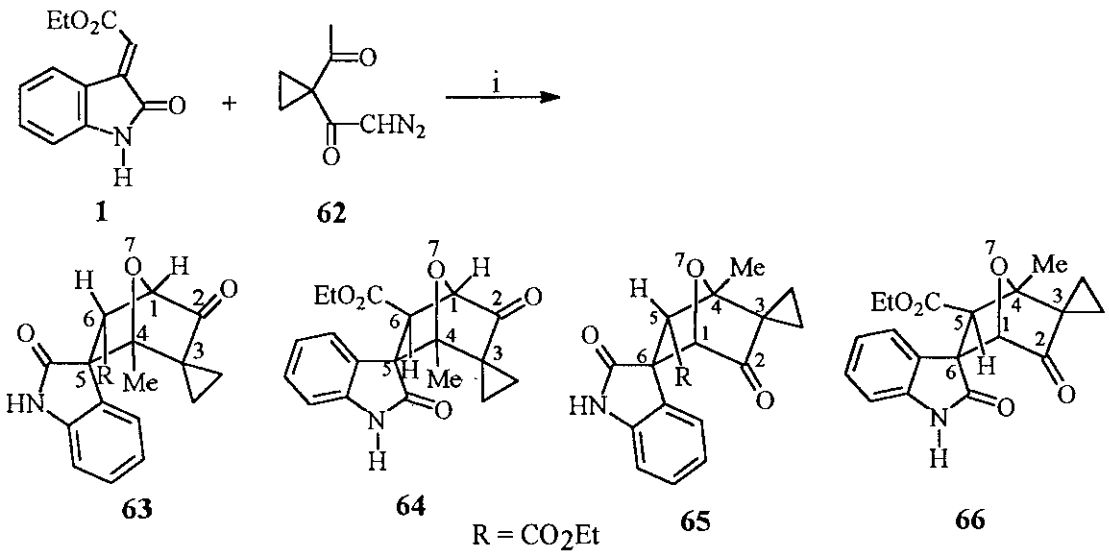


59 **60** **61** **62** **39**

i. NaOH, H_2O; ii. (a) $ClCO_2Me$, Et_3N (b) CH_2N_2; iii. $Rh_2(OAc)_4$

Scheme 15

When a solution of 1-acetyl-1-diazoacetyl cyclopropane **62** and oxoindolinylidene **1** was treated with catalytic amount of rhodium(II) acetate at room temperature, the reaction afforded all the four possible isomeric products as shown in Scheme 16.



1 **62** **63** **64** **65** **66**

R = CO_2Et

i. $Rh_2(OAc)_4$, Toluene, Argon, RT, 30 min, 93% (2:2:3:2)

Scheme 16

The products were separated by column chromatography and fractional crystallization. The *exo* adducts **64** and **66** were obtained as a mixture after chromatography. Further separation of these products was effected by fractional crystallization. The structures of the products were ascertained on the basis of spectroscopic analysis. The FT-IR spectrum of the adduct **63** showed the -NH absorption band at 3193 cm^{-1} and the carbonyl absorption peaks were seen at 1762 and 1709 cm^{-1}. In the ^1H NMR spectrum, the -NH proton (exchangeable with D_2O) resonated to give a singlet at δ 8.98. The bridgehead proton on C-1 and the proton on C-6 displayed a doublet at δ 4.89 (J = 5.6 Hz, 1H) and 3.99 (J = 5.6 Hz, 1H), respectively. The coupling constant of these protons is characteristic of the *endo* adduct **63**. The bridgehead methyl group gave a singlet at δ 1.18. The characteristic carbonyl signals in the ^{13}C NMR spectrum were observed at δ 208.49, 179.97 and 167.79.

The *exo* isomer **64** exhibited the -NH absorption band at 3204 cm^{-1} and the carbonyl absorption peaks at 1763 and 1710 cm^{-1}. In the ^1H NMR spectrum, the bridgehead proton displayed a singlet at δ 5.10 and the proton on the vicinal carbon showed a singlet at δ 3.61.[#] The carbonyl groups displayed ^{13}C signals at δ 210.25, 176.51 and 168.45.

In the IR spectrum of the cycloadduct **65**, characteristic -NH and carbonyl absorption peaks were seen at 3281 and 1730 cm^{-1}, respectively. The -NH proton signal was visible at δ 9.02 in ^1H NMR spectrum. The bridgehead proton and the methine proton appeared as singlets at δ 4.53 and 3.66 respectively. In the ^{13}C NMR spectrum, the carbonyl signals were observed at δ 207.36, 180.03 and 168.15.

The *exo* adduct **66** displayed the -NH absorption band at 3187 cm^{-1} and the carbonyl absorptions were seen at 1747 and 1707 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum, the -NH signal was observed at δ 9.04. The bridgehead

[#] In high resolution NMR, these protons showed a vicinal coupling of 0.8 Hz.

proton resonated to give a singlet at δ 4.27 and the methine proton was discernible at δ 3.56. The ^{13}C NMR spectrum showed the carbonyl peaks at δ 207.56, 175.98 and 167.97.

These assignments were confirmed with the help of detailed ^{1}H NMR analysis. NOESY and nOe difference experiments were carried out on these samples to assign the resonances and to establish the molecular structure.

The adduct **64** showed characteristic coupling of 0.8 Hz for the bridge-head proton which indicated that the protons involved are attached to vicinal carbons in the norbornane framework and that the proton on the adjacent carbon is on the *endo* side of the bicyclic system. NOESY spectrum showed cross peaks between H15-Me17, Me17-H15, Me17-H16 and H4-H5. The nOe intensities measured by difference nOe experiments and the NOESY spectrum are shown in Figures **5a** and **5b**.

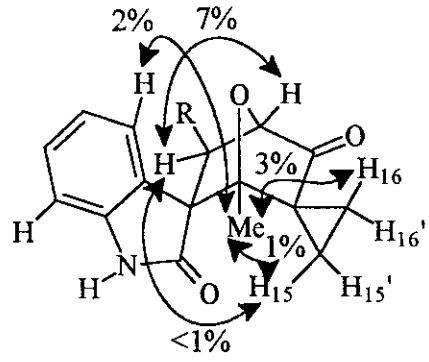


Figure 5a. Selected nOe data of **64**

The structure of **65** was ascertained with the help of NOESY and nOe difference experiments. The characteristic NOESY cross peaks observed are shown in Figure 6a.

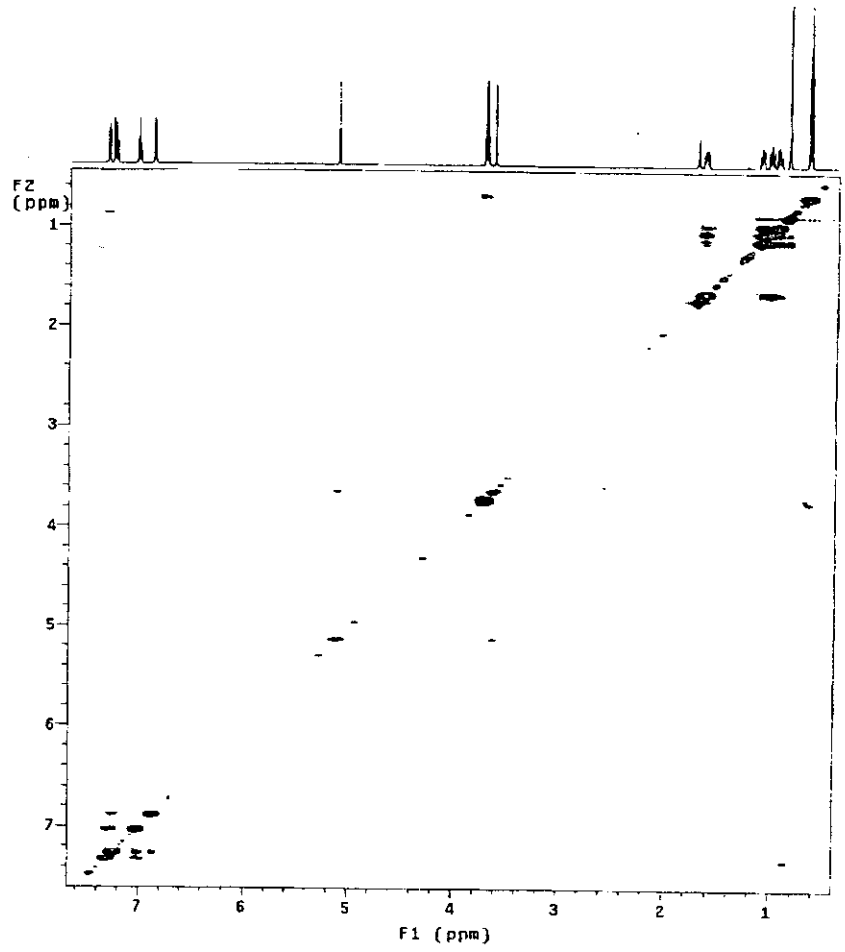


Figure 5b. NOESY spectrum of **64**

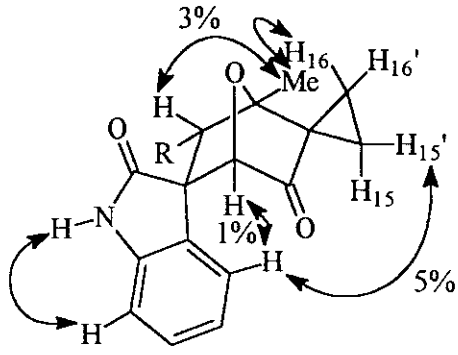


Figure 6a. Selected NOESY and nOe data of **65**

The *endo* structure of the adduct was confirmed by the nOe of H13-H5 = 5% which is possible only if the aromatic ring is *endo.* The nOe difference spectrum is displayed in Figure 6b.

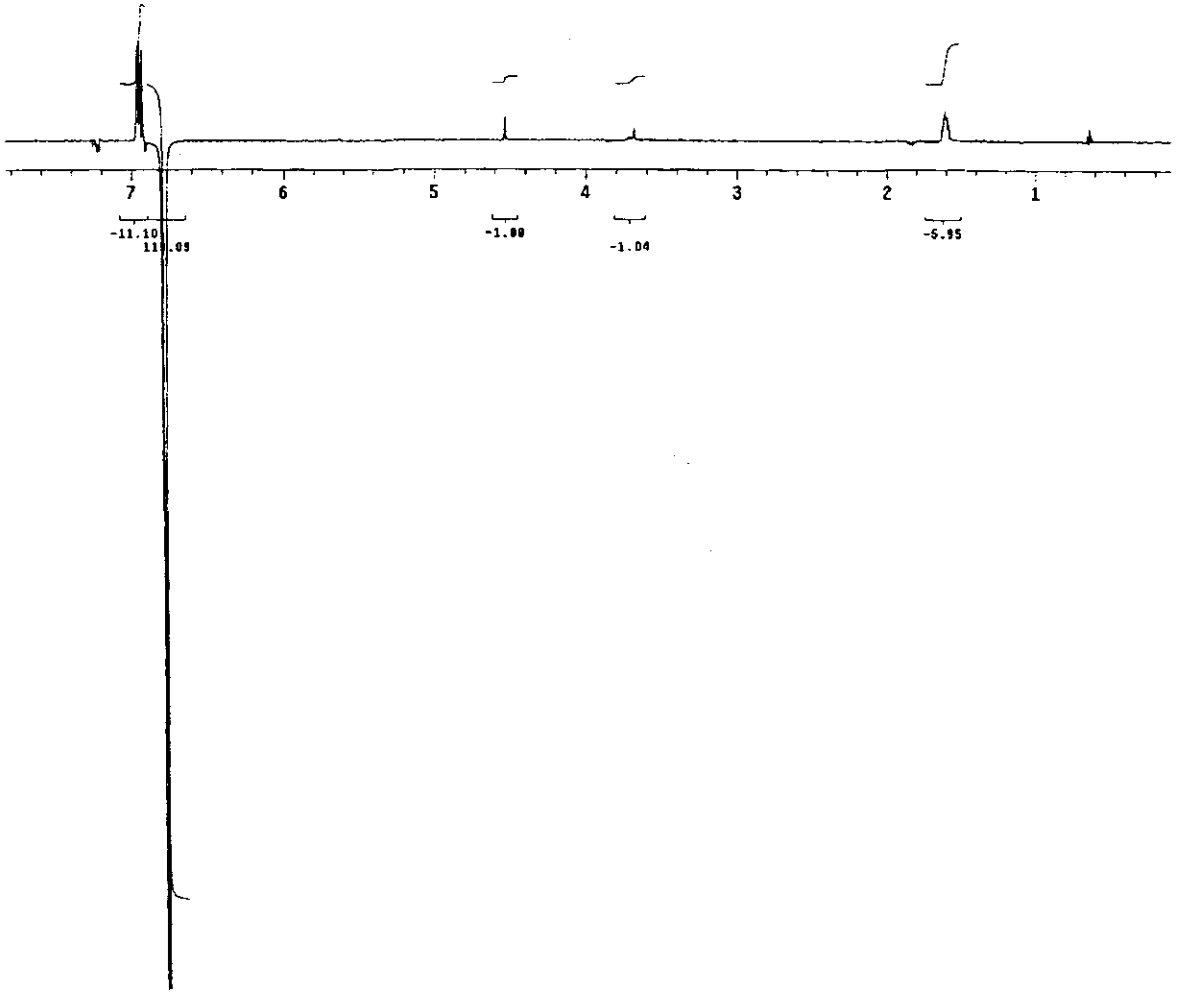
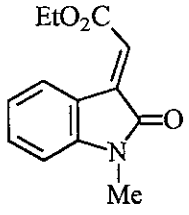
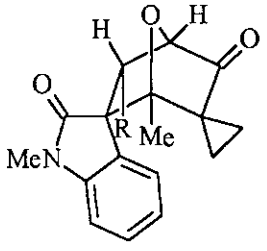
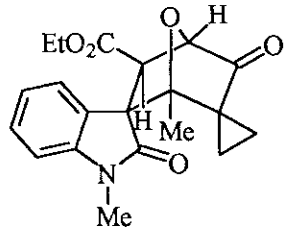
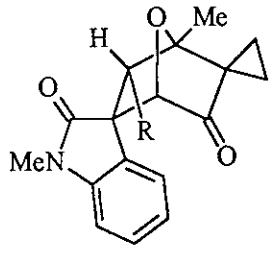
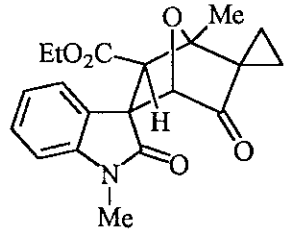
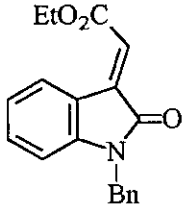
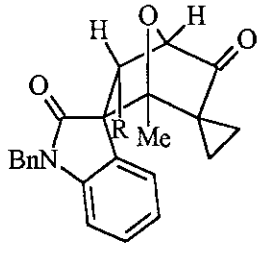
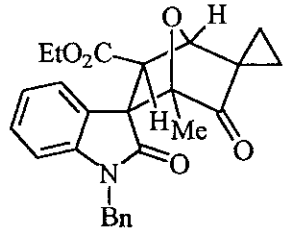
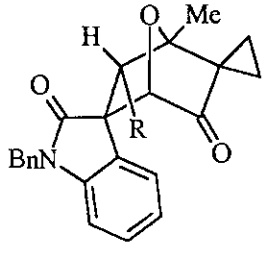


Figure 6b. nOe spectrum of **65** (irradiated at δ 6.79)

The reaction of N-methyl and N-benzyl oxoindolinylidenes **34** and **35** with the diazoketone **62** followed a similar course. The results of these experiments are given in Table 3.

Table 3. Reaction of oxoindolinylidenes with the diazocompound **62**

Entry	Oxoindolin-ylidene	Time (h)	Products	Yield %[a] (Ratio)
1	 **34**	0.5	 **67**  **68**  **69**  **70**	93 (3:2:3:2
2	 **35**	1	 **71**  **72**  **73** R= CO_2Et	98 (1:1:1)

Reaction conditions: $Rh_2(OAc)_4$, Toluene, RT, Argon, [a]Isolated yield.

As in the previous experiment, the products were separated by column chromatography followed by fractional crystallization. The structure of the products was assigned by spectroscopic methods and by correlating with the adducts **63**, **64, 65** and **66**.

For the sake of completeness, addition of a seven membered carbonyl ylide to the oxoindolinylidene **1** was attempted. However, the reaction afforded only an inseparable mixture of *exo* and *endo* adducts in very low yields. The reaction was not pursued further.

2.2.3. THEORETICAL CALCULATIONS

Frontier molecular orbital theory generally rationalizes the regioselectivity of most 1,3-dipolar cycloaddition reactions. The HOMO of the dipole is dominant in reaction with electron deficient dipolarophiles, whereas, LUMO of the dipole is the controlling molecular orbital in reactions with electron rich dipolarophiles.[16] In order to explain the observed mode of addition, we have carried out some theoretical calculations using semi-empirical PM3 method with the aid of TITAN software (version 1).[17] The correlation diagram for the reaction of oxoindolinylidene **1** with the carbonyl ylide **37** is given in Figure 7 as an illustrative example.

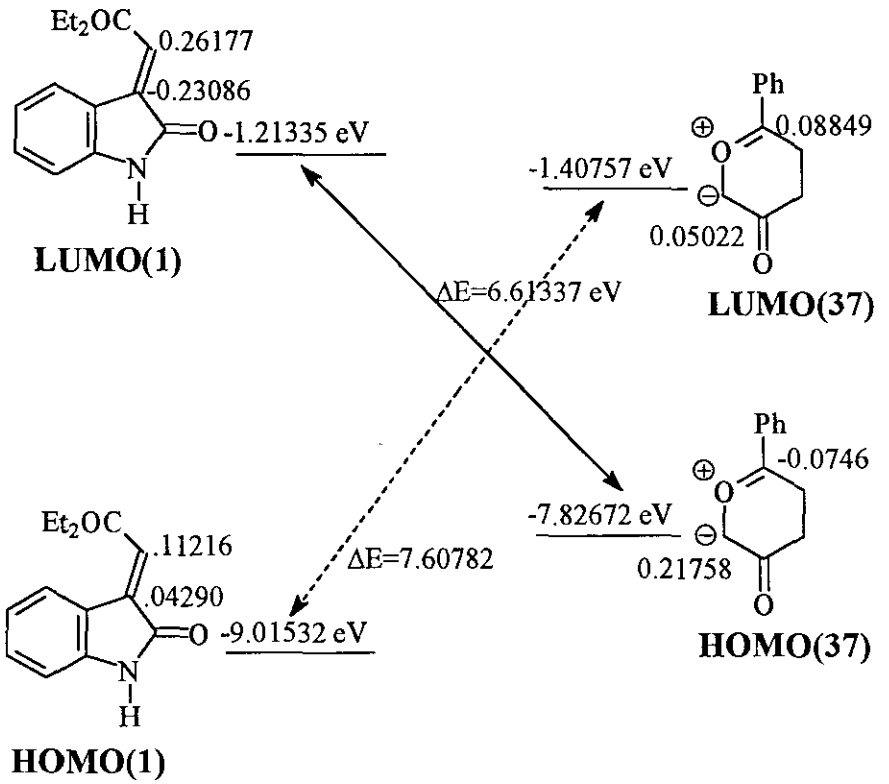


Figure 7. The correlation diagram for the reaction of **1** with carbonyl ylide **37**

From the correlation diagram in Figure 7, it is clear that the most favorable interaction is HOMO(dipole)-LUMO(dipolarophile) interaction. HOMO(dipole)-LUMO(dipolarophile) and LUMO(dipole)-HOMO(dipolarophile) interactions are symmetry allowed. However, the LUMO(dipole)-HOMO(dipolarophile) interaction is unimportant due to the large energy gap compared to the other. Thus, it is a HOMO controlled reaction according to Sustmann's classification of 1,3-dipolar cycloaddition reactions.[16]

In conclusion, we have shown that highly functionalized spiroindolenin systems can be synthesized using the simple one step addition of carbonyl ylides to oxoindolinylidene derivatives. It is conceivable that the cycloadducts may be amenable to a number of useful synthetic transformations.

2.3. EXPERIMENTAL DETAILS

All reactions were carried out in oven dried glassware under an atmosphere of argon, unless otherwise mentioned. Analytical thin layer chromatography was performed on silica gel TLC plates. Purification by column chromatography was carried out using silica gel (100-200 mesh). Mixtures of ethyl acetate and hexane were used as eluents. After the chromatographic separation, the solvents were removed using a Büchi-EL rotary evaporator. Melting points were recorded on Fisher Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bomem MB series FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Brüker 300 MHz NMR spectrometer using chloroform-d as solvent, unless otherwise mentioned. The chemical shifts are given in δ scale with tetramethylsilane as internal standard. High-resolution mass spectra were recorded on a Finnigan MAT model 8430 instrument. Elemental analyses were done using Perkin-Elmer 2400 CHNS Analyzer. All solid products were purified by recrystallization from an appropriate solvent system. Solvents used for the experiments (toluene, ether and dichloromethane) were distilled and dried by employing standard procedures.

The diazoketones were prepared from the corresponding carboxylic acids following the literature procedures.[13, 14]

General procedure for the rhodium(II) catalyzed cycloaddition reaction of 1-diazoalkane diones with oxoindolinylidenes

A toluene solution of oxoindolinylidene acetate and 1.5 equivalents of appropriate diazoalkanedione was purged with argon. To this solution, catalytic amount of rhodium(II) acetate (2 mg) was added and stirred under argon atmosphere at room temperature. When the reaction was over (as indicated by TLC), the solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel using the appropriate hexane-ethyl acetate mixture as the eluent to give the pure cycloadducts. Wherever

necessary, further separation of the isomeric products was carried out by fractional crystallization. The products were identified on the basis of spectroscopic data.

Cycloadducts 43 and 44

A solution of oxoindolinylidene acetate **1** (0.217 g, 1 mmol) and 1-diazo-5-phenyl-2,5-pentanedione **42** (0.303 g, 1.5 mmol) in toluene (15 mL) was treated with catalytic amount of rhodium(II) acetate at room temperature under an atmosphere of argon and was stirred for 45 min. On completion of the reaction, toluene was removed under reduced pressure in a rotary evaporator. The residue on chromatography on a silica gel column (100-200 mesh) using 10% ethyl acetate-hexane as eluent afforded the *endo* adduct **43** (0.203 g, 52%) as an off-white crystalline solid and the *exo* adduct **44** (0.180 g, 46%) as colorless crystalline solid. The products were further purified by recrystallization from ethyl acetate-hexane solvent system.

Ethyl (1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-5'-phenyl spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 43

Recrystallized from ethyl acetate-hexane, mp. 164 °C (decomposed)

IR (KBr) $\nu_{(max)}$: 3225, 1734, 1707, 1619, 1473, 1446, 1372, 1347, 1303, 1185, 1160, 1029 cm^{-1}.

^1H NMR : δ 8.18 (s, 1H, exchangeable with D_2O), 7.45 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 7.12 (brs, 5H), 6.86 (d, J = 7.6 Hz, 2H), 4.81 (d, J = 8.1 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 3.85-3.79 (m, 2H), 3.13-3.07 (m, 1H), 2.81-2.67 (m, 2H), 2.24-2.15 (m, 1H), 0.81 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 203.34, 179.50, 168.44, 142.63, 140.51, 129.74, 127.88, 127.64, 123.76, 122.43, 110.38, 87.75, 82.25, 63.34, 61.25, 55.32, 33.83, 33.05, 13.65.

Anal. calcd. for $C_{23}H_{21}NO_5$: C, 70.57; H, 5.40; N, 3.57. Found: C, 70.76; H, 5.42; N, 3.73.

Ethyl (1'R,3S,5'S,7'R)-7'-1,2-dihydro-2,2'-dioxo-5'-phenyl spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 44

Recrystallized from ethyl acetate-hexane, mp. 195-197 °C.

IR (KBr) $\nu_{(max)}$: 3219, 1735, 1700, 1619, 1473, 1447, 1372, 1345, 1303, 1242, 1188, 1160 cm^{-1}.

^1H NMR : δ 8.35 (s, 1H), 7.10-6.90 (m, 7H), 6.70 (t, J = 7.4 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.18 (d, J = 3.1 Hz, 1H), 3.82 (d, J = 3.1 Hz, 1H), 3.65 (q, J = 6.9 Hz, 2H), 3.25-3.08 (m, 2H), 2.69-2.60 (m, 1H), 2.30-2.17 (m, 1H), 0.62 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 205.75, 176.85, 167.91, 141.30, 139.82, 129.16, 128.38, 127.84, 127.19, 126.56, 123.31, 122.24, 108.70, 90.05, 81.00, 63.01, 61.27, 57.26, 33.34, 31.92, 13.34.

X-RAY Crystal data: $C_{23}H_{20}NO_5.H_2O$ Fw: 408.42. Crystal size: 0.40 x 0.36 x 0.12 mm^3, Monoclinic, Space group: P2(1)/n. Unit cell dimensions a = 8.8733(4) Å, α = 90°; b = 14.8316(7) Å, β = 97.245(4)°; c = 15.4797(8) Å, γ = 90°. R indices (all data) R1 = 0.0873, wR2 = 0.1461. Volume, Z = 2020.94(17) $Å^3$, 4. D calc. = 1.342 mg/m^3. F (000) = 860. Absorption Coefficient = 0.098 mm^{-1}. Reflections collected = 38290. λ = 0.71073 Å. (Sheldrick, G. M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

Cycloadducts 45 and 46

Treatment of 1-diazo-5-phenyl-2,5-pentane dione **42** (0.303 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **34** (0.231 g, 1 mmol) in toluene (10 mL), in the presence of a catalytic amount of rhodium(II) acetate at room temperature for 2 h followed by chromatographic purification of the product afforded the adduct **45** (0.231 g, 57%) as a pale yellow semi-solid and the adduct **46** (0.121 g, 30%) as colorless crystals.

Ethyl (1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-1-methyl-5'-phenyl spiro [3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 45

IR (KBr) $\nu_{(max)}$: 1723 (broad band), 1611, 1493, 1470, 1375, 1331, 1194, 1160, 1028 cm^{-1}.

^1H NMR : δ 7.49-7.38 (m, 2H), 7.13-7.11 (m, 5H), 6.76 (d, J = 7.7 Hz, 2H), 4.85 (d, J = 8.3 Hz, 1H), 4.15 (d, J = 8.4 Hz, 1H), 3.91-3.75 (m, 2H), 3.16-3.04 (m, 1H), 2.74-2.60 (m, 2H) 2.67 (s, 3H), 2.23-2.16 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 203.25, 176.92, 168.53, 145.29, 140.24, 129.65, 127.50, 125.18, 122.21, 108.60, 87.78, 82.40, 63.09, 61.05, 54.52, 33.45, 32.89, 25.79, 13.59.

Ethyl (1'R,3S,5'S,7'R)-7'-1,2-dihydro-2,2'-dioxo-1-methyl-5'-phenyl spiro [3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 46

Recrystallized from ethyl acetate-hexane solvent system, mp. 180-182 °C.

IR (KBr) $\nu_{(max)}$: 1741, 1702, 1607, 1469, 1378, 1351, 1133, 1094, 1025 cm^{-1}.

^1H NMR : δ 7.03-6.96 (m, 7H), 6.72 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 5.17 (d, J = 1.7 Hz, 1H), 3.80 (d, J = 3.1 Hz, 1H), 3.60-3.53 (m, 2H), 3.30 (s, 3H), 3.26-3.09 (m, 2H), 2.68-2.59 (m, 1H), 2.26-2.17 (m, 1H), 0.57 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 205.76, 174.83, 167.89, 142.91, 141.32, 128.32, 127.73, 127.06, 123.18, 122.23, 107.10, 89.87, 62.60, 61.02, 57.00, 33.30, 31.83, 26.72, 13.32.

Cycloadducts 47 and 48

Treatment of 1-diazo-5-phenyl-2,5-pentane dione **42** (0.303 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **35** (0.307 g, 1 mmol) in toluene (10 mL), in the presence of a catalytic amount of rhodium(II) acetate at room temperature for 1 h followed by chromatographic purification of the product afforded the adduct **47** (0.274 g, 57%) as an off-white crystalline solid and the adduct **48** (0.154 g, 32%) as a colorless solid.

Ethyl(1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-5'-phenyl-1-(phenylmethyl) spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 47

Recrystallized from CH_2Cl_2-hexane, mp. 168-170 °C.

IR (KBr) $\nu_{(max)}$: 1737, 1719, 1610, 1492, 1467, 1368, 1179, 1029 cm^{-1}.

^1H NMR : δ 7.47 (d, J = 7.5 Hz, 1H), 7.28-7.07 (m, 10H), 6.71 (m, 2H), 6.62 (d, J = 7.7 Hz, 1H), 4.88 (d, J = 8.3 Hz, 1H), 4.58 (d, J = 15.7 Hz, 1H), 4.38 (d, J = 15.7 Hz, 1H), 4.24 (d, J = 8.4 Hz, 1H), 3.89-3.68 (m, 2H), 3.19-3.07 (m, 1H), 2.87-2.79 (m, 1H), 2.73-2.64 (m, 1H), 2.31-2.20 (m, 1H), 0.74 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 203.20, 177.50, 168.45, 144.66, 140.56, 135.03, 128.59, 128.01, 127.61, 127.41, 127.01, 125.26, 124.62, 124.06, 122.37, 109.55, 87.56, 82.18, 62.87, 61.09, 56.07, 44.00, 34.12, 33.15, 13.56.

Anal calcd. for $C_{30}H_{27}NO_5$: C, 74.82; H, 5.65; N, 2.90. Found: C, 74.87; H, 5.76; N, 2.93.

Ethyl(1'R,3S,5'S,7'R)-7'-1,2-dihydro-2,2'-dioxo-5'-phenyl-1-(phenylmethyl) spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 48

Recrystallized from ethyl acetate-hexane, mp. 165-167 °C.

IR (KBr) $\nu_{(max)}$: 1740, 1702, 1607, 1468, 1377, 1350, 1094, 1025 cm^{-1}.

^1H NMR : δ 7.36-7.29 (m, 5H), 7.03-6.86 (m, 7H), 6.68 (t, J = 7.3 Hz, 1H), 6.51 (d, J = 7.7 Hz, 1H), 5.19 (d, J = 2.9 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 4.86 (d, J = 15.2 Hz, 1H), 3.88 (d, J = 2.9 Hz, 1H), 3.61-3.49 (m, 2H), 3.29-3.14 (m, 2H), 2.70-2.61 (m, 1H), 2.27-2.16 (m, 1H), 0.39 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 205.57, 175.02, 167.87, 142.14, 141.19, 135.67, 128.73, 128.18, 127.88, 127.68, 127.07, 126.23, 123.37, 122.17, 108.07, 90.09, 81.10, 62.50, 61.11, 57.21, 44.38, 33.33, 32.08, 13.11.

Anal calcd. for $C_{30}H_{27}NO_5$: C, 74.82; H, 5.65; N, 2.90. Found: C, 74.88; H, 5.67; N, 2.93.

Cycloadducts 49 and 50

Treatment of 1-diazo-5-phenyl-2,5-pentane dione **42** (0.303 g, 1.5 mmol) with 5-bromo-3-ethoxycarbonyl methylene-2-oxoindoline **36** (0.296 g, 1 mmol) in toluene (20 mL), in presence of a catalytic amount of rhodium(II) acetate at room temperature for 30 min followed by chromatographic purification of the product afforded the *endo* adduct **49** (0.310 g, 66%) a colorless crystalline solid and the *exo* adduct **50** (0.146 g, 31%) as an off-white crystalline solid.

Ethyl (1'R,3R,5'S,7'S)-7'-5-bromo-1,2-dihydro-2,2'-dioxo-5'-phenyl spiro [3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 49

Recrystallized from ethyl acetate-hexane solvent system, mp. 240-242 °C.

IR (KBr) $\nu_{(max)}$: 3306, 1730, 1699, 1619, 1474, 1445, 1372, 1311, 1241, 1187 1034 cm^{-1}.

^1H NMR : δ 8.13 (s, 1H), 7.53-7.47 (m, 2H), 7.12 (brs, 4H), 6.94-6.85 (m, 1H), 6.75 (d, J = 8.2 Hz, 1H), 4.80 (d, J = 8.4 Hz, 1H), 4.06 (d, J = 8.3 Hz, 1H), 3.93-3.91 (m, 2H), 3.03-2.94 (m, 1H), 2.80-2.62 (m, 2H), 2.31-2.23 (m, 1H), 0.91 (t, J = 6.9 Hz, 3H).

^{13}C NMR : δ 203.15, 178.89, 168.26, 141.61, 140.13, 132.62, 128.82, 127.95, 127.85, 127.04, 123.80, 115.03, 111.69, 87.89, 82.26, 63.48, 61.67, 55.19, 33.35, 32.84, 13.80.

Ethyl (1'R,3S,5'S,7'R)-7'-5-bromo-1,2-dihydro-2,2'-dioxo-5'-phenyl spiro [3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 50

Recrystallized from ethyl acetate-hexane solvent system, mp. 225-227 °C.

IR (KBr) $\nu_{(max)}$: 3170, 3107, 1737, 1704, 1617, 1471, 1447, 1305, 1268, 1184, 1029 cm^{-1}.

^1H NMR ($CDCl_3$+DMSO-d_6): δ 9.99 (s, 1H), 7.07-6.99 (m, 7H), 6.49 (d, J = 8.2 Hz, 1H), 5.15 (d, J = 1.2 Hz, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.76-3.66 (m, 2H), 3.24-3.07 (m, 2H), 2.68-2.59 (m, 1H), 2.22-2.16 (m, 1H), 0.71 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 205.53, 176.26, 167.67, 140.90, 140.00, 131.14, 130.85, 128.99, 128.20, 127.77, 127.23, 123.12, 113.93, 110.40, 89.79, 80.86, 63.07, 61.31, 57.12, 33.15, 31.67, 13.29.

Cycloadducts 52 and 53

Treatment of 1-diazo-5-(2-thienyl)-2,5-pentane dione **51** (0.312 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **1** (0.217 g, 1 mmol) in toluene (15 mL), in the presence of a catalytic amount of rhodium(II) acetate at room temperature for 30 min followed by chromatographic purification of the product afforded 0.460 g of the cycloadduct as a mixture of *endo* and *exo* isomers. Further separation of the isomers was effected by fractional crystallization.

Ethyl (1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 52

Recrystallised from CH_2Cl_2-hexane solvent system, mp. 190 °C (decomposed).

IR (KBr) $\nu_{(max)}$: 3318, 1737, 1716, 1615, 1470, 1378, 1346, 1301, 1242, 1190 cm^{-1}.

^{1}H NMR : δ 8.43 (s, 1H, exchangeable with D_2O), 7.43-7.33 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 4.4 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 6.74 (t, J = 6.7 Hz, 1H), 6.42 (d, J = 2.5 Hz, 1H), 4.80 (d, J = 8.3 Hz, 1H), 4.17 (d, J = 8.3 Hz, 1H), 3.91-3.78 (m, 2H), 3.17-3.04 (m, 1H), 2.77-2.63 (m, 2H), 2.42-2.31 (m, 1H), 0.83 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 202.50, 179.41, 168.53, 142.87, 142.67, 129.86, 126.42, 125.69, 124.40, 124.15, 122.50, 122.44, 110.65, 87.36, 82.63, 63.74, 54.86, 35.09, 33.06, 13.69.

Anal. Calcd. for $C_{21}H_{19}NO_5S$: C, 63.46; H, 4.81; N, 3.52; S, 8.06. Found: C, 63.48; H, 4.78; N, 3.82; S, 8.10.

Ethyl (1'R,3S,5'S,7'R)-7'-1,2-dihydro-2,2'-dioxo-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 53

Recrystallized from CH_2Cl_2-hexane, mp. 180 °C (decomposed).

IR (KBr) $\nu_{(max)}$: 3171, 1740, 1696, 1474, 1240, 1194 cm^{-1}.

^1H NMR : δ 8.12 (s, 1H, exchangeable with D_2O), 7.11 (d, J = 7.4 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.92-6.91 (m, 1H), 6.79 (t, J = 7.5 Hz, 1H), 6.67-6.64 (m, 3H), 5.17 (d, J = 1.2 Hz, 1H), 3.82 (d, J = 2.8 Hz, 1H), 3.68 (q, J = 7.1 Hz, 2H), 3.21-3.10 (m, 2H), 2.70-2.62 (m, 1H), 2.41-2.39 (m, 1H), 0.63 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 204.96, 176.25, 167.73, 143.54, 140.00, 128.79, 128.63, 126.68, 126.26, 123.73, 122.28, 121.91, 108.83, 89.19, 81.46, 63.55, 61.35, 56.92, 33.31, 33.09, 13.34.

Anal. Calcd. for $C_{21}H_{19}NO_5S.H_2O$: C, 60.71; H, 5.10; N, 3.37; S, 7.71. Found: C, 60.57; H, 5.15; N, 3.67; S, 7.96.

Ethyl (1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-1-methyl-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 54

Treatment of 1-diazo-5-(2-thienyl)-2,5-pentane dione **51** (0.312 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **34** (0.231 g, 1 mmol) in toluene (10 mL), in the presence of a catalytic amount of rhodium(II) acetate at room temperature for 1.5 h followed by chromatographic purification of the product afforded 0.390 g (95%) of the cycloadduct **54** as a white crystalline solid which was recrystallized from CH_2Cl_2-hexane solvent system, mp. 122-124 °C.

IR (KBr) $\nu_{(max)}$: 1743, 1719, 1609, 1493, 1468, 1376, 1350, 1189, 1157, 1098 cm^{-1}.

^1H NMR : δ 7.46-7.34 (m, 2H), 7.14-7.10 (m, 2H), 6.80 (d, J = 5.9 Hz, 2H), 6.41 (d, J = 3.1 Hz, 1H), 4.85 (d, J = 8.2 Hz, 1H), 4.22 (d, J = 8.2 Hz, 1H), 3.88-3.81 (m, 2H), 3.13-3.05 (m, 1H), 2.83 (s, 3H), 2.72-2.64 (m, 2H), 2.41-2.35 (m, 1H), 0.83 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 202.59, 176.85, 168.53, 145.53, 142.57, 129.86, 126.11, 125.40, 124.27, 123.71, 122.50, 122.34, 108.38, 87.49, 82.79, 63.49, 61.24, 54.33, 35.02, 33.04, 26.15, 13.70.

Anal. Calcd. for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.09; H, 5.22; N, 3.81; S, 8.14.

Cycloadducts 55 and 56

Treatment of 1-diazo-5-(2-thienyl)-2,5-pentane dione **51** (0.312 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **35** (0.307 g, 1 mmol) in toluene (10 mL), in presence of a catalytic amount of rhodium(II) acetate at room temperature for 1 h followed by chromatographic purification of the product afforded the adduct **55** (0.278 g, 57%) as an off-white crystalline solid and the adduct **56** (0.156 g, 32%) as colorless crystals.

Ethyl(1'R,3R,5'S,7'S)-7'-1,2-dihydro-2,2'-dioxo-1-(phenylmethyl)-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 55

Recrystallized from ethyl acetate-hexane, mp. >300 °C.

IR (KBr) $\nu_{(max)}$: 1742, 1716, 1609, 1488, 1462, 1372, 1178, 1018 cm^{-1}.

^{1}H NMR : δ 7.45 (d, J = 7.4 Hz, 1H), 7.24-7.08 (m, 8H), 6.84-6.78 (m, 2H), 6.65 (d, J = 7.6 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.86 (d, J = 8.4 Hz, 1H), 4.68 (d, J = 15.7 Hz, 1H), 4.50 (d, J = 15.7 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 3.87-3.72 (m, 2H), 3.19-3.07 (m, 1H), 2.81-2.65 (m, 1H), 2.45-2.34 (m, 1H), 0.75 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 202.40, 177.26, 168.37, 144.83, 142.70, 135.12, 129.78, 128.66, 127.51, 127.12, 126.43, 125.40, 124.45, 123.90, 122.97, 122.40, 109.64, 87.17, 82.49, 63.28, 61.19, 55.64, 44.16, 35.49, 33.21, 13.59.

Ethyl (1'R,3S,5'S,7'R)-7'-1,2-dihydro-2,2'-dioxo-1-(methylphenyl)-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 56

Recrystallized from ethylacetate-hexane, mp. 184-186 °C.

IR (KBr) $\nu_{(max)}$: 1735, 1705, 1610, 1489, 1467, 1370 cm^{-1}.

^1H NMR : δ 7.37-7.29 (m, 5H), 7.12 (d, J = 7.3 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.88-6.86 (m, 1H), 6.76 (t, J = 7.5 Hz, 1H), 6.58-6.53 (m, 2H), 6.47-6.46 (m, 1H), 5.21 (d, J = 15.2 Hz, 1H), 5.17 (d, J = 1.2 Hz, 1H), 4.78 (d, J = 15.4 Hz, 1H), 3.87 (d, J = 3.0 Hz, 1H), 3.70-3.50 (m, 2H), 3.28-3.15 (m, 2H), 2.69-2.63 (m, 1H), 2.43-2.32 (m, 1H), 0.38 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 204.87, 174.43, 167.71, 143.43, 142.21, 135.62, 128.72, 128.45, 127.91, 127.75, 126.35, 126.10, 123.67, 122.23, 122.08, 108.25, 89.26, 81.55, 63.02, 61.23, 56.86, 44.40, 33.34, 30.86, 13.70.

Cycloadducts 57 and 58

Treatment of 1-diazo-5-(2-thienyl)-2,5-pentane dione **51** (0.312 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **36** (0.296 g, 1 mmol) in toluene (20 mL), in presence of a catalytic amount of rhodium(II) acetate at room temperature for 30 min followed by chromatographic purification of the product afforded the adducts **57** and **58** as a mixture in the ratio 2:1. The *endo* and *exo* isomers were separated by crystallization and Pasteur style physical separation.

Ethyl (1'R,3R,5'S,7'S)-7'-5-bromo-1,2-dihydro-2,2'-dioxo-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 57

Recrystallized from ethyl acetate-hexane, mp. 212-214 °C.

IR (KBr) $\nu_{(max)}$: 3298, 1741, 1708, 1616, 1475, 1434, 1303, 1276, 1182 cm^{-1}.

^1H NMR : δ 9.44 (s, 1H), 7.49-7.44 (m, 2H), 7.12-7.10 (m, 1H), 6.82-6.78 (m, 2H), 6.50-6.49 (m, 1H), 4.80 (d, J = 8.4 Hz, 1H), 4.17 (d, J = 8.4 Hz, 1H), 3.98-3.87 (m, 2H), 3.06-2.97 (m, 1H), 2.76-2.65 (m, 2H), 2.45-2.34 (m, 1H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 202.24, 178.45, 168.22, 142.65, 132.57, 128.58, 126.38, 126.26, 124.34, 122.62, 114.40, 111.84, 87.30, 82.55, 63.64, 61.54, 54.77, 34.96, 32.92, 13.70.

Ethyl (1'R,3S,5'S,7'R)-7'-5-bromo-1,2-dihydro-2,2'-dioxo-5'-(2-thienyl)-spiro[3H-indole-3,6'-[8]oxabicyclo[3.2.1]octane]-7'-carboxylate 58

Recrystallized from ethyl acetate-hexane, mp. 180 °C (decomposed).

IR (KBr) $\nu_{(max)}$: 3301, 1728, 1701, 1618, 1474, 1302, 1183 cm^{-1}.

^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 10.36 (s, 1H), 7.15 (s, 1H), 7.15-7.11 (m, 1H), 6.96-6.94 (m, 1H), 6.67-6.62 (m, 2H), 6.53 (m, 1H), 5.11 (d, J = 1.5 Hz, 1H), 3.78 (d, J = 2.9 Hz, 1H), 3.78-3.66 (m, 2H), 3.14-3.09 (m, 2H), 2.66-2.56 (m, 1H), 2.37-2.30 (m, 1H), 0.69 (t, J = 7.2 Hz, 3H).

^{13}C NMR : δ 204.56, 175.43, 167.39, 142.96, 140.25, 130.92, 128.85, 126.10, 123.65, 121.69, 113.66, 110.42, 88.80, 81.16, 63.38, 61.23, 56.53, 33.03, 32.82, 13.13.

Anal calcd. for $C_{21}H_{18}NO_5SBr$: C, 52.95; H, 3.80; N, 2.94; S, 6.73. Found: C, 52.65; H, 4.09; N, 2.96; S, 6.68.

Cycloadducts 63, 64, 65 and 66

Treatment of 1-acetyl-1-diazoacetyl cyclopropane **62** (0.228 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **1** (0.217 g, 1 mmol) in toluene (15 mL), in presence of a catalytic amount of rhodium(II) acetate at room temperature for 30 min followed by chromatographic purification afforded the adducts **63** (0.070 g, 20%) and **65** (0.106 g, 31%) as colorless crystalline solids. The adducts **64** and **66** were obtained as a mixture of regioisomers (0.141 g, 41%, 1:1) and were separated by fractional crystallization.

Ethyl(1'R,3''R,4'R,5'S)-1'',2''-dihydro-1'-methyl-2'',3'-dioxodispiro[cyclo-propane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3''-[3H]-indole]-5'-carboxylate 63

Recrystallized from CH_2Cl_2-hexane, mp. 224-226°C.

IR (KBr) $\nu_{(max)}$: 3193, 3086, 1762, 1709, 1618, 1472, 1381, 1333, 1189, 1140, 1104 cm^{-1}.

^1H NMR : δ 8.98 (s, 1H, exchangeable with D_2O), 7.26-7.19 (m, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.98-6.89 (m, 2H), 4.89 (d, J = 5.6 Hz, 1H), 3.99 (d, J = 5.6 Hz, 1H), 3.85-3.78 (m, 2H), 1.62-1.59 (m, 1H), 1.18 (s, 3H), 1.12-1.06 (m, 1H), 0.92-0.85 (m, 1H), 0.80 (t, J = 7.1 Hz, 3H), 0.74-0.69 (m, 1H).

^{13}C NMR : δ 208.49, 179.97, 167.79, 141.86, 129.13, 128.01, 124.74, 121.35, 110.02, 90.54, 81.76, 61.11, 60.91, 54.28, 38.72, 15.45, 14.39, 13.68, 13.56.

Ethyl(1'R,3"S,4'R,5'R)-1",2"-dihydro-1'-methyl-2",3'-dioxodispiro[cyclo-propane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3"-[3H]-indole]-5'-carboxylate 64

Recrystallized from $CHCl_3$-hexane, mp. 143-145 °C.

IR (KBr) $\nu_{(max)}$: 3204, 3089, 1763, 1710, 1617, 1473, 1390, 1339, 1219 cm^{-1}.

^1H NMR : δ 9.07 (s, 1H), 7.31-7.22 (m, 2H), 7.04-6.99 (m, 1H), 6.89 (d, J = 7.6 Hz, 1H), 5.10 (s, 1H), 3.71 (q, J = 7.1 Hz, 2H), 3.61 (s, 1H), 1.64-1.59 (m, 1H), 1.13-0.92 (m, 3H), 0.86 (s, 3H), 0.67 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 210.25, 176.51, 168.45, 140.90, 129.31, 128.93, 125.99, 122.70, 109.53, 90.84, 81.82, 62.25, 61.07, 55.49, 35.83, 14.67, 14.35, 14.18, 13.48.

Anal. Calcd. for $C_{19}H_{19}NO_5.H_2O$: C, 63.50; H, 5.89; N, 3.89. Found: C, 63.93; H, 5.41; N, 3.36.

Ethyl (1'R,3"R,4'S,6'S)-1",2"-dihydro-1'methyl-2",3'-dioxodispiro[cyclo propane-1,2'-[7]oxabicyclo[2.2.1]heptane-5',3"-[3H]-indole]-6'-carboxylate 65

Recrystallized from $CHCl_3$-hexane solvent system, mp. 95-97 °C.

IR (KBr) $\nu_{(max)}$: 3281, 2984, 1730, 1612, 1472, 1331, 1201, 1041 cm^{-1}.

^{1}H NMR : δ 9.18 (s, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.98-6.91 (m, 2H), 6.76 (d, J = 7.4 Hz, 1H), 4.53 (s, 1H), 3.76-3.65 (m, 2H), 3.66 (s, 1H), 1.87-1.80 (m, 1H), 1.58 (s, 3H), 1.42-1.35 (m, 1H), 1.12-1.05 (m, 1H), 0.90-0.83 (m, 1H), 0.63 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 207.36, 180.03, 168.15, 141.34, 129.19, 125.33, 124.63, 122.28, 110.14, 86.67, 86.56, 60.33, 60.14, 56.28, 37.07, 17.57, 14.52, 14.45, 13.39.

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.59; N, 4.10. Found: C, 66.67; H, 5.59; N, 4.07.

Ethyl(1'R,3''S,4'S,6'R)-1'',2''-dihydro-1'methyl-2'',3'-dioxodispiro[cyclo-propane-1,2'-[7]oxabicyclo[2.2.1]heptane-5',3''-[3H]-indole]-6'-carboxylate 66

Recrystallized from $CHCl_3$-hexane, mp. 188-190 °C.

IR (KBr) $\nu_{(max)}$: 3187, 1747, 1707, 1619, 1470, 1340, 1183, 1032 cm^{-1}.

^{1}H NMR : δ 9.04 (s, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.25-7.20 (m, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 4.27 (s, 1H), 3.62 (q, J = 7.0 Hz, 2H), 3.56 (s, 1H), 1.64 (s, 3H), 1.56-1.43 (m, 2H), 1.24-1.19 (m, 1H), 0.90-0.85 (m, 1H), 0.66 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 207.56, 175.98, 167.97, 141.08, 129.24, 129.08, 125.63, 122.72, 109.79, 87.21, 86.76, 60.24, 60.07, 59.17, 40.65, 14.98, 14.03, 13.79, 13.47.

Cycloadducts 67, 68, 69, and 70

Treatment of 1-acetyl-1-diazoacetyl cyclopropane **62** (0.228 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **34** (0.231 g, 1 mmol) in toluene (15 mL), in presence of a catalytic amount of rhodium(II) acetate at room temperature for 30 min followed by chromatographic purification afforded the adducts **67** (0.099 g, 28%) and **69** (0.067 g, 19%) as colorless crystalline solids. The adducts **68** and **70** were obtained as a mixture of regioisomers

(0.163 g, 46%) and were separated by fractional crystallization. The cycloadduct **68** was obtained as colorless crystals and **70** as a pale yellow oil.

Ethyl (1'R,3"R,4'R,5'S)-1",2"-dihydro-1',1"-dimethyl-2",3'-dioxodispiro [cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3"-[3H]-indole]-5'-carboxylate 67

Recrystallized from EtOAc-hexane, mp. 169-171 °C.

IR (KBr) $\nu_{(max)}$: 1758, 1712, 1613, 1492, 1374,1350, 1265, 1188, 1141, 1091 cm^{-1}.

^1H NMR : δ 7.30-7.25 (m, 1H), 7.10 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 4.87 (d, J = 5.6 Hz, 1H), 3.96 (d, J = 5.6 Hz, 1H), 3.84-3.72 (m, 2H), 3.28 (s, 3H), 1.62-1.55 (m, 1H), 1.11-1.01 (m, 1H), 1.07 (s, 3H), 0.94-0.87 (m, 1H), 0.77 (t, J = 7.1 Hz, 3H), 0.69-0.62 (m, 1H).

^{13}C NMR : δ 208.66, 177.31, 161.81, 144.57, 129.03, 127.64, 124.24, 121.26, 107.86, 90.40, 81.71, 60.71, 60.46, 54.28, 38.75, 26.65, 15.37, 14.36, 13.59, 13.35.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.59; H, 5.95; N, 3.45.

Ethyl (1'R,3"S,4'R,5'R)-1",2"-dihydro-1',1"-dimethyl-2",3'-dioxodispiro [cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3"-[3H]-indole]-5'-carboxylate 68

Recrystallized from CH_2Cl_2-MeOH, mp. 119-121°C.

IR (KBr) $\nu_{(max)}$: 1752, 1708, 1609, 1467, 1576, 1342, 1209, 1089 cm^{-1}.

^1H NMR : δ 7.34-7.27 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.08 (s, 1H), 3.68-3.61 (m, 2H), 3.57 (s, 1H), 3.23 (s, 3H), 1.68-1.64 (m, 1H), 1.11-0.94 (m, 3H), 0.81 (s, 3H), 0.62 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 210.05, 173.92, 168.36, 143.72, 128.75, 125.65, 122.57, 107.55, 90.53, 81.58, 61.58, 60.78, 55.60, 43.88, 29.24, 26.69, 14.66, 14.03, 13.33.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.59; H, 5.95; N, 4.42.

Ethyl (1'R,3"R,4'S,6'S)-1",2"-dihydro-1',1"-dimethyl-2",3'-dioxodispiro [cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-5',3"-[3H]-indole]-6'-carboxylate 69

Recrystallized from hexane-ethyl acetate, mp. 164-166 °C.

IR (KBr) $\nu_{(max)}$: 1748, 1728, 1611, 1497, 1472, 1377, 1332, 1194, 1178, 1154, 1035 cm^{-1}.

^{1}H NMR : δ 7.30-7.26 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.7 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 4.43 (s, 1H), 3.68-3.63 (m, 2H + s, 1H), 3.28 (s, 3H), 1.84-1.77 (m, 1H), 1.74-1.61 (m, 1H), 1.55 (s, 3H), 1.39-1.37 (m, 1H), 1.10-1.04 (m, 1H), 0.58 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 207.62, 177.34, 168.19, 144.12, 129.18, 125.09, 124.18, 122.26, 107.97, 86.66, 86.53, 60.29, 60.15, 55.66, 37.05, 26.85, 17.54, 14.54, 14.40, 13.33.

Ethyl (1'R,3"S,4'S,6'R)-1",2"-dihydro-1',1"-dimethyl-2",3'-dioxodispiro [cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-5',3"-[3H]-indole]-6'-carboxylate 70

IR (KBr) $\nu_{(max)}$: 1744, 1715, 1611, 1492, 1470, 1374, 1349, 1335, 1183, 1135 cm^{-1}.

^{1}H NMR : δ 7.45 (d, J = 7.5 Hz, 1H), 7.34-7.28 (m, 1H), 7.07-7.02 (m, 1H), 6.83 (d, J =7.3 Hz, 1H), 4.23 (s, 1H), 3.67-3.57 (m, 2H), 3.55 (s, 1H), 3.24 (s, 3H), 1.64 (s, 3H), 1.52-1.42 (m, 1H), 1.28-1.20 (m, 1H), 0.90-0.83 (m, 2H), 0.62 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 207.22, 173.60, 167.90, 143.51, 128.64, 125.34, 122.83, 107.66, 86.95, 86.67, 60.23, 60.11, 59.98, 40.50, 26.61, 14.83, 14.14, 13.95, 13.37.

Cycloadducts 71, 72 and 73

Treatment of 1-acetyl-1-diazoacetyl cyclopropane **62** (0.228 g, 1.5 mmol) with 3-ethoxycarbonyl methylene-2-oxoindoline **35** (0.307 g, 1 mmol) in toluene (10 mL), in the presence of a catalytic amount of rhodium(II) acetate at room temperature for 1 h followed by chromatographic purification afforded the adducts **71** (0.147 g, 34%). The adducts **72** and **73** were obtained as a mixture of regioisomers (0.276 g, 64%). On fractional crystallization, **72** was obtained as pale yellow oil and **73** as colorless crystals.

Ethyl (1'R,3''R,4'R,5'S)-1'',2''-dihydro-1'-methyl-1''-(phenylmethyl)-2'',3'-dioxodispiro[cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3''-[3H]-indole]-5'-carboxylate 71

Recrystallized from ethyl acetate-hexane, mp. 198-200 °C.

IR (KBr) $\nu_{(max)}$: 1766, 1742, 1612, 1492, 1462, 1381, 1354, 1184, 1140 cm^{-1}.

^{1}H NMR : δ 7.28 (brs, 5H), 7.17-7.07 (m, 2H), 6.89 (t, J = 7.6 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.97 (s, 2H), 4.89 (d, J = 5.6 Hz, 1H), 4.05 (d, J = 5.6 Hz, 1H), 3.81-3.73 (m, 2H), 1.61-1.55 (m, 1H), 1.26-1.24 (m, 1H), 1.11 (s, 3H), 1.10-1.05 (m, 1H), 0.91-0.87 (m, 1H), 0.69 (t, J = 7.1 Hz, 3H).

^{13}C NMR : δ 208.63, 177.53, 167.79, 143.72, 135.43, 128.93, 128.78, 127.62, 127.23, 124.46, 121.28, 109.06, 90.53, 81.68, 60.70, 60.40, 54.89, 44.16, 38.90, 15.43, 14.49, 13.61, 13.53.

Ethyl (1'R,3''S,4'R,5'R)-1'',2''-dihydro-1'-methyl-1''-(phenylmethyl)-2'',3'-dioxodispiro[cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-6',3''-[3H]-indole]-5'-carboxylate 72

IR (KBr) $\nu_{(max)}$: 1758, 1715, 1611, 1487, 1467, 1368, 1210, 1179, 1035 cm^{-1}.

^{1}H NMR : δ 7.43 (d, J = 7.4 Hz, 1H), 7.34-7.27 (m, 5H), 7.15 (t, J = 7.6 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.68 (t, J = 6.8 Hz, 1H), 5.09 (s, 1H), 5.07 (d, J = 15.7 Hz, 1H), 4.78 (d, J = 15.5 Hz, 1H), 3.66 (s, 1H), 3.63-3.51 (m, 2H), 1.67-1.58 (m, 1H), 1.10-0.87 (m, 3H), 0.83 (s, 3H), 0.45 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 209.96, 174.08, 168.33, 142.66, 135.58, 128.64, 127.66, 127.13, 125.66, 122.82, 108.69, 90.68, 81.65, 60.83, 60.29, 55.63, 44.00, 35.75, 14.71, 14.20, 13.94, 13.16.

Ethyl (1'R,3"R,4'S,6'S)-1",2"-dihydro-1'-methyl-1"-(phenylmethyl)-2",3'-dioxodispiro[cyclopropane-1,2'-[7]oxabicyclo[2.2.1]heptane-5',3"-[3H]-indole]-6'-carboxylate 73

Recrystallized from CH_2Cl_2-MeOH, mp. 200-202 °C.

IR (KBr) $\nu_{(max)}$: 1745, 1072, 1609, 1491, 1372, 1348, 1086 cm^{-1}.

^{1}H NMR : δ 7.28-7.25 (m, 5H), 7.14 (t, J = 7.6 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.4 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 5.17 (d, J = 15.7 Hz, 1H), 4.80 (d, J = 15.7 Hz, 1H), 4.49 (s, 1H), 3.75 (s, 1H), 3.64-3.62 (m, 2H), 1.86-1.82 (m, 1H), 1.58 (s, 3H + m, 1H), 1.41-1.39 (m, 1H), 1.11-1.07 (m, 1H), 0.48 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 207.67, 177.58, 168.25, 143.15, 135.43, 129.07, 128.77, 127.75, 127.15, 124.99, 124.26, 122.30, 109.20, 86.76, 86.58, 60.60, 60.24, 55.71, 44.16, 37.13, 17.56, 14.58, 14.53, 13.27.

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CHAPTER 3

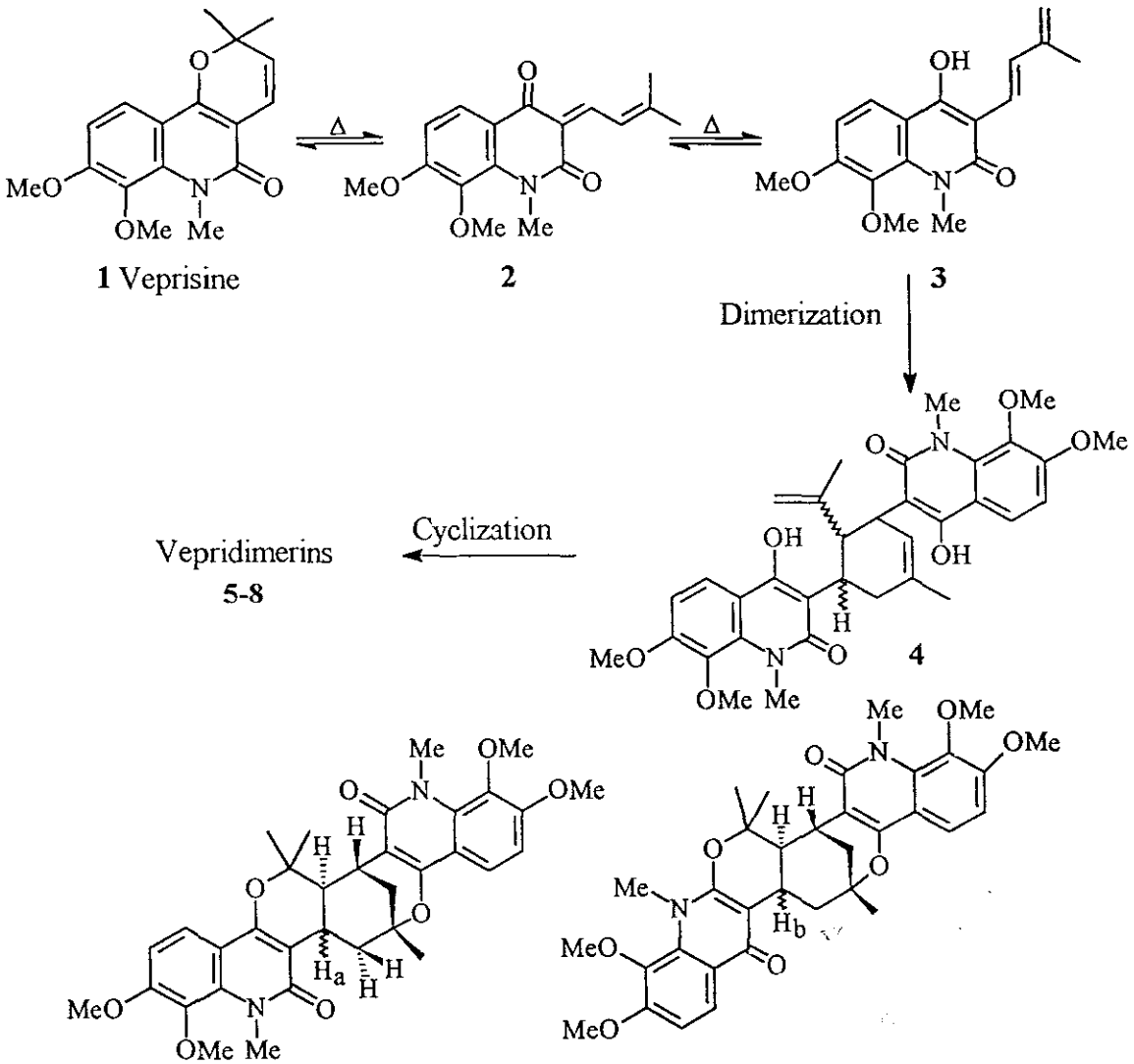
CYCLOADDITION REACTIONS OF 1-METHYL-3-METHYLENEQUINOLIN-2,4-DIONE

3.1. INTRODUCTION

Heterocyclic quinone methides are useful intermediates for the synthesis of a variety of important heterocyclic compounds.[1] The discovery of the synthetic potential of these quinone methides has aroused considerable interest in their generation and subsequent transformations. These are usually generated *in situ* from the corresponding 1,3-dicarbonyl compounds. 3-Methylenechroman-2,4-dione,[2] 3-methylenepyran-2,4-dione,[3] 1,2,3,4-tetrahydro-3-methylenepyridine-2,4-dione[4] and 3-methylenequinolin-2,4-dione have found application in organic synthesis. However, in comparison to their carbon analogues these heterocyclic quinone methides have not received much attention.

3.1.1. QUINOLINONE QUINONE METHIDE: A VERSATILE INTERMEDIATE IN ORGANIC SYNTHESIS

Quinolinone quinone methides constitute a class of versatile synthons for naturally occurring, biologically active pyranoquinolinones, dimeric quinolinone alkaloids and other polycyclic heterocycles. The synthesis of natural products vepridimerins **5-8** from veprisine **1** provides an illustrative example (Scheme 1).[5]

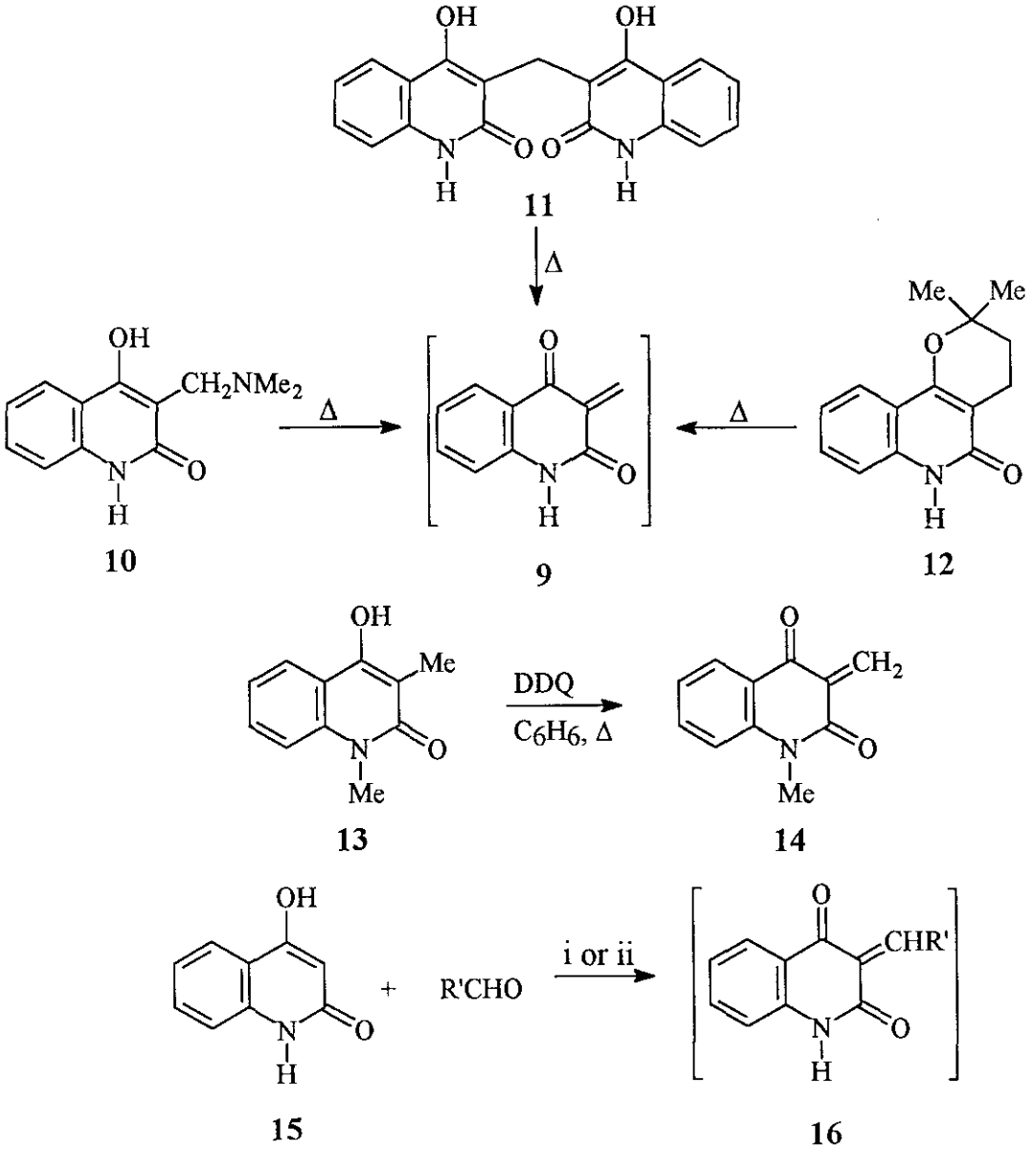


Scheme 1

3.1.2. GENERATION AND REACTIONS OF QUINOLINONE QUINONE METHIDES

Quinolinone quinone methides are usually too reactive to be isolated and are generated *in situ* and trapped with suitable reagents. Different methods known for the generation of quinolinone quinone methides include elimination of a secondary

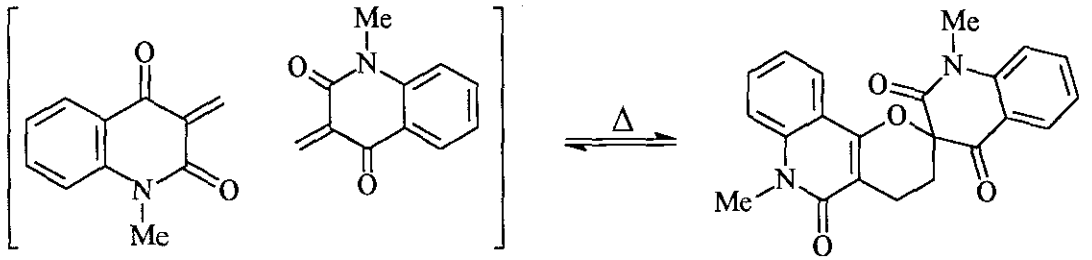
amine from a Mannich base **10**, pyrolysis of bisquinolinone **11** or dihydroflindersine **12**,[6] DDQ oxidation of 1,3-dimethyl-4-hydroxyquinolinone **13**[7] and Knoevenagel condensation of 4-hydroxyquinolin-2-one **15** with an aldehyde[8] (Scheme 2).



i. Et_2NH, benzene, reflux; ii. Et_3N, benzene, hν

Scheme 2

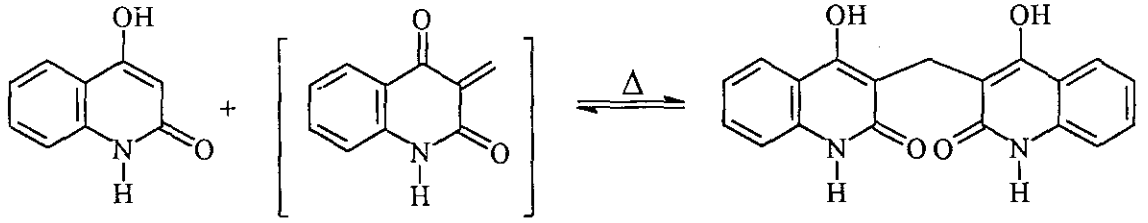
The quinolinone quinone methide is so reactive that it undergoes dimerization in the absence of an external dienophile (Scheme 3).[9]



14 **17**

Scheme 3

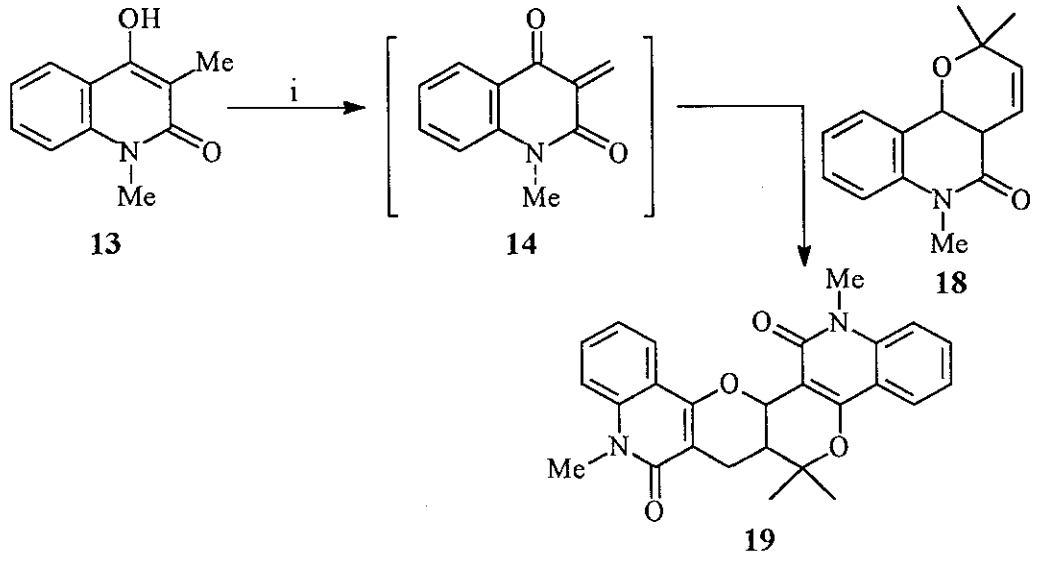
The methide is also known to undergo condensation with the quinolinone yielding the corresponding bisquinolinone (Scheme 4).[6, 8]



15 **9** **11**

Scheme 4

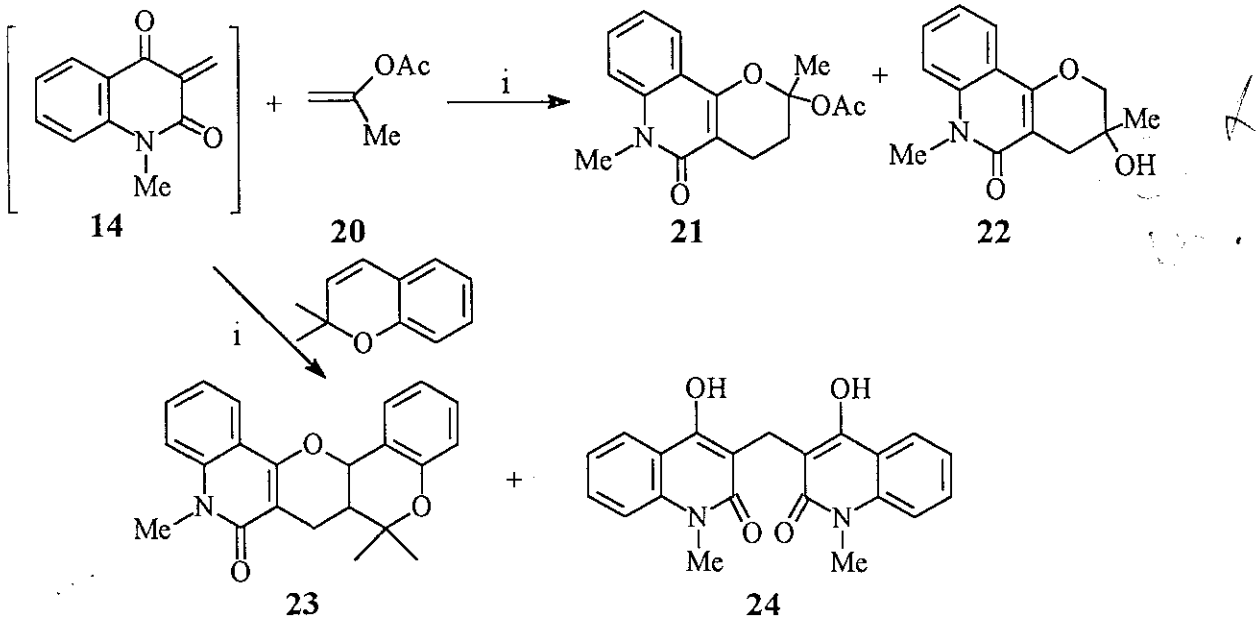
There are very few reports on the cycloaddition reactions of quinolinone quinone methide. The earliest report of a cycloaddition reaction of the latter deals with the Diels-Alder reaction of N-methyl flindersine **18** with **14** generated *in situ* by DDQ oxidation of 1,3-dimethyl-4-hydroxyquinolin-2-one **13** (Scheme 5).[7]



i. DDQ, C_6H_6, reflux

Scheme 5

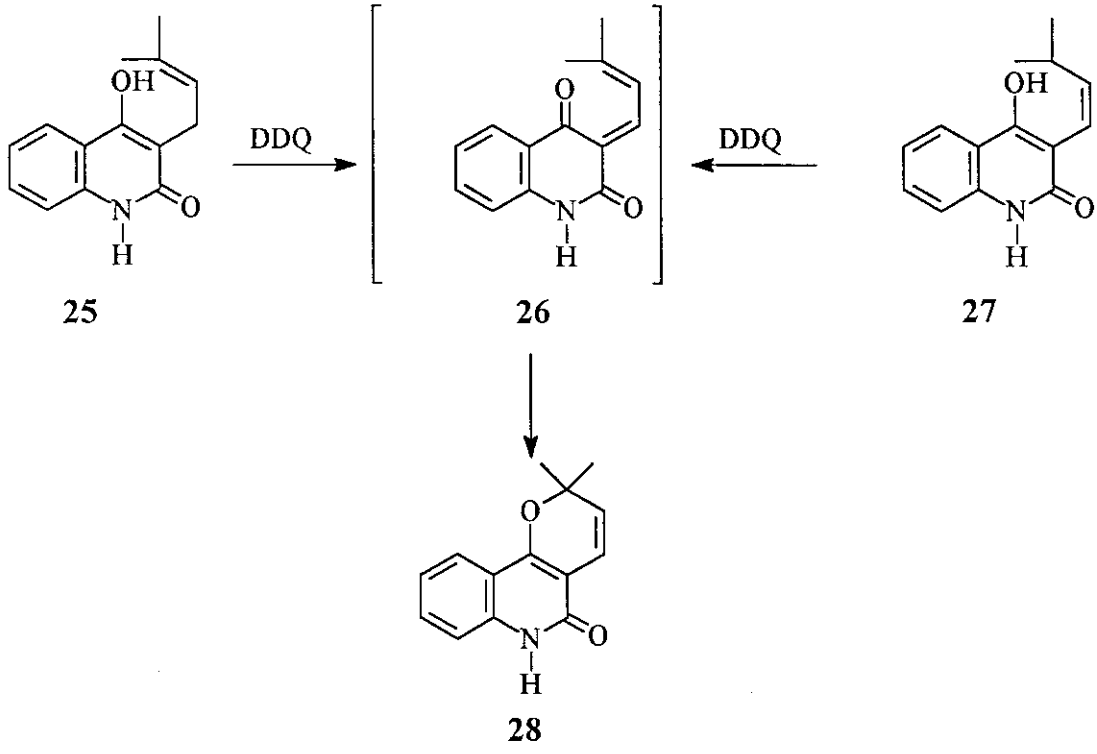
Under similar experimental conditions, isopropenyl acetate and benzopyran afforded the Diels-Alder adducts in low yields (Scheme 6).[9]



i. C_6H_6, reflux, 24 h

Scheme 6

The formation of flindersine **28** and its derivatives by dehydrocyclization of prenyl quinolinone and vinyl quinolinone *via* the intermediate heterocyclic quinone methide provides an example of electrocyclic reaction of a quinolinone quinone methide (Scheme 7).[10]

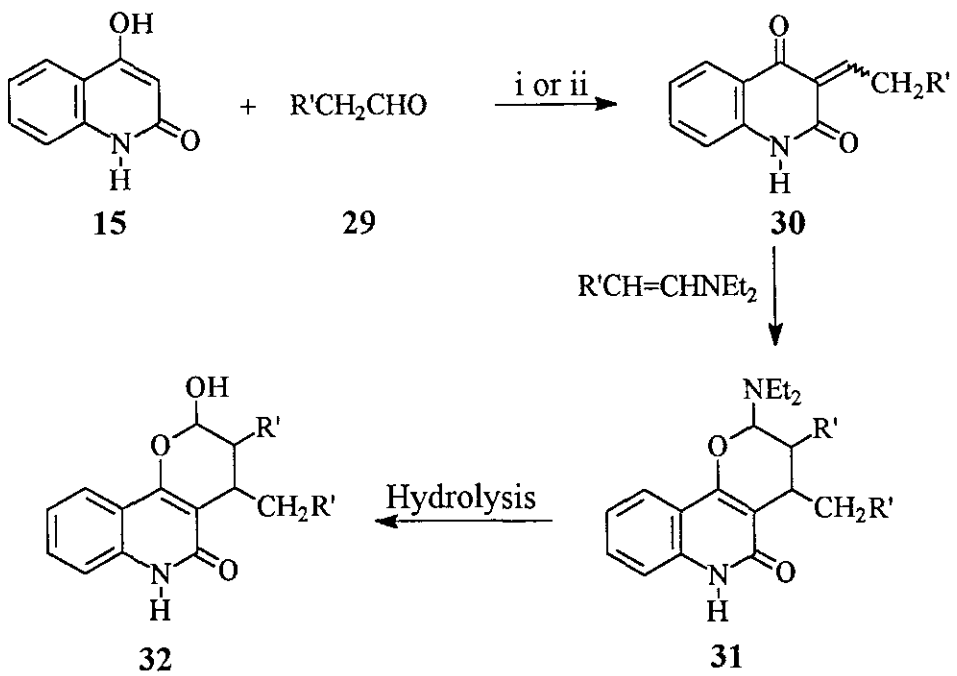


Scheme 7

Interestingly, it has been proposed that the biogenesis of flindersine **28** and related compounds occurs *via* the intermediate quinone methide formed from 3-isopropenyl quinolinone.[11]

Recently, enamines have been reported to add to quinolinone quinone methide in a 1,4-Michael addition reaction.[8] The hydroxyquinolinone **15** when treated with an aldehyde, thermally or photochemically in presence of a base,

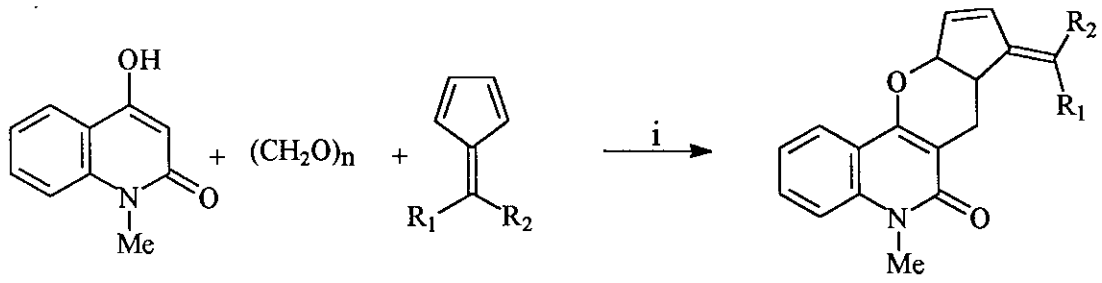
generated the quinone methide which was trapped with the enamines formed *in situ* (Scheme 8).



i. Et_2NH, benzene, reflux, 3-5 h; ii. Et_3N, benzene, hν

Scheme 8

Experiments in our laboratory have shown that this quinone methide can be generated and trapped conveniently in refluxing dioxane as shown by the reaction of fulvenes with 4-hydroxy-1-methylquinolin-2-one **33** in the presence of paraformaldehyde (Scheme 9).[12]



33 **34** **35** **36**

$R_1 = R_2 =$ H, alkyl, aryl

i. Dioxane, 100 °C, 2-3.5 h, 50-98%

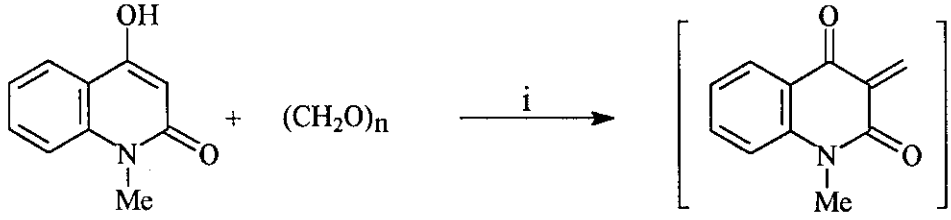
Scheme 9

3.1.2. THE PRESENT WORK

From the above discussion, it is clear that the cycloaddition reactions of quinolinone quinone methide have received only scant attention. As a part of our general interest in the chemistry of quinonoid compounds and their cycloaddition reactions in particular,[13] it was decided to study the cycloaddition profile of this heterocyclic quinone methide.

3.2. RESULTS AND DISCUSSION

The quinolinone quinone methide was generated *in situ* by treating 4-hydroxy-1-methylquinolin-2-one with paraformaldehyde in refluxing dioxane (Scheme 10).



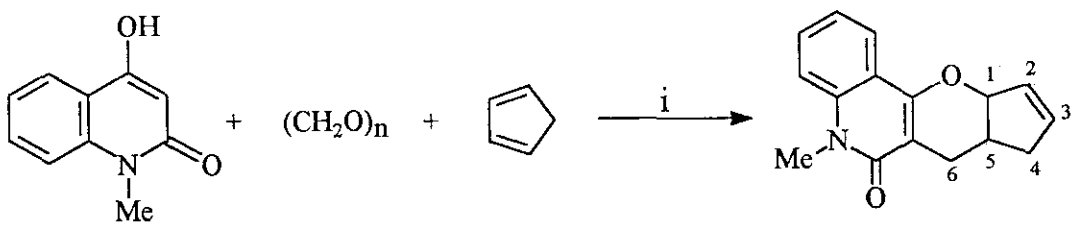
33 **34** **14**

i. Dioxane, 100 °C

Scheme 10

3.2.1. REACTION WITH CYCLIC DIENES

Our investigations were initiated with the reaction of 1-methyl-3-methylene-quinolin-2,4-dione **14** with cyclopentadiene. When 4-hydroxy-1-methylquinolin-2-one **33** was treated with paraformaldehyde in refluxing dioxane in the presence of cyclopentadiene, the *in situ* generated quinone methide **14** underwent facile hetero Diels-Alder reaction with cyclopentadiene in a chemo- and regioselective manner to afford a colorless product in 84% yield (Scheme 11).



33 **34** **37** **38**

i. Dioxane, 100 °C, 1 h, 84%

Scheme 11

The structure of the cycloadduct **38** was established by spectroscopic analysis. The IR spectrum of the product showed a strong absorption at 1639 cm^{-1}, attributable to the lactam carbonyl group. In the ^1H NMR spectrum, the olefinic protons appeared as two separate multiplets at δ 6.07 and 6.02 integrating for one proton each. The ring junction proton on C-1 showed a doublet at δ 5.23 (J = 4.9 Hz). The multiplet due to methine proton on the ring junction carbon C-5 appeared together with the signal due to one of the methylene protons in the region δ 2.88-2.82. The N-methyl protons resonated to give a singlet at δ 3.69. The signal due to the two methylene protons on C-6 appeared as a broad multiplet centered at

δ 2.60. In the ^{13}C NMR spectrum, the carbonyl carbon gave a signal at δ 163.41. The signal due to the sp^3 carbon C-1 was discernible at δ 83.03. All other signals in the ^1H and ^{13}C NMR spectra were in agreement with the assigned structure. Further support for the regiochemistry of the product was obtained from ^1H-^1H relayed COSY spectrum (Figure 1).

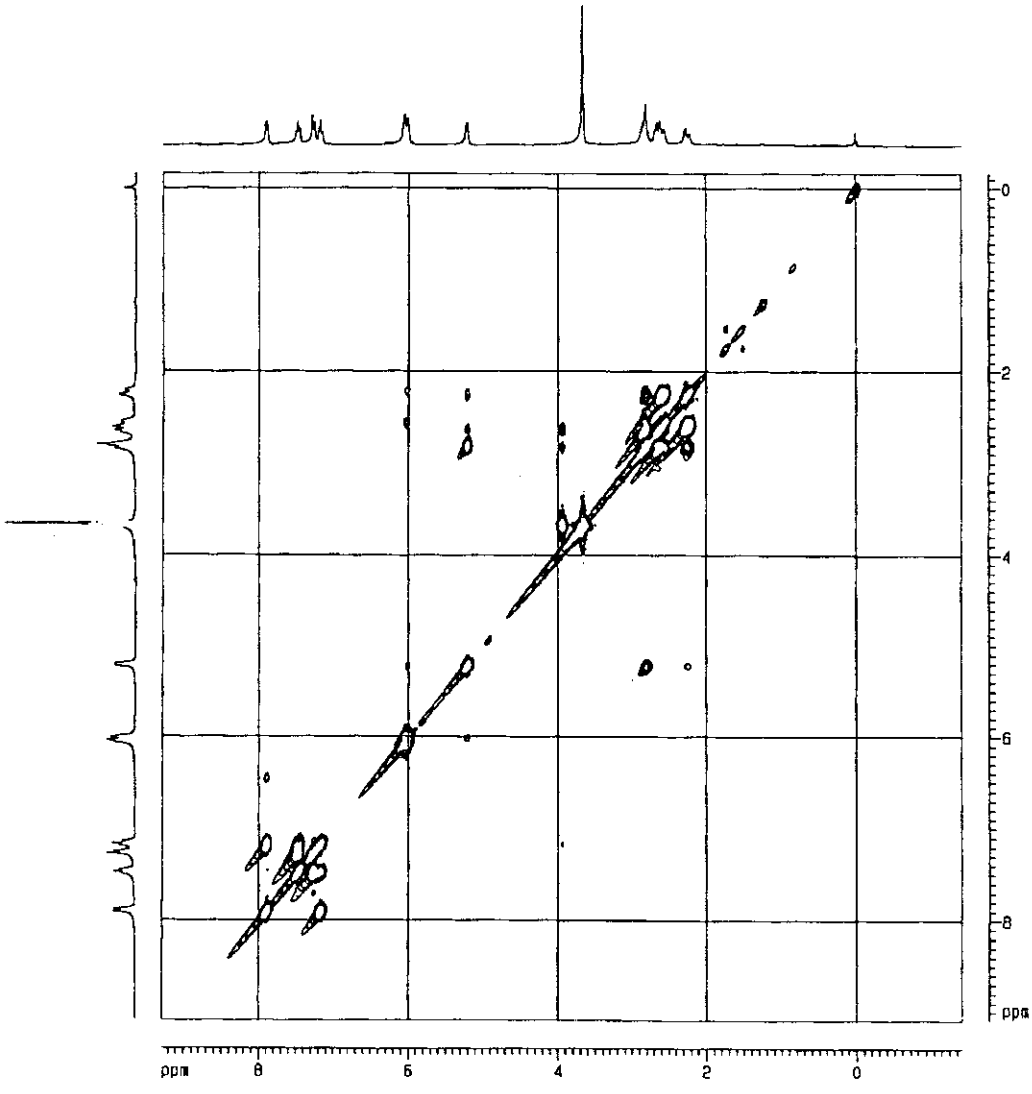
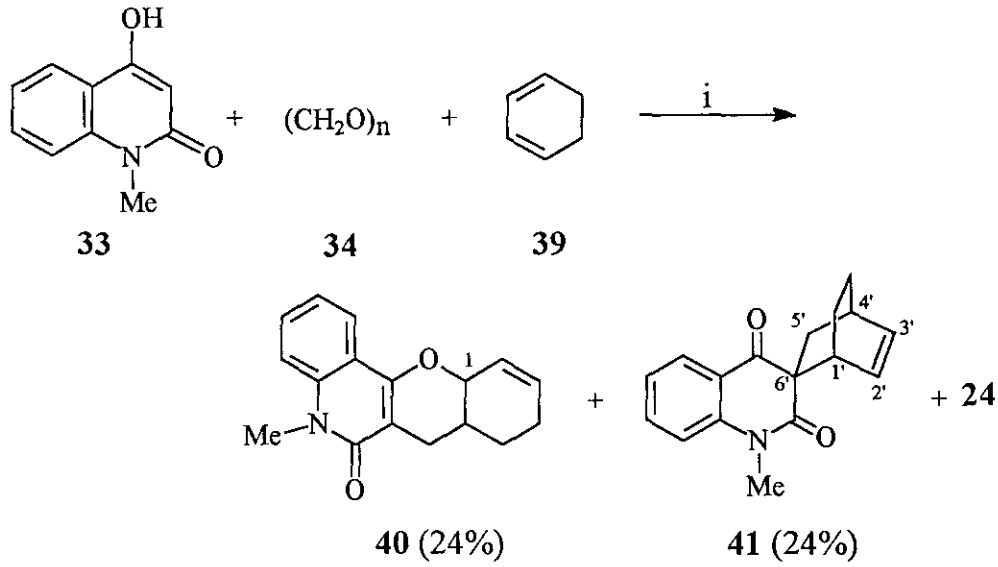


Figure 1. ^1H - ^1H COSY spectrum of **38**

The correlation spectrum clearly showed the connectivity between the different sets of protons. The most diagnostic of these is the connectivity shown by the ring junction proton on C-1 (δ 5.23), which is connected to the olefinic proton on C-2 (δ 6.07) and the ring junction proton on C-5 (δ 2.83).

Interestingly, when quinolinone **33** was treated with paraformaldehyde in the presence of cyclohexadiene under similar experimental conditions, spiroquinolinone **41** was also obtained along with the [3,2-c]pyranoquinolinone **40** and small amount of bisquinolinone **24** (Scheme 12).



i. Dioxane, 100 °C, 6 h

Scheme 12

The structure of the products was ascertained by spectroscopic analysis. The lactam carbonyl of **40** showed the IR absorption band at 1639 cm^{-1}. The ^1H NMR spectrum exhibited a broad multiplet centered at δ 5.94 due to the olefinic protons.

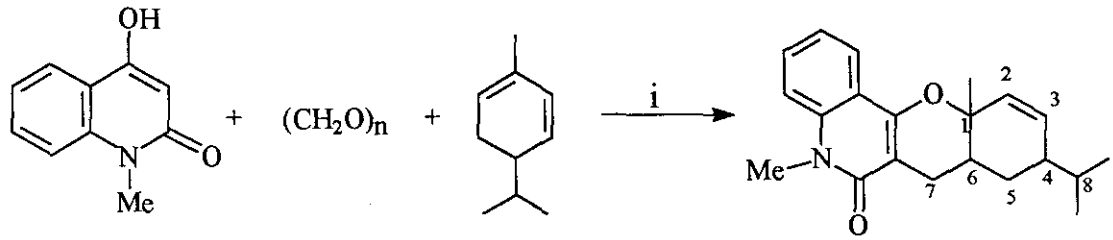
The ring junction proton on C-1 appeared as a broad singlet at δ 4.61. In the ^{13}C NMR spectrum, the carbonyl signal was seen at δ 163.33.

The IR spectrum of the spirocompound **41** showed two carbonyl absorptions at 1698 (ketone carbonyl) and 1647 cm^{-1} (lactam carbonyl). In the ^{1}H NMR spectrum, the olefinic protons appeared as two separate triplets at δ 6.38 (J = 7.2 Hz) and 5.88 (J = 7.1 Hz). The N-methyl protons displayed a singlet at δ 3.35. The signal due to the bridgehead protons on C-1' and C-4' appeared as multiplets centered at δ 2.70. One of the methylene protons on C-5' appeared as a double doublet at δ 2.35 (J = 12.5, 1.9 Hz). The other proton on the same carbon displayed a multiplet centered at δ 2.02. In the ^{13}C NMR spectrum, the two carbonyls gave signals at δ 196.21 and 172.27. The signal due to the spirocarbon was observed at δ 63.06.

Evidently, the spirocompound is formed by a Diels-Alder reaction where the quinone methide is taking part as a 2π component. There has been no previous report of this quinone methide acting as a 2π system except in the dimerization of quinone methide reported by Grundon *et al.*[9]

The formation of bisquinolinone **24** has enough literature precedence.[6, 8, 9] It was characterized by comparing the ^{1}H NMR data and melting point with those reported in the literature.[9]

When α-phellandrene **42** was treated with 4-hydroxy-1-methylquinolin-2-one **33** under usual conditions, the corresponding pyranoquinolinone **43** was obtained in 73% yield (Scheme 13).



33 **34** **42** **43**

i. Dioxane, 100 °C, 6 h, 73%

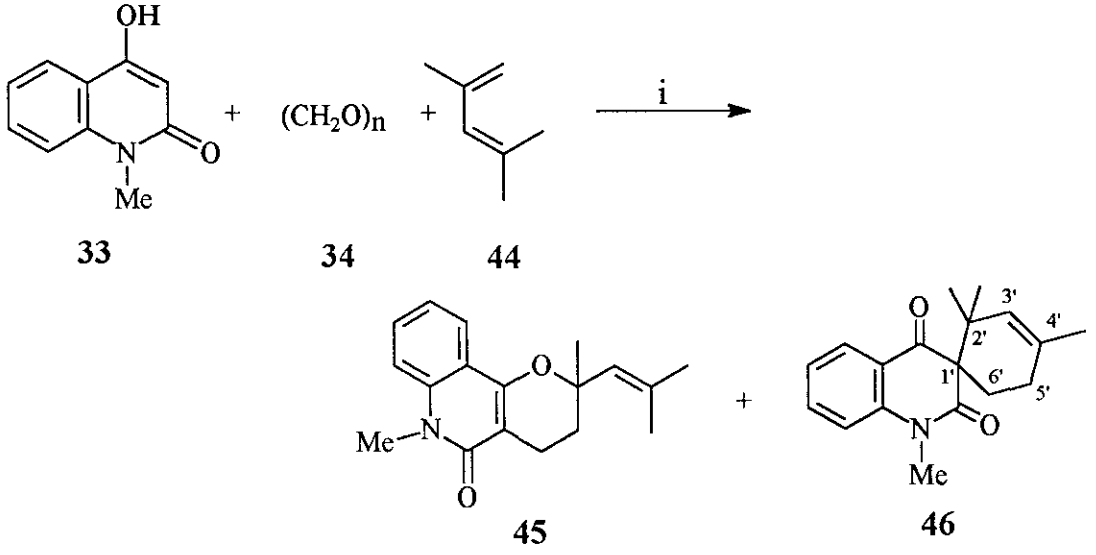
Scheme 13

The IR spectrum of **43** showed the lactam carbonyl absorption at 1633 cm^{-1}. In the ^1H NMR spectrum, the methylene protons on the pyran ring displayed separate double doublets at δ 2.72 (J = 17.6, 6.4 Hz) and 2.47 (J = 17.7, 7.2 Hz) integrating for one proton each. The signal due to the two olefinic protons appeared as a broad singlet at δ 5.72. The ring junction proton on C-6 and the proton on C-4 showed a multiplet centered at δ 2.14. The methylene protons on C-5 and the one proton on isopropyl group resonated together as a broad multiplet centered at δ 1.73. The methyl group on the ring junction carbon C-1 showed a singlet at δ 1.52 and the two methyl groups of the isopropyl moiety resonated as doublets at δ 0.95 and 0.93 (J = 6.6 Hz). In the ^{13}C NMR spectrum, the signal due to the lactam carbonyl was visible at δ 163.15. All the other signals were in agreement with the proposed structure.

3.2.2. REACTION WITH ACYCLIC DIENES

Subsequent to the above studies, we turned our attention to Diels-Alder trapping of the quinone methide **14** with acyclic dienes. When a mixture of 4-hydroxy-1-methylquinolin-2-one, paraformaldehyde and 2,4-dimethyl-1,3-

pentadiene was heated in dioxane under reflux for 3 h, the pyranoquinolinone **45** and spirocompound **46** were obtained in a total yield of 70% (Scheme 14).



i. Dioxane, 100 °C, 3 h, 70% (1:2)

Scheme 14

The structure of the products was ascertained on the basis of spectroscopic analysis. The IR spectrum of the pyranoquinolinone **45** showed the absorption due to the amide carbonyl at 1639 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton signal appeared as a singlet at δ 5.20. The geminal methyl groups on the olefinic carbon gave two separate singlets at δ 1.78 and 1.66 integrating for three protons each. The other possible regioisomeric structure was discarded on the basis of ^1H NMR analysis. In the other possible regioisomeric structure, there will be two olefinic protons and one proton on the sp^3 carbon adjacent to the pyran oxygen. However, the ^1H NMR spectrum of the adduct showed only one proton in the region δ 7.10-4.00. In the ^{13}C NMR spectrum, the signal due to the lactam carbonyl was seen at δ 163.14.

The IR spectrum of the spirocompound **46** showed two carbonyl absorption bands at 1689 (ketone carbonyl) and 1664 cm^{-1} (lactam carbonyl). In the ^{1}H NMR spectrum, the olefinic proton displayed a singlet at δ 4.88. The broad multiplet between δ 2.54-2.22 was attributed to three of the four methylene protons of the spirocyclohexene ring. The other proton resonated to give a separate multiplet centered at δ 2.05. In the ^{13}C NMR spectrum, the carbonyl groups were observed at δ 197.26 (ketone carbonyl) and 172.02 (lactam carbonyl). The signal due to the spirocarbon was discernible at δ 60.23 and that due to the quaternary carbon C-2' appeared at δ 39.39.

Finally, the structure of **46** was unequivocally established by single crystal X-ray analysis (Figure 2).

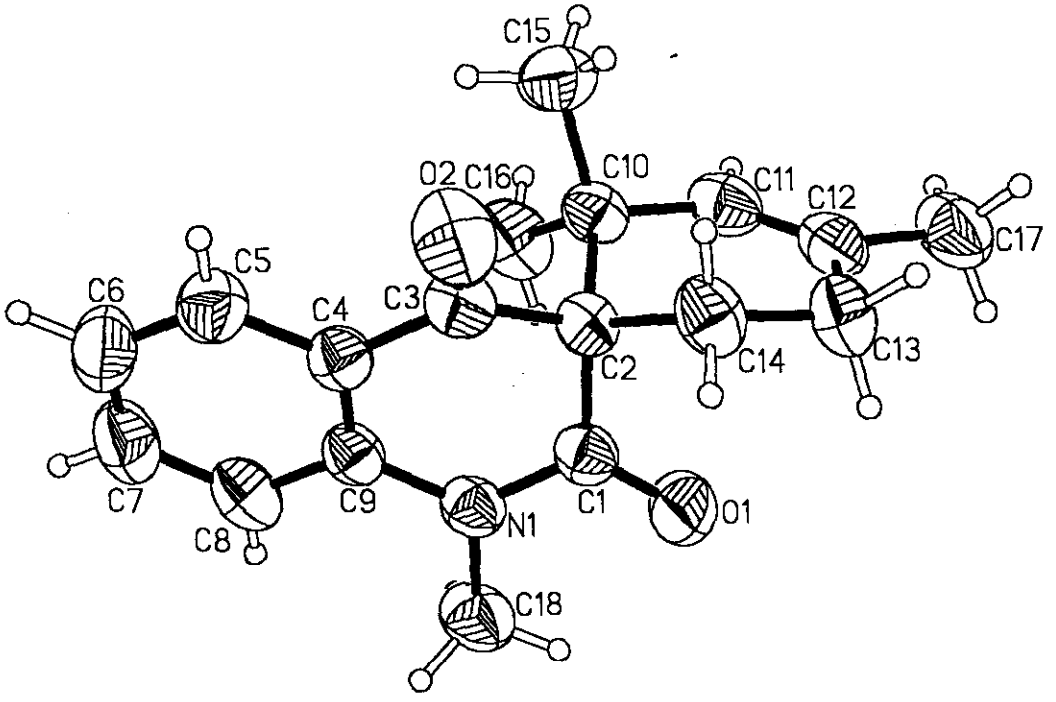
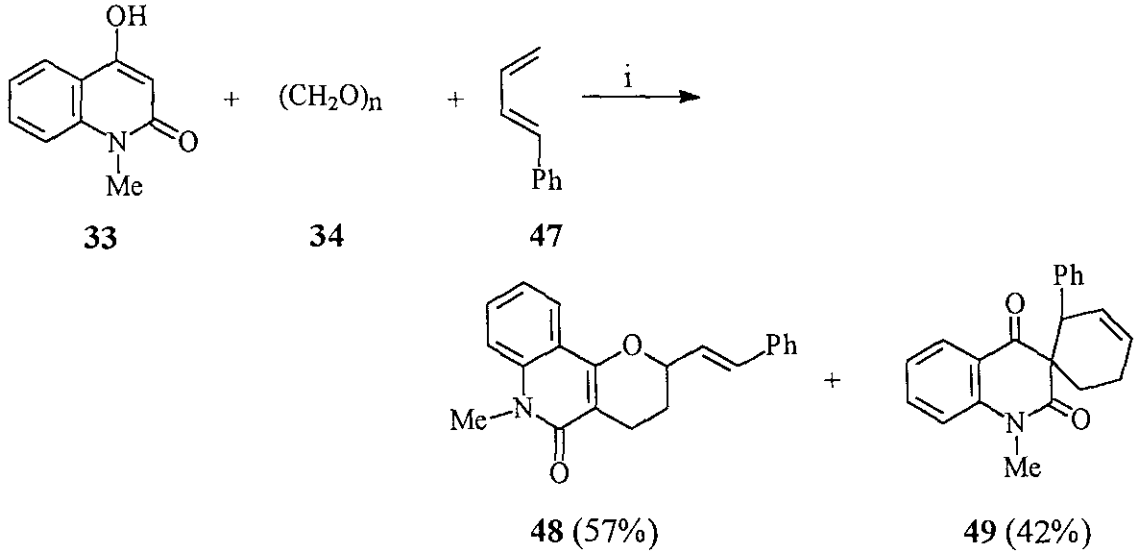


Figure 2. X-ray structure of **46**

A similar reaction was observed with 1-phenyl-1,3-butadiene and 4-hydroxy-1-methylquinolin-2-one **33** (Scheme 15).



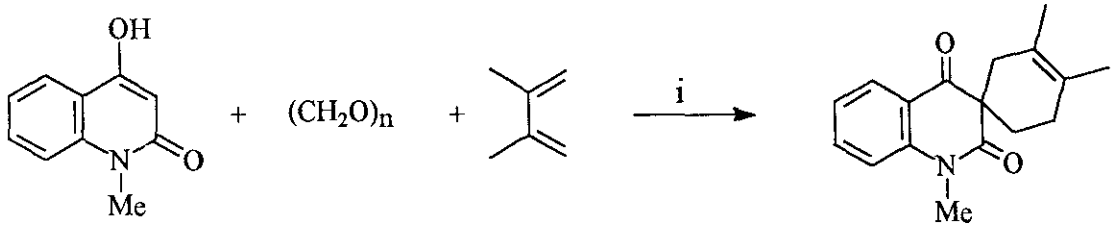
i. Dioxane, 100 °C, 4 h

Scheme 15

As usual the products were separated and characterized by spectroscopic analysis. The pyranoquinolinone **48** exhibited the characteristic IR absorption at 1633 cm^{-1}. The terminal olefinic proton resonated to give a doublet at δ 6.72 and the other olefinic proton signal appeared as a doublet at δ 6.35. The signal due to the carbonyl group was seen in the ^{13}C NMR spectrum at δ 162.97.

The spirocompound **49** showed two carbonyl absorptions at 1697 (ketone carbonyl) and 1657 cm^{-1} (lactam carbonyl) in the IR spectrum. In the ^{13}C NMR spectrum, the keto group displayed a signal at δ 197.49 and signal due to the lactam carbonyl was observed at δ 169.93.

Interestingly when the hydroxyquinolinone was treated with 2,3-dimethyl-1,3-butadiene under the usual conditions, the spirocompound **51** was the only product (Scheme 16).



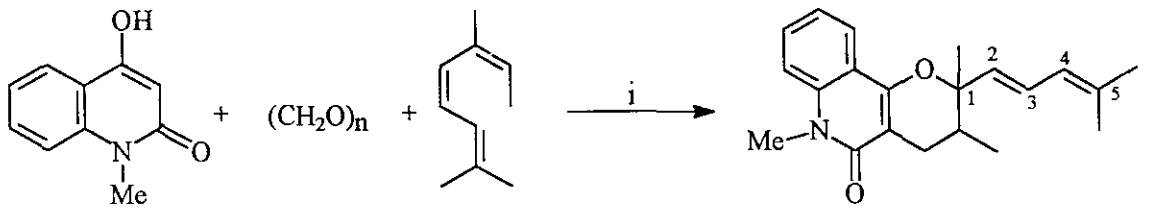
33 **34** **50** **51**

i. Dioxane, 100 °C, 2 h, 87%

Scheme 16

After chromatographic purification, the structure of the product was ascertained by spectroscopic analysis. The IR spectrum exhibited the carbonyl absorption peaks at 1696 and 1665 cm^{-1}. The ^1H NMR spectrum was devoid of any olefinic proton signal. The methyl groups attached to the sp^2 carbons were seen as singlets at δ 1.73 and 1.64. In the ^{13}C NMR spectrum, the carbonyl groups were discernible at δ 196.57 and 173.17.

In continuation of the above studies, 2,6-dimethyl-2,4,6-octatriene (alloocimene) was treated with **33** and paraformaldehyde under the usual conditions. The reaction afforded the pyranoquinoline derivative **53** (Scheme 17).



33 **34** **52** **53**

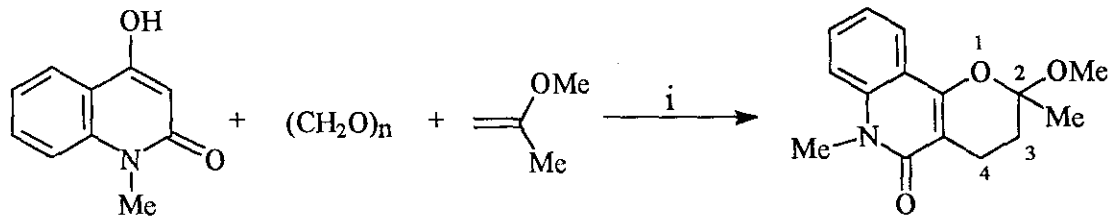
i. Dioxane, 100 °C, 6 h, 54%

Scheme 17

The product was purified by column chromatography and its structure was established on the basis of spectroscopic data. The IR spectrum of **53** showed characteristic lactam carbonyl absorption at 1637 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton on C-3 appeared as double doublet at δ 6.49 (J = 15.2, 10.9 Hz). The protons on C-2 and C-4 displayed doublets at δ 5.82 (J = 10.5 Hz) and 5.67 (J = 15.3 Hz). The two methylene protons on the pyran ring displayed separate double doublets at δ 2.71 (J = 17.6, 5.5 Hz) and 2.34 (J = 17.6, 8.1 Hz). The signal due to the methine proton was visible as a multiplet centered at δ 2.01.

3.2.3. REACTION WITH VINYL ETHERS

After completing the above investigations, we turned our attention to cycloaddition of the quinone methide to vinyl ethers. When 4-hydroxy-1-methylquinolin-2-one was refluxed with paraformaldehyde in dioxane in the presence of methoxypropene, the quinone methide was trapped efficiently giving pyranoquinoline **55** in high yield (Scheme 18).



33 **34** **54** **55**

i. Dioxane, 100 °C, 2 h, 81%

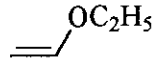
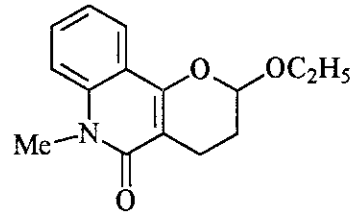
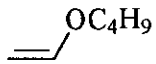
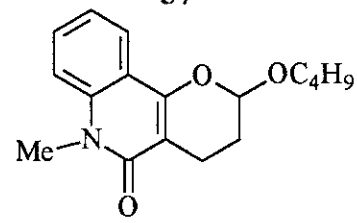
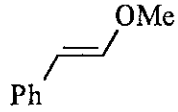
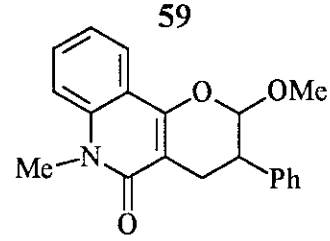
Scheme 18

The IR spectrum of **55** showed strong carbonyl absorption at 1636 cm^{-1}. In the ^1H NMR spectrum, the methoxy protons gave a sharp singlet at δ 3.30. The methylene protons on C-4 appeared as a multiplet at δ 2.67 and the other methylene protons displayed two separate multiplets centered at δ 2.18 and 1.83 integrating for one proton each. The amide carbonyl was visible at δ 162.88 in the ^{13}C NMR spectrum and the signal due to the acetal carbon was seen at δ 99.72. All the other signals in the ^1H and ^{13}C NMR spectra were in good agreement with the assigned structure.

Similar reactivity was exhibited by other vinyl ethers. Table 1 summarizes the results of these experiments.

As usual, the products were purified by column chromatography and characterized by spectroscopic analysis. All the products showed characteristic IR absorption and ^1H and ^{13}C NMR signals.

Table 1. Hetero-Diels-Alder reaction of **14** with vinyl ethers

Entry	Vinyl ether	Time (h)	Product	Yield (%)[a]
1	 **56**	2	 **57**	66
2	 **58**	4	 **59**	90
3	 **60**	6	 **61**	20*

Reaction conditions: Dioxane, 100 °C, [a] Isolated yield, * In this case most of the quinolinone was converted to bisquinolinone **24**.

The foregoing results show that depending on the reaction partner, 3-methylene quinolin-2,4-dione can act as a 2π and/or 4π component, resulting in Diels-Alder and/or hetero Diels-Alder adducts. The hetero Diels-Alder reaction exhibited excellent chemoselectivity. The methylene group of the quinone methide **14** is adjacent to two carbonyls, a ketone and a lactam carbonyl. Although not surprising, in all the above hetero Diels-Alder reactions, the ketone carbonyl was

found to take part in the reaction. Furthermore, the reaction was regioselective *i.e* in all the adducts the allylic, more substituted or hetero atom substituted carbon of the dienophile was bound to the heterodiene oxygen. This is in analogy with the regioselectivity observed in the [4+2] cycloaddition reactions of 1-oxa-1,3-butadienes, in which the latter act as 4π components in Diels-Alder reactions. Theoretical treatment of [4+2] cycloaddition reactions of 1-oxa-1,3-butadienes predict the preferential formation of 2-substituted 3,4-dihydro-2H-pyrans and accommodate the preferred *endo* approach of the reactants in which the carbon-carbon bond formation is more advanced than carbon-oxygen bond formation, *i.e.* a concerted but nonsynchronous [4+2] cycloaddition reaction.[1, 14]

3.2.4. THEORETICAL CALCULATIONS

In order to explain the observed mode of addition, theoretical calculations were carried out using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models.[15] The correlation diagram for the reaction of the quinone methide **14** with cyclopentadiene is provided as an illustrative example (Figure 3).

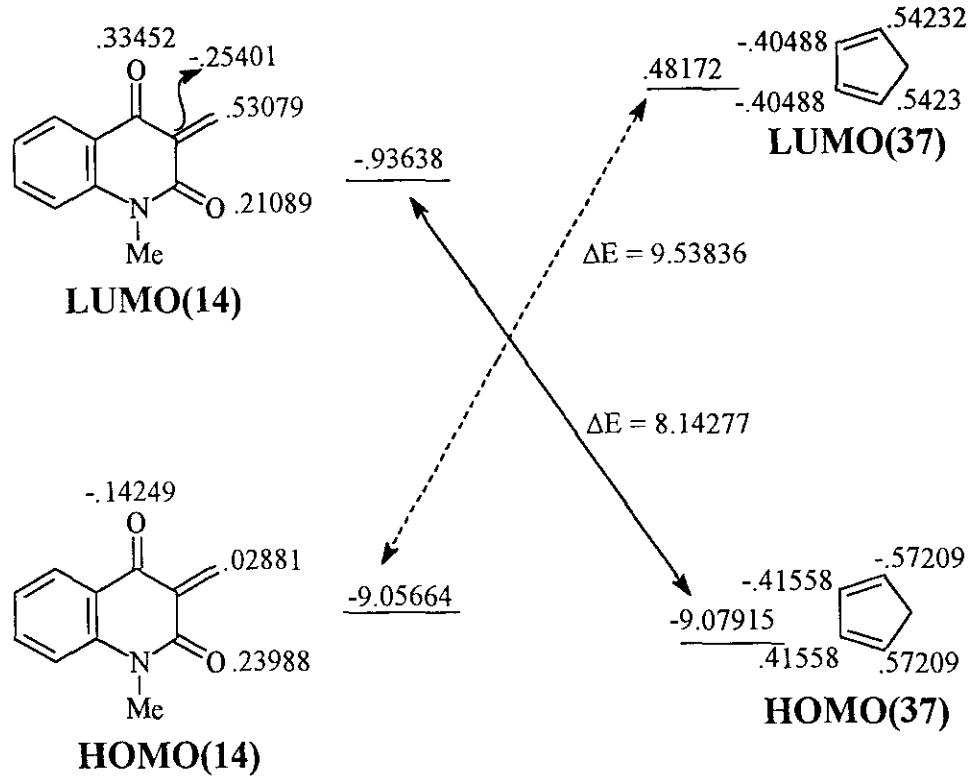


Figure 3. The correlation diagram for the reaction of **14** with cyclopentadiene

The correlation diagram indicates that HOMO(**14**)-LUMO(**37**) interaction and HOMO(**37**)-LUMO(**14**) interactions are symmetry allowed. However, HOMO(**37**)-LUMO(**14**) interaction is energetically more favorable compared to the other. Thus, it is an inverse electron demand Diels-Alder reaction. The regioselectivity of addition can be clearly explained by comparing the size of the orbital coefficients at the reacting centers. The favorable overlap between the orbitals of comparable size leads to the formation of the observed product. The major factor effecting the chemoselectivity is the LUMO coefficient at the carbonyl oxygens of **14**. The larger coefficient at the ketone oxygen (0.33452) compared to that at the lactam carbonyl oxygen (0.21089) explains the observed chemo-selectivity.

Similarly, the correlation diagram for the reaction between the quinone methide (**14**) and 2,3-dimethyl-1,3-butadiene shows that in this case the quinone methide is participating in a normal Diels-Alder reaction (Figure 4).

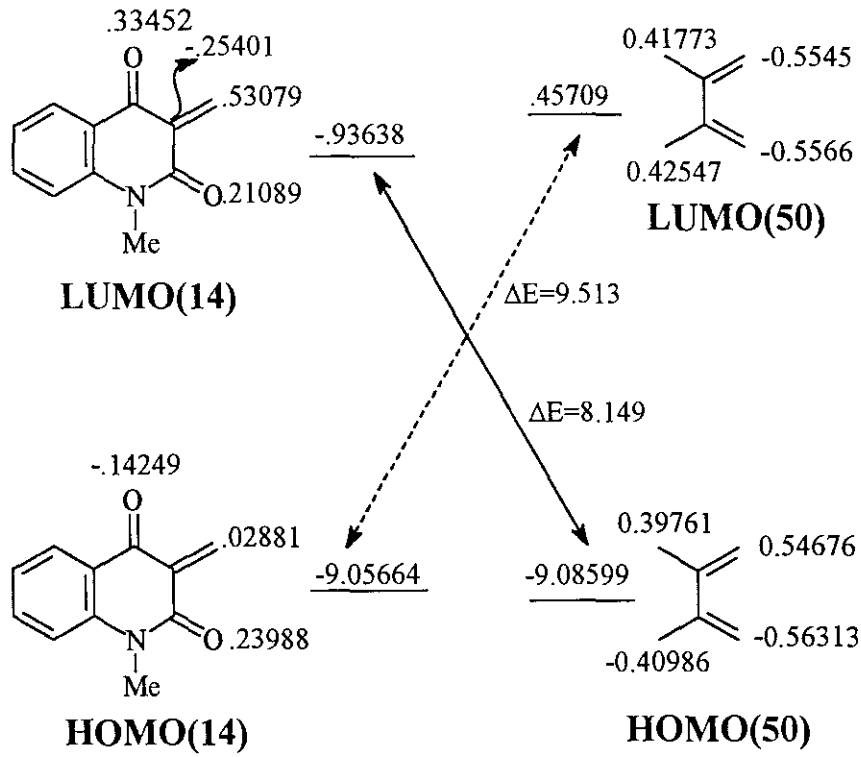


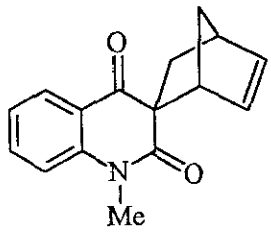
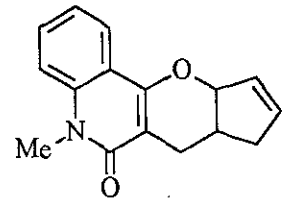
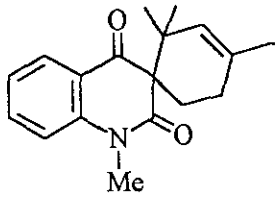
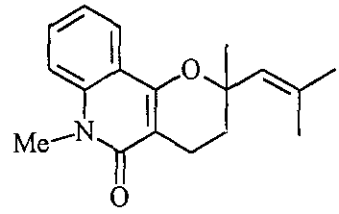
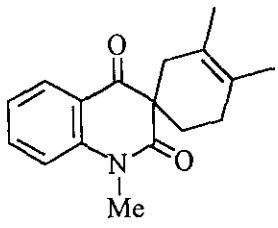
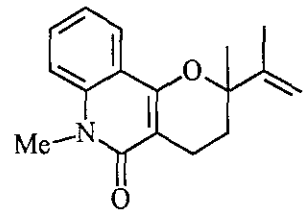
Figure 4. The correlation diagram for the reaction of **14** with **50**

HOMO(**14**)-LUMO(**50**) and HOMO(**50**)-LUMO(**14**) interactions are symmetry allowed. Here also, the HOMO(**50**)-LUMO(**14**) interaction is more favorable than the HOMO(**14**)-LUMO(**50**) interaction. The latter interaction is unimportant due to larger energy gap. Thus, it is a normal Diels-Alder reaction.

To explain the difference in reactivity of the quinone methide **14** towards different dienes, the heats of formation of the Diels-Alder and hetero Diels-Alder adducts were calculated using PM3 method of semi-empirical calculations (TITAN

software, version 1).[16] The heats of formation of some representative examples are given in Table 2.

Table 2. Heats of formation of Diels-Alder and hetero Diels-Alder adducts

Entry	Diels-Alder adduct	ΔHf (A) kcal/mol	Hetero Diels-Alder adduct	ΔHf (B) kcal/mol	Δ(A-B) kcal/mol
1	 **62**	13.029	 **38**	-1.671	14.70
2	 **46**	-30.167	 **45**	-32.313	2.14
3	 **51**	-38.367	 **63**	-20.434	17.93

An examination of the data in Table 2 shows that the hetero Diels-Alder adduct **38** is more stable than the corresponding normal Diels-Alder adduct by

14.70 kcal/mol, thus explaining the exclusive formation of **38** in the reaction of **14** with cyclopentadiene. In the case of normal Diels-Alder adduct **46** and hetero Diels-Alder adduct **45** of 2,4-dimethyl-1,3-pentadiene, the energy difference is only 2.14 kcal/mol which makes their interconversion possible *via* a [3,3]-sigmatropic rearrangement.[17] As evident from the heats of formation of **51** and **63**, obtained from 2,3-dimethyl butadiene, calculations predict substantial stability (17.93 kcal/mol) of the normal Diels-Alder adduct over the hetero Diels-Alder adduct. The experimental observation is in complete agreement with the theoretical prediction. The spiro compound **51** was the only product isolated from this reaction.

In summary, the present investigations have shown that *in situ* generation and Diels-Alder trapping of quinolinone quinone methide can lead to the formation of a variety of pyranoquinolinones and spiroquinolinediones. It is noteworthy that pyranoquinolinones have important applications in medicinal and synthetic organic chemistry.[1] In addition, pyranoquinolines are potentially useful as optical brightners and laser dyes.[18]

3.3. EXPERIMENTAL DETAILS

For general information, see **Section 2.3.** in **Chapter 2**.

1-Phenyl-1,3-butadiene was prepared from cinnamaldehyde by Wittig olefination. All the other reagents (dienes, vinyl ethers and 4-hydroxy-1-methyl-quinolin-2-one) were purchased from Aldrich.

General procedure for the reaction of 4-hydroxy-1-methylquinolin-2-one

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformalde-hyde (0.240 g, 8 mmol) and the diene/vinyl ether (3 mmol) were refluxed in dry dioxane under argon. On completion of the reaction, the solvent was removed *in vacuo* and the residue was taken up in chloroform, washed with sodium carbonate and brine. The extract was dried over anhydrous sodium sulfate and concentrated.

The crude product was then purified by column chromatography on silica gel (100-200 mesh). Mixtures of ethyl acetate and hexane were used as eluents.

7,7a,8,10a-Tetrahydro-5-methyl-6H-cyclopenta[5,6]pyrano[3,2-c] quinolin-6-one 38

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and cyclopentadiene (0.264 g, 4 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 1 h. The solvent was removed *in vacuo* and the residue was extracted with chloroform. The organic layer was washed with sodium carbonate solution and brine and dried over anhydrous sodium sulfate. The chloroform was evaporated off and the residue was subjected to chromatography on silica gel to afford 0.213 g (84%) of the pyranoquinolinone **38** as a colorless solid. It was recrystallized from CH_2Cl_2-hexane, mp. 113-115 °C.

IR (KBr) $\nu_{(max)}$: 1639, 1496, 1465, 1402, 1303, 1159, 1116 cm^{-1}.

^1H NMR : δ 7.93-7.90 (m, 1H), 7.52-7.47 (m, 1H), 7.31-7.26 (m, 1H), 7.21-7.16 (m, 1H), 6.08-6.06 (m, 1H), 6.02-6.00 (m, 1H), 5.23 (d, J = 4.9 Hz, 1H), 3.69 (s, 3H), 2.88-2.82 (m, 2H), 2.66-2.55 (m, 2H), 2.28-2.27 (m, 1H).

^{13}C NMR : δ 163.41, 157.54, 138.65, 136.97, 131.57, 130.29, 123.12, 121.67, 116.77, 113.94, 105.92, 83.03, 38.35, 35.49, 29.57, 21.54.

HRMS calcd. for $C_{16}H_{15}NO_2$: 253.1102. Found: 253.1099.

Cycloadducts 40 and 41

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and cyclohexadiene (0.240 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The aqueous work-up followed by chromatographic purification afforded the product **41** as a colorless solid (0.064 g, 24%) followed by 0.064 g (24%) of the adduct **40** as a colorless semisolid.

7,7a,8,9-Tetrahydro-5-methyl-6H,11aH-[1]benzopyrano[3,2-c]quinolin-6-one 40

IR (neat) $\nu_{(max)}$: 1639, 1496, 1396, 1315, 1166, 1116 cm^{-1}.

^1H NMR : δ 7.92-7.90 (m, 1H), 7.46-7.43 (m, 1H), 7.28-7.23 (m, 1H), 7.17-7.13 (m, 1H), 5.99-5.89 (m, 2H), 4.61 (brs, 1H), 3.66 (s, 3H), 2.74 (dd, J = 17.7, 6.8 Hz, 1H), 2.52 (dd, J = 17.7, 3.9 Hz, 1H), 2.26-2.19 (m, 3H), 1.63 (m, 2H).

^{13}C NMR : δ 163.33, 154.76, 138.51, 133.10, 129.97, 125.63, 122.87, 121.38, 116.19, 113.64, 105.12, 71.59, 29.76, 29.24, 24.77, 24.25, 23.46.

1-Methylspiro[2H,4H-quinoline-3,2'-bicyclo[2.2.2]oct-5'-ene]-2,4-dione 41

Recrystallized from CH_2Cl_2-hexane, mp. 118-120 °C.

IR (KBr) $\nu_{(max)}$: 1698, 1647, 1607, 1555, 1502, 1466, 1366 cm^{-1}.

^1H NMR : δ 7.83 (d, J = 7.6 Hz, 1H), 7.51-7.48 (m, 1H), 7.10-7.02 (m, 2H), 6.38 (t, J = 7.2 Hz, 1H), 5.88 (t, J = 7.1 Hz, 1H), 3.35 (s, 3H), 2.73-2.66 (m, 2H), 2.35 (dd, J = 12.5, 1.9 Hz, 1H), 2.06-2.01 (m, 1H), 1.59-1.55 (m, 2H), 1.43-1.35 (m, 2H).

^{13}C NMR : δ 196.21, 172.27, 142.84, 136.83, 134.99, 130.71, 128.31, 127.70, 122.70, 114.21, 63.06, 40.41, 30.44, 29.91, 27.76, 22.30, 22.01.

EIMS, m/z : 267 (M^+, 60), 266 (68), 188 (100), 134 (15), 104 (15), 80 (80).

7,7a,8,9-Tetrahydro-5,9,11a-trimethyl-6H,11H-[1]benzopyrano[3,2-c]quinolin-6-one 43

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and R-α-phellandrene (0.408 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The aqueous work-up followed by chromatographic purification afforded the product **43** as a semisolid (0.236 g, 73%).

IR (neat) $\nu_{(max)}$: 1633, 1596, 1502, 1463, 1397, 1321, 1261, 1183, 1115, 1091, 1048 cm^{-1}.

^1H NMR : δ 7.98 (d, J = 7.7 Hz, 1H), 7.52-7.47 (m, 1H), 7.31-7.16 (m, 2H), 5.72 (brs, 2H), 3.69 (s, 3H), 2.72 (dd, J = 17.6, 6.4 Hz, 1H), 2.47 (dd, J = 17.7, 7.2 Hz, 1H), 2.15-2.13 (m, 2H), 1.79-1.61 (m, 3H), 1.52 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H).

^{13}C NMR : δ 163.15, 154.32, 138.42, 132.78, 131.28, 129.79, 122.78, 121.24, 116.36, 113.55, 105.29, 77.33, 38.36, 33.57, 31.54, 29.13, 27.25, 26.85, 22.60, 19.87, 19.47.

HRMS calcd. for $C_{21}H_{25}NO_2$: 323.1885. Found: 323.1873.

Cycloadducts 45 and 46

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,4-dimethyl-1,3-pentadiene (0.288 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 3 h. The aqueous work-up and chromatography on silica gel afforded 0.136 g (48%) of **46** as a colorless solid and 0.062 g (22%) of **45** as a colorless semisolid.

2,3,4,6-Tetrahydro-2,6-dimethyl-2-(2-methylpropenyl)-pyrano[3,2-c]quinolin-5-one 45

IR (neat) $\nu_{(max)}$: 1639, 1502, 1458, 1396, 1315, 1178, 1110, 1072 cm^{-1}.

^1H NMR : δ 7.97 (d, J = 7.9 Hz, 1H), 7.52-7.46 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 5.20 (s, 1H), 3.69 (s, 3H), 2.66-2.57 (m, 2H), 2.06-2.00 (m, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.56 (s, 3H).

^{13}C NMR : δ 163.14, 155.34, 138.60, 136.35, 129.80, 127.62, 122.70, 121.28, 116.59, 113.67, 106.41, 78.08, 32.93, 29.14, 27.12, 26.83, 19.10, 17.92.

HRMS calcd. for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1580.

1,2',2',4'-Tetramethylspiro[2H,4H-quinolin-3,1'-cyclohex-3'-ene]-2,4-dione 46

Recrystallized from CH_2Cl_2-hexane, mp. 83-85 °C.

IR (neat) $\nu_{(max)}$: 1689, 1664, 1602, 1465, 1346, 1309 cm^{-1}.

^1H NMR : δ 7.85 (dd, J = 7.6, 1.2 Hz, 1H), 7.58-7.53 (m, 1H), 7.13-7.05 (m, 2H), 4.88 (s, 1H), 3.42 (s, 3H), 2.54-2.22 (m, 3H), 2.09-2.01 (m, 1H), 1.73 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H).

^{13}C NMR : δ 197.26, 172.02, 143.52, 135.20, 132.65, 127.52, 127.12, 123.22, 122.64, 113.96, 60.23, 39.39, 29.31, 27.91, 27.86, 26.98, 24.19, 23.41.

HRMS calcd. for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1579.

X-RAY Crystal data: $C_{18}H_{21}NO_2$. FW: 283.36. Crystal size: 0.28 x 0.22 x 0.20 mm^3, Crystal system: Monoclinic, Space group: $P2_1/c$. Unit cell dimensions a = 9.2857(3) Å, α = 90°; b = 21.7197(7) Å, β = 115.619(2)°; c = 8.3199(3) Å, γ = 90° R indices (all data) R1 = 0.0844, wR2 = 0.1329. Volume, Z = 1109.85(4) $Å^3$, 4. D calc. = 1.244 mg/m^3. F (000) = 608. Absorption Coefficient = 0.081 mm^{-1}. Reflections collected = 27675. λ = 0.71073 Å. (Sheldrick, G. M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

Cycloadducts 48 and 49

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 1-phenyl-1,3-butadiene (0.260 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 4 h. The aqueous work-up followed by chromatographic purification afforded the product **48** (0.181 g, 57%) and **49** (0.133 g, 42%) as semisolids.

2,3,4,6-Tetrahydro-6-methyl-2-(phenylvinyl)pyrano[3,2-c]quinolin-5-one 48

IR (neat) $\nu_{(max)}$: 1633, 1502, 1452, 1408, 1334, 1303 cm^{-1}.

^{1}H NMR : δ 7.97 (d, J = 7.9 Hz, 1H), 7.49-7.17 (m, 7H), 6.72 (d, J = 15.9 Hz, 1H), 6.35 (dd, J = 15.9, 6.2 Hz, 1H), 4.80 (t, J = 6.3 Hz, 1H), 4.19 (brs, 1H), 3.66 (s, 3H), 2.81-2.57 (m, 2H), 2.23-2.13 (m, 1H), 2.02-1.86 (m, 1H).

^{13}C NMR : δ 162.97, 155.94, 138.40, 136.09, 132.02, 130.06, 128.51, 127.95, 127.45, 126.54, 124.50, 122.63, 121.43, 116.05, 113.67, 106.60, 81.73, 29.17, 27.08, 19.24.

HRMS calcd. for $C_{21}H_{19}NO_2$: 317.1415. Found: 317.1401.

1-Methyl-2'-phenylspiro[2H,4H-quinoline-3,1'-cyclohex-3'-ene]-2,4-dione 49

IR (neat) $\nu_{(max)}$: 1697, 1657, 1595, 1471, 1346, 1303 cm^{-1}.

^{1}H NMR : δ 7.96-7.93 (m, 1H), 7.47-7.41 (m, 1H), 7.09-7.02 (m, 6H), 6.80 (d, J = 8.2 Hz, 1H), 6.04-6.01 (m, 1H), 5.73-5.70 (m, 1H), 4.17 (s, 1H), 3.10 (s, 3H), 2.61-2.34 (m, 1H), 2.41-2.26 (m, 2H), 2.08-2.01 (m, 1H).

^{13}C NMR : δ 197.49, 169.93, 142.98, 139.86, 135.47, 129.10, 127.79, 127.39, 126.87, 126.75, 122.35, 113.96, 47.76, 28.96, 22.72.

EIMS *m/z* : 269 (M^+, 100), 254 (68), 241 (38), 214 (40), 200 (98), 188 (46), 134 (13), 104 (9), 91 (11), 77 (17), 69 (14), 55 (6).

1,3',4'-Trimethylspiro[2H,4H-quinolin-3,1'-cyclohex-3-ene]-2,4-dione 51

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,3-dimethyl-1,3-butadiene (0.246 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 2 h. The aqueous work-up followed by chromatographic purification afforded the product **51** as a colorless solid (0.234 g, 87%). It was recrystallized from CH_2Cl_2-hexane, mp. 88-90 °C.

IR (KBr) $\nu_{(max)}$: 1696, 1665, 1598, 1470, 1351, 1300, 1096 cm^{-1}.

^{1}H NMR : δ 7.90 (dd, J = 7.5, 1.2 Hz, 1H), 7.58 (dt, J = 8.3, 1.5 Hz, 1H), 7.20-7.09 (m, 2H), 3.45 (s, 3H), 2.60 (d, J = 17.3 Hz, 1H), 2.49 (d, J = 17.3 Hz, 2H), 1.98-1.85 (m, 4H), 1.73 (s, 3H), 1.64 (s, 3H).

^{13}C NMR : δ 196.57, 173.17, 142.85, 135.16, 128.02, 123.72, 122.91, 120.75, 114.34, 57.74, 32.78, 32.44, 30.09, 28.69, 19.00, 18.96.

2,3,6-Trimethyl-2-(4-methyl-1,3-pentadienyl)-pyrano[3,2-c]quinolin-5-one 53

4-Hydroxy-1-methylquinolin-2-one **16** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,6-dimethyl-2,4,6-octatriene (0.272 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The aqueous work-up followed by chromatographic purification afforded the product **53** as a semisolid (0.174 g, 54%).

IR (neat) $\nu_{(max)}$: 1637, 1593, 1398, 1180, 1118 cm^{-1}.

^{1}H NMR : δ 8.02-7.99 (m, 1H), 7.54-7.49 (m, 1H), 7.23-7.13 (m, 2H), 6.49 (dd, J = 15.2, 10.9 Hz, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.67 (d, J = 15.3 Hz, 1H), 3.70 (s, 3H), 2.71 (dd, J = 17.6, 5.5 Hz, 1H), 2.34 (dd, J = 17.6, 8.1 Hz, 1H), 2.04-1.97 (m, 1H), 1.77 (s, 3H), 1.70 (s, 3H), 1.38 (s, 3H), 1.04 (d, J = 9.2 Hz, 3H).

^{13}C NMR : δ 163.16, 154.94, 138.64, 136.08, 133.67, 129.98, 125.93, 124.46, 122.76, 121.43, 116.46, 113.70, 105.72, 81.27, 34.42, 29.79, 26.38, 26.02, 19.81, 18.37, 15.95.

HRMS calcd. for $C_{21}H_{25}NO_2$: 323.1885. Found: 323.1871.

2,3,4,6-Tetrahydro-2-methoxy-2,6-dimethylpyrano[3,2-c]quinolin-5-one 55

4-Hydroxy-1-methylquinolin-2-one **33** (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and methoxypropene (0.216 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 2 h. The aqueous work-up

followed by chromatographic purification afforded the product **55** (0.210 g, 81%) as a colorless solid. It was recrystallized from CH_2Cl_2-hexane, mp. 118-120 °C.

IR (KBr) $\nu_{(max)}$: 1636, 1619, 1593, 1503, 1465, 1396, 1323, 1164, 1063 cm^{-1}.

^1H NMR : δ 7.97 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.1 Hz, 1H), 3.71 (s, 3H), 3.30 (s, 3H), 2.68-2.66 (m, 2H), 2.21-2.16 (m, 1H), 1.87-1.76 (m, 1H), 1.65 (s, 3H).

^{13}C NMR : δ 162.88, 153.59, 138.66, 129.90, 122.16, 121.38, 116.05, 113.71, 107.79, 99.72, 49.26, 31.31, 29.17, 22.61, 17.07.

EIMS, m/z : 259 (M^+, 45), 244 (40), 228 (15), 202 (100), 186 (12).

2-Ethoxy-2,3,4,6-tetrahydro-6-methylpyrano[3,2-c]quinolin-5-one 57

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and ethyl vinyl ether (0.216 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 2 h. The aqueous work-up followed by chromatographic purification afforded the product **57** (0.171 g, 66%) as a colorless semisolid.

IR (KBr) $\nu_{(max)}$: 1639, 1595, 1508, 1465, 1402, 1321, 1091, 1054 cm^{-1}.

^1H NMR : δ 7.93 (d, J = 7.9 Hz, 1H), 7.54-7.49 (m, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 5.40 (d, J = 2.5 Hz, 1H), 3.93-3.90 (m, 1H), 3.74-3.69 (m, 1H), 3.70 (s, 3H), 2.70-2.66 (m, 2H), 2.16-2.08 (m, 1H), 1.99-1.92 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 162.79, 153.58, 138.64, 129.95, 122.33, 121.37, 116.13, 113.68, 107.61, 98.05, 64.36, 29.16, 26.00, 16.01, 15.11.

HRMS calcd. for $C_{15}H_{17}NO_3$: 259.1208. Found: 259.1207.

2-Butoxy-2,3,4,6-tetrahydro-6-methylpyrano[3,2-c]quinolin-5-one 59

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and butyl vinyl ether (0.216 g, 3 mmol) were refluxed (100 °C)

in dioxane (6 mL) under argon atmosphere for 4 h. The aqueous work-up followed by chromatographic purification afforded the product **59** (0.258 g, 90%) as a colorless oil.

IR (neat) $\nu_{(max)}$: 1640, 1596, 1579, 1502, 1464, 1399, 1354, 1318, 1157, 1092 cm^{-1}.

^1H NMR : δ 7.91 (d, J = 7.9 Hz, 1H), 7.51-7.48 (m, 1H), 7.31(d, J = 8.4 Hz, 1H), 7.23-7.17 (m, 1H), 5.38 (dd, J = 4.5, 2.6 Hz, 1H), 3.88-3.85 (m, 1H), 3.70 (s, 3H), 3.66-3.62 (m, 1H), 2.70-2.65 (m, 2H), 2.11-2.10 (m, 1H), 1.97-1.95 (m, 1H), 1.57-1.52 (m, 2H), 1.35-1.27 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H).

^{13}C NMR : δ 162.87, 153.69, 138.70, 130.00, 122.41, 121.44, 116.22, 113.74, 107.67, 98.30, 68.68, 31.66, 29.24, 26.06, 19.22, 16.05, 13.79.

HRMS calcd. for $C_{17}H_{21}NO_3$: 287.1521. Found 287.1514.

2,3,4,6-Tetrahydro-2-methoxy-6-methyl-3-phenylpyrano[3,2-c]quinolin-5-one 61

4-Hydroxy-1-methylquinolin-2-one (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and β-methoxystyrene (0.238 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The aqueous work-up followed by chromatographic purification afforded the product **61** (0.064 g, 20%) as a colorless solid. It was recrystallized from CH_2Cl_2-hexane, mp. 117-119 °C.

IR (KBr) $\nu_{(max)}$: 1638, 1614, 1592, 1497, 1457, 1412, 1256, 1227, 1137, 1115, 1098 cm^{-1}.

^1H NMR : δ 7.96 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.1 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.26-7.20 (m, 6H), 5.30 (d, J = 3.78 Hz, 1H), 3.73 (s, 3H), 3.56 (s, 3H), 3.37-3.35 (m, 1H), 3.08 (dd, J = 17.8, 6.7 Hz, 1H), 2.95 (dd, J = 17.8, 4.6 Hz, 1H).

^{13}C NMR : δ 162.52, 153.53, 140.74, 138.72, 128.54, 127.49, 126.93, 122.45, 121.49, 115.80, 113.77, 107.10, 102.81, 56.29, 41.03, 29.23, 23.47.

HRMS calcd. for $C_{20}H_{19}NO_3$: 321.1364. Found: 321.1354.

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CHAPTER 4

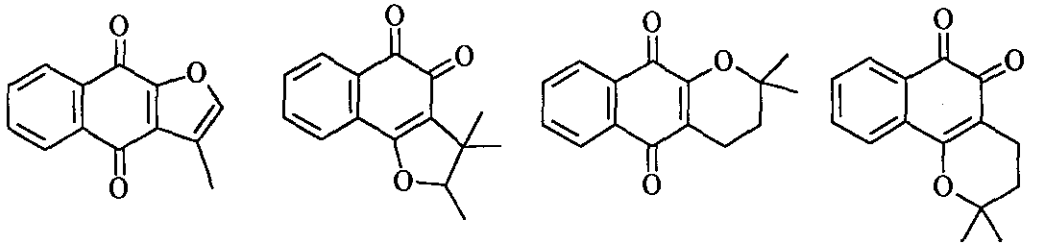
CYCLOADDITION REACTIONS OF 3-METHYLENE-1,2,4-NAPHTHALENETRIONE AND CAN MEDIATED OXIDATIVE ADDITION OF 2-HYDROXY-1,4-NAPHTHOQUINONE

This chapter is divided into two sections. The first section deals with the generation and hetero Diels-Alder reactions of the quinone methide derived from 2-hydroxy-1,4-naphthoquinone. The second section gives an account of cerium(IV) ammonium nitrate (CAN) mediated oxidative addition of 2-hydroxy-1,4-naphthoquinone to dienes.

4.1. CYCLOADDITION REACTIONS OF 3-METHYLENE-1,2,4-NAPHTHALENETRIONE

4.1.1. INTRODUCTION

Naphthofurandiones, dihydronaphthofurandiones and dihydronaphthopyrandiones comprise an important group of heterocyclic quinones.[1] Some representative examples of this class of compounds are given in Figure 1.

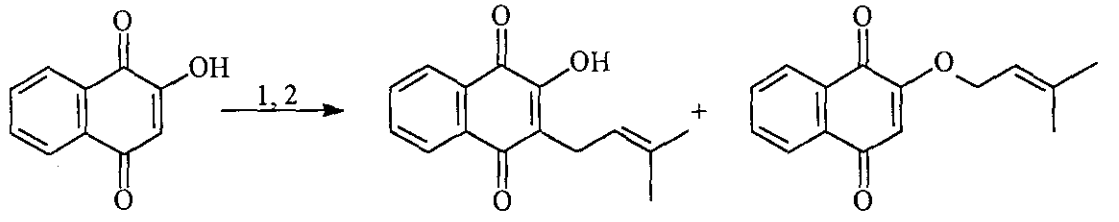


Maturinone **Dunnione** ***α*-Lapachone** ***β*-Lapachone**

Figure 1

A number of these compounds exhibit wide range of pharmacological activities.[1] For example, *β*-lapachone induces apoptosis in human prostate cancer cells *in vitro*[2,3] and several of its derivatives are cytotoxic agents.[4,5]

The synthesis of these compounds is essentially dependent on the elaboration of lapachol **2** and this has been the target of many synthetic efforts.[6] Recently, a novel protocol for the synthesis of lapachol was reported by Frydman *et al.* (Scheme 1).[7]



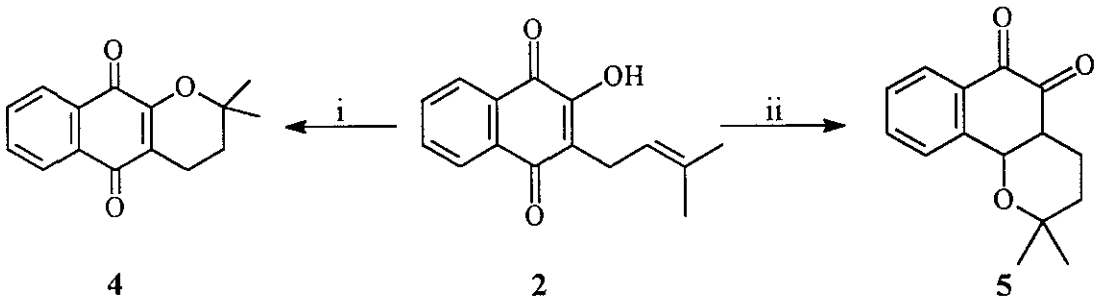
1 **2** **3**

1. i) DMSO, -78 °C, LiH; ii) LiI, $Me_2C{=}CHCH_2Br$, 25 °C; iii) 45 °C, 5 h, H^+

2. i) EtOAc, 5% $NaHCO_3$, HCl; ii) EtOAc, Et_2O, 2N NaOH, HCl

Scheme 1

The acid catalyzed cyclization of lapachol by classical methods leads to the formation of lapachones (Scheme 2).[8]



4 **2** **5**

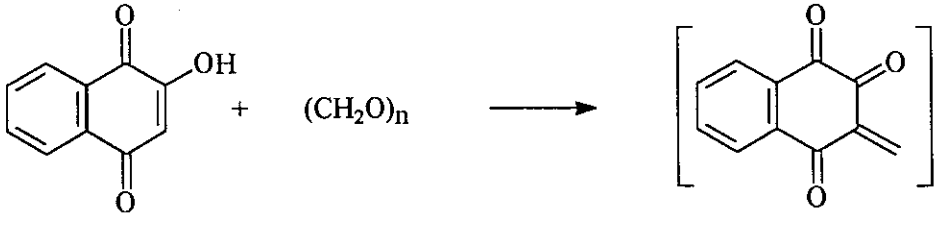
i. HCl, 25 °C, H_2O; ii. H_2SO_4, 25 °C, H_2O

Scheme 2

As part of our research program focused on the Diels-Alder and other cycloaddition reactions of quinonoid compounds,[9] we became interested in the construction of dihydronaphthopyrandiones by hetero Diels-Alder reactions of 3-methylene-1,2,4-(3H)naphthalenetrione, the quinone methide generated from 2-hydroxy-1,4-naphthoquinone. The results of these investigations are presented here.

4.1.2. RESULTS AND DISCUSSION

The quinone methide 7 was generated by an uncatalyzed Knoevenagel condensation of 2-hydroxy-1,4-naphthoquinone **1** with paraformaldehyde (Scheme 3).



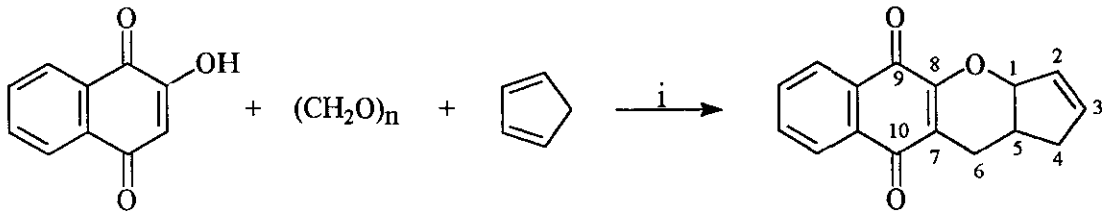
1 **6** **7**

i. Dioxane, 100 °C

Scheme 3

4.1.2.1. REACTION WITH CYCLIC DIENES

Our studies started with the reaction of cyclopentadiene with the quinone methide 7. When a mixture of 2-hydroxy-1,4-naphthoquinone 1 and paraformaldehyde was refluxed in dioxane in the presence of cyclopentadiene, the reaction proceeded smoothly to afford the cycloadduct 9 in 90% yield (Scheme 4).



1 **6** **8** **9**

i. Dioxane, 100 °C, 3 h, 90%

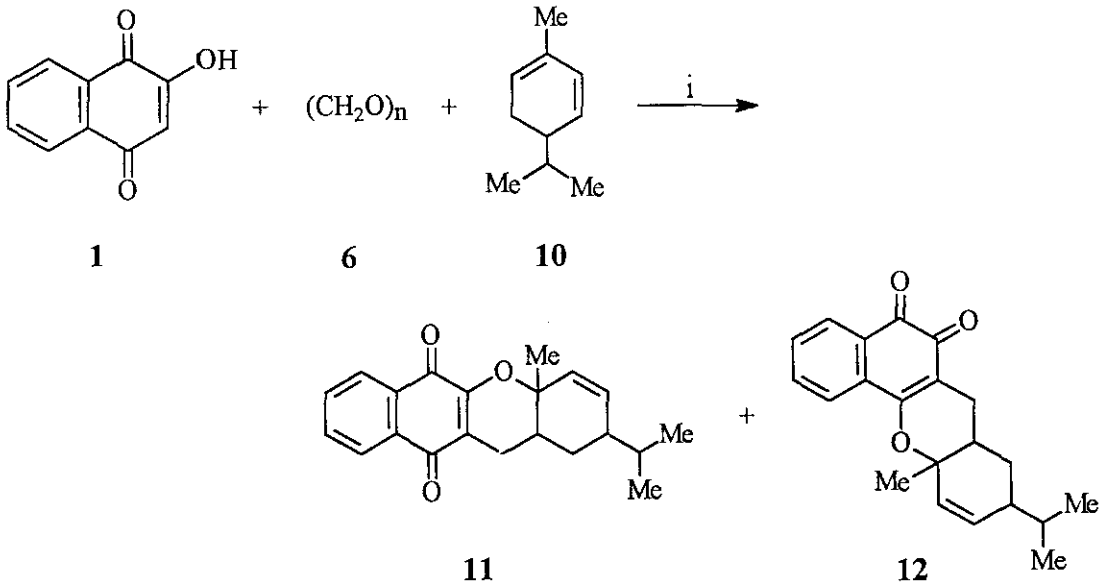
Scheme 4

The structure of the product was ascertained on the basis of spectroscopic data. The IR spectrum of the cycloadduct showed strong carbonyl absorption at 1676 cm^{-1}. In the ^1H NMR spectrum, the aromatic protons were seen as two multiplets centered at δ 8.07 and 7.65 integrating for two protons each. The olefinic protons were seen as a broad singlet at δ 6.07. The ring junction proton on the carbon adjacent to the pyran oxygen resonated to give a doublet at δ 5.29 (J = 5.2 Hz) and the other ring junction proton displayed a mulitplet centered at δ 2.84. In the ^{13}C NMR spectrum, the signals due to the carbonyl groups were discernible at δ 183.78 (C-9) and 179.22 (C-10). The sp^3 carbon adjacent to the pyran oxygen showed a signal at δ 83.77.

The regiochemistry of the cycloadduct was confirmed by 2D-^1H NMR spectroscopy. ^1H-^1H Relayed COSY spectrum of the adduct showed through-bond connectivity between the two sets of hydrogen atoms. The ring junction proton on C-1 (δ 5.29, d, J = 5.2 Hz) is connected to the olefinic proton on C-2

(δ 6.07, brs) and the other ring junction proton on C-5 (δ 2.84, m) which in turn is connected to both the methylene moieties.

When a mixture of 2-hydroxy-1,4-naphthoquinone **1**, α-phellandrene and paraformaldehyde was heated under reflux in dioxane for 6 h, two products, **11** and **12** were obtained in almost equal amounts (Scheme 5).



i. Dioxane, 100 °C, 6 h, 62% (1:1)

Scheme 5

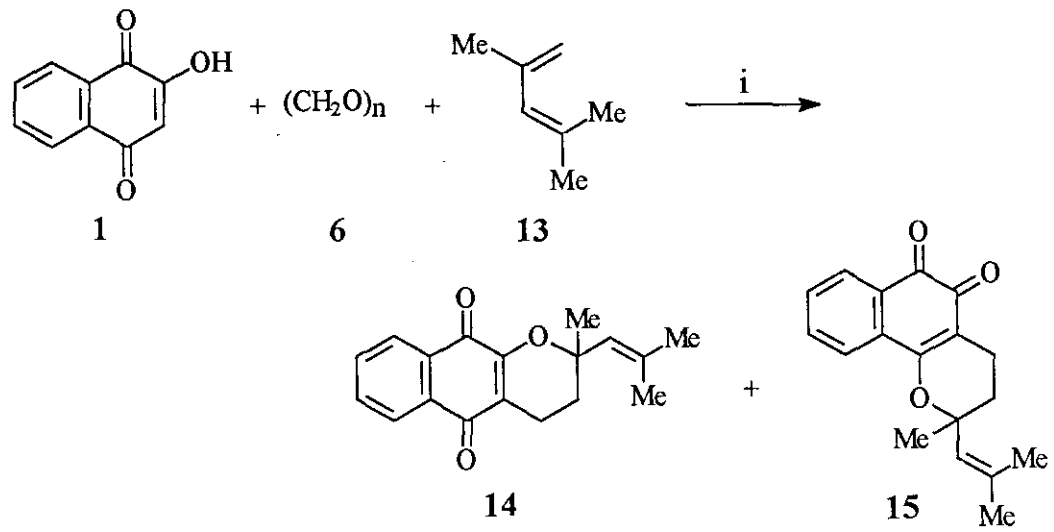
The products were separated by column chromatography and the structure of the products was assigned on the basis of spectroscopic data. The cycloadduct **11** showed the carbonyl absorption at 1679 cm^{-1} in the IR spectrum. The ^1H NMR spectrum exhibited the olefinic protons as a multiplet centered at δ 5.74. The methylene protons of the pyran ring resonated to give double doublets at δ 2.68 (J = 18.7, 6.2 Hz, 1H) and 2.41 (J = 18.7, 7.8 Hz, 1H). The methyl group on the ring junction carbon appeared as a singlet at δ 1.55 and the methyl protons of the isopropyl moiety displayed doublets at δ 0.95 (J = 6.7 Hz,

3H) and 0.93 (J = 6.8 Hz, 3H). The signals due to the carbonyl groups were discernible in the ^{13}C NMR spectrum at δ 184.20 and 180.10. The assigned structure was further confirmed by DEPT-135 spectrum. DEPT-135 spectrum of **11** ascertained that the sp^3 carbon adjacent to the pyran oxygen is a quaternary centre, which cannot be true in the other possible regioisomer.

The IR spectrum of **12** showed a sharp absorption at 1698 cm^{-1}. In the ^1H NMR spectrum, the aromatic protons gave four separate signals at δ 8.05 (d, J = 6.7 Hz), 7.81 (d, J = 7.1 Hz), 7.61 (t, J = 7.5 Hz) and 7.49 (t, J = 7.5 Hz) integrating for one proton each. The signals due to the carbonyl groups were visible at δ 179.52 and 178.93 in the ^{13}C NMR spectrum. The ^1H and ^{13}C NMR spectra displayed all the other characteristic peaks. Ultimately the structure assignment was confirmed by DEPT-135 NMR spectrum.

4.1.2.2. REACTION WITH ACYCLIC DIENES

Subsequently we turned our attention to the hetero Diels-Alder reaction of quinone methide **7** with acyclic dienes. Initially 2,4-dimethyl-1,3-pentadiene was treated with 2-hydroxy-1,4-naphthoquinone **1** and paraformaldehyde in refluxing dioxane. The reaction proceeded smoothly to afford 2,3-dihydro-2-methyl-2-(2-methylpropenyl)-4H-naphtho[2,3-b]pyran-5,10-dione **14** and 3,4-dihydro-2-methyl-2-(2-methylpropenyl)-2H-naphtho[1,2-b]-5,6-dione **15** in a total yield of 94% (Scheme 6).



i. Dioxane, 100 °C, 6 h, 94% (4:3)

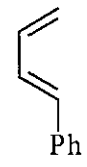
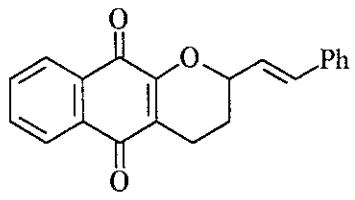
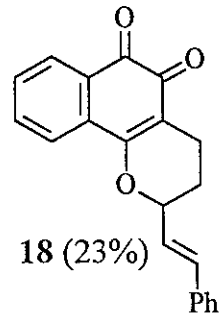
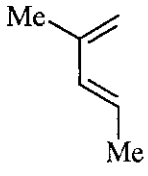
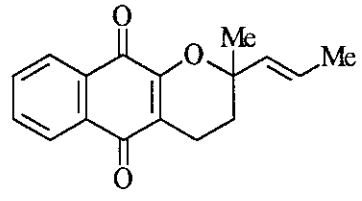
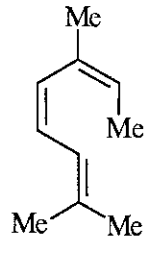
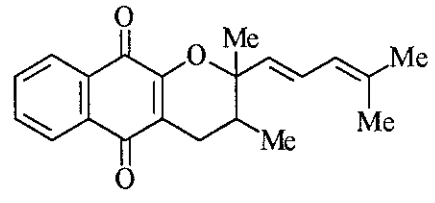
Scheme 6

As usual, the products were separated by column chromatography and the structure of the products was established by spectroscopic analysis. The IR spectrum of **14** exhibited the carbonyl absorption at 1678 cm^{-1}. The ^1H NMR spectrum showed the aromatic protons as two separate multiplets centered at δ 8.06 and 7.66. The signal due to the olefinic proton was visible as a singlet at δ 5.10. The absence of any other proton signal in the region δ 7.00-3.00 excluded the regioisomeric structure. The terminal methyl groups gave singlets at δ 1.81 and 1.68 and the methyl group at the quaternary center displayed a singlet at δ 1.60. The signals due to the carbonyl groups were observed at δ 184.11 and 179.47 in the ^{13}C NMR spectrum.

The IR spectrum of **15** showed the carbonyl absorption band at 1698 cm^{-1}. The four aromatic protons gave four separate signals in the region δ 8.06-7.49 in the ^1H NMR spectrum. The singlet due to the olefinic proton was discernible at δ 5.21. The ^{13}C NMR spectrum exhibited the carbonyl signals at δ 179.64 and 178.42.

Although the product distribution was found to vary from diene to diene, the reaction was found to be general. The results of these experiments are summarized in Table 1.

Table 1. Hetero Diels-Alder reaction of dienes with the quinone methide 7

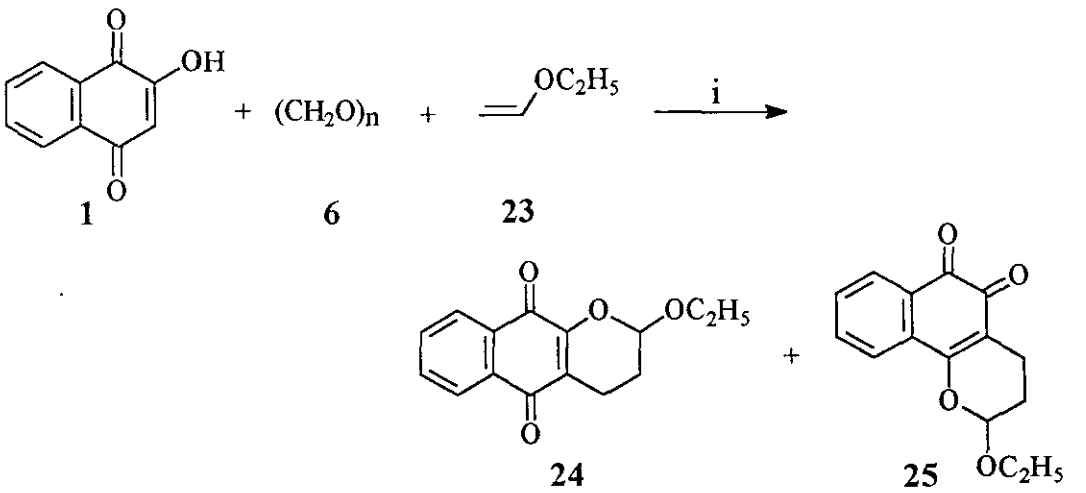
Entry	Diene	Product(s) (Yield %)[a]	
1	 **16**	 **17** (42%)	 **18** (23%)
2	 **19**	 **20** (78%)	
3	 **21**	 **22** (30%)	

Reaction conditions: Dioxane, 100 °C, 6 h, [a] Isolated yield

All these products showed characteristic carbonyl absorption in the IR spectrum and ^{1}H and ^{13}C signals in the NMR spectra.

4.1.2.3. REACTION WITH VINYL ETHERS

Subsequent to the above investigations, reaction of the quinone methide **7** with vinyl ethers was explored. When 2-hydroxy-1,4-naphthoquinone **1** was treated with ethyl vinyl ether and paraformaldehyde in refluxing dioxane, dihydronaphthopyran-5,10-dione **24** and dihydronaphthopyran-5,6-dione **25** were obtained in a total yield of 80% (Scheme 7).



i. Dioxane, 100 °C, 4 h, 80% (8:5)

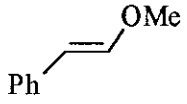
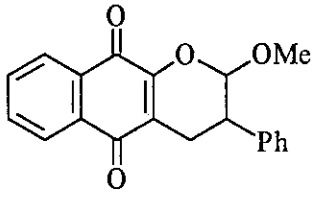
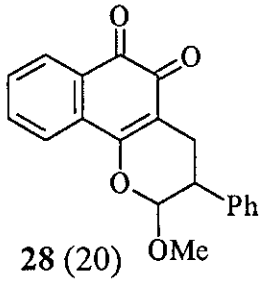
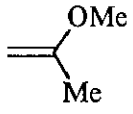
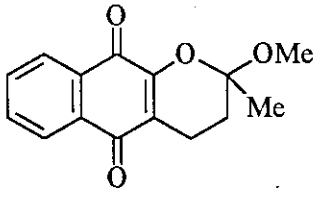
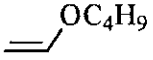
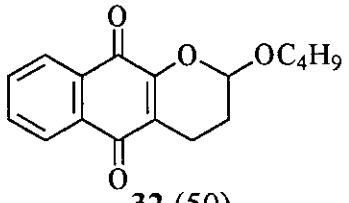
Scheme 7

The products were separated by chromatography and their structures ascertained by spectroscopic analysis. The carbonyl absorption peak was visible at 1676 cm^{-1} in the IR spectrum of **24**. In the ^1H NMR spectrum, the proton on the acetal carbon exhibited a singlet at δ 5.47. The methylene protons of the alkoxy moiety displayed two separate multiplets in the region δ 3.97-3.91 and 3.75-3.70 and the methyl protons appeared as a triplet at δ 1.21 (J = 7.0 Hz). In the ^{13}C NMR spectrum, the carbonyl signals were seen at δ 183.95 and 179.50. The signal due to the acetal carbon was observed at δ 98.11. All other ^1H and ^{13}C NMR signals were in agreement with the assigned structure.

The IR spectrum of **25** showed characteristic carbonyl absorption at 1698 cm^{-1}. The ^{1}H NMR spectrum displayed the acetal proton as a singlet at δ 5.47. The methylene protons of alkoxy group were discernible as mutiplets in the regions δ 4.00-3.92 and 3.78-3.70. In the ^{13}C NMR spectrum, the carbonyl signals were observed at δ 179.19 and 178.45 and the signal due to the acetal carbon was visible at δ 99.75.

Other vinyl ethers also underwent facile hetero Diels-Alder reaction with the quinone methide **7**. The results of these experiments are summarized in Table 2.

Table 2. Hetero Diels-Alder trapping of quinone methide **7** with vinyl ethers

Entry	Vinyl ether	Time (h)	Product(s) (Yield%)[a]
1	 **26**	9	 **27** (75)  **28** (20)
2	 **29**	6	 **30** (60)
3	 **31**	6	 **32** (50)

Reaction conditions: Dioxane, 100 °C, [a] Isolated yield.

The products were isolated as usual and characterized by spectroscopic analysis. All these products showed characteristic IR absorptions and ^{1}H and ^{13}C NMR signals.

The foregoing results show that the above cycloaddition is always regioselective, *i.e.* in all the adducts, the allylic, more substituted or hetero atom substituted carbon of the dienophile bonds to the heterodiene oxygen. This is analogous to the regioselectivity observed in the [4+2] cycloaddition reactions of 1-oxa-1,3-butadienes. The [4+2] cycloaddition reactions of the latter are known to proceed with high regioselectivity with the preferential or exclusive formation of 2-substituted 3,4-dihydro-2H pyrans. Theoretical treatment of [4+2] cycloaddition reactions of 1-oxa-1,3-butadienes predicts the preferential formation of 2-substituted 3,4-dihydro-2H-pyrans and accommodates the preferred *endo* approach of the reactants in which the carbon-carbon bond formation is more advanced than carbon-oxygen bond formation. Such reactions proceed *via* a concerted but nonsynchronous mechanism.[10,11]

4.1.2.4. THEORETICAL CALCULATIONS

In order to explain the observed reactivity and regioselectivity in the above reactions, we have carried out some theoretical calculations using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models.[12] The correlation diagram for the reaction of the quinone methide 7 with cyclopentadiene is provided as an illustrative example (Figure 2).

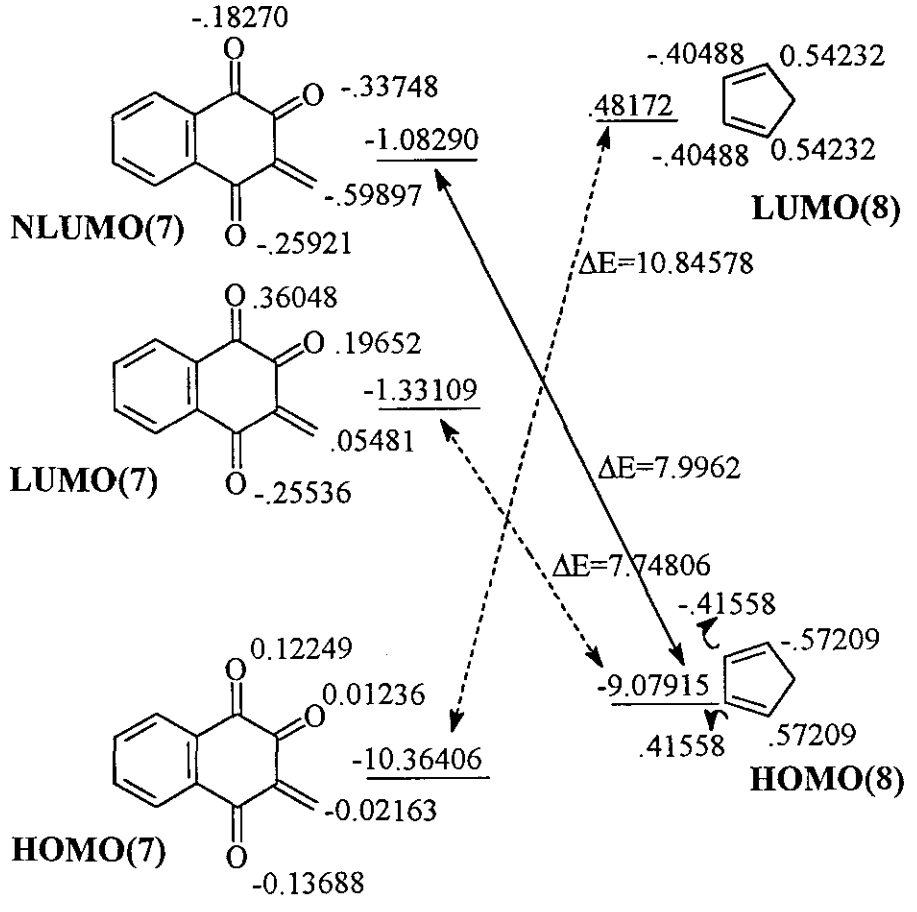


Figure 2. The correlation diagram for the reaction between 7 and 8

From the correlation diagram in Figure 2, it is evident that NLUMO(7)-HOMO(8) interaction is the most favored one. The HOMO(7)-LUMO(8) interaction is unimportant due to the large energy gap. The very small coefficient at the reacting center in LUMO(7) indicates that the LUMO(7)-HOMO(8) interaction would not lead to effective overlap. Therefore the reaction is controlled by NLUMO(7)-HOMO(8) interaction and thus the reaction can be classified as an inverse electron demand Diels-Alder reaction. It is noteworthy that the observed regioselectivity and the preferential formation of 5,10-dione **9** over the corresponding 5,6-dione can be perfectly rationalized by the size and sign of the interacting orbitals.

In conclusion, we have shown that the generation of quinone methide from 2-hydroxynaphthoquinone as well as its hetero Diels-Alder reactions provide an efficient protocol for the one pot synthesis of dihydronaphthopyran derivatives.

4.1.3. EXPERIMENTAL DETAILS

For general information, see **Section 2.3.** in **Chapter 2**

General procedure for the reaction of hydroxyquinone

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and diene or vinyl ether (3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere. On completion of the reaction, the solvent was removed *in vacuo* and the residue was extracted into chloroform. The organic layer was washed with sodium carbonate solution and brine and dried over anhydrous sodium sulfate. The chloroform was evaporated off and the residue was subjected to chromatography on silica gel using ethyl acetate in hexane as eluent. All solid products were purified by recrystallization from CH_2Cl_2-hexane solvent system.

1,3a,11,11a-Tetrahydro-cyclopenta-4H-naphtho[2,3-b]pyran-5,10-dione 9

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and cyclopentadiene (0.264 g, 4 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 3 h. The usual work-up followed by chromatographic purification afforded the product **9** as a yellow solid (0.227 g, 90%). It was recrystallized from CH_2Cl_2-hexane, mp. 102-104 °C.

IR (KBr) $\nu_{(max)}$: 1676, 1626, 1589, 1384, 1203 cm^{-1}.

^1H NMR : δ 8.09-8.04 (m, 2H), 7.69-7.63 (m, 2H), 6.07 (brs, 2H), 5.29 (d, J = 5.2 Hz, 1H), 2.85-2.83 (m, 1H), 2.77-2.71 (m, 1H), 2.66-2.49 (m, 2H), 2.25 (dd, J = 16.3, 2.8 Hz, 1H).

^{13}C NMR : δ 183.78, 179.22, 155.85, 136.13, 133.71, 132.84, 132.04, 131.33, 130.91, 126.27, 125.95, 119.85, 83.77, 37.96, 34.10, 20.04.

Anal. calcd. for $C_{16}H_{12}O_3$: C, 76.17; H, 4.79. Found: C, 75.87; H, 4.75.

Xanthenediones 11 and 12

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and R-α-phellandrene (0.408 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded **11** as a yellow solid (0.094 g, 30%) and **12** as a red solid (0.103 g, 32%).

2,4a,12,12a-Tetrahydro-4a-methyl-2-(1-methylethyl)-1H-benzo[b]xanthene-6,11-dione 11

Recrystallized from CH_2Cl_2-hexane, mp. 76-78 °C.

IR (KBr) $\nu_{(max)}$: 1679, 1646, 1622, 1595, 1578, 1462, 1381, 1377, 1306, 1263, 1208, 1093 cm^{-1}.

^{1}H NMR : δ 8.08-8.03 (m, 2H), 7.68-7.63 (m, 2H), 5.75-5.73 (m, 2H), 2.68 (dd, J = 18.7, 6.2 Hz, 1H), 2.41 (dd, J = 18.7, 7.8 Hz, 1H), 2.15-2.10 (m, 2H), 1.78-1.63 (m, 3H), 1.55 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H).

^{13}C NMR : δ 184.20, 180.10, 154.51, 133.67, 132.85, 132.80, 132.20, 131.19, 130.77, 126.29, 125.93, 120.04, 78.66, 38.57, 33.34, 31.79, 27.47, 27.35, 21.46, 20.01, 19.79.

7a,8,9,11a-Tetrahydro-11a-methyl-9-(1-methylethyl)-5H-benzo[c]xanthene-5,6(7H)-dione 12

Recrystallized from CH_2Cl_2-hexane, mp. 91-93 °C.

IR (KBr) $\nu_{(max)}$: 1698, 1650, 1608, 1573, 1486, 1389, 1370, 1261, 1055 cm^{-1}.

^{1}H NMR : δ 8.05 (d, J = 6.7 Hz, 1H), 7.81 (d, J = 7.1 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 5.79-5.70 (m, 2H), 2.62 (dd, J = 17.5, 6.1 Hz, 1H), 2.37 (dd, J = 17.5, 7.8 Hz, 1H), 2.22-

2.19 (m, 2H), 1.78-1.66 (m, 3H), 1.57 (s, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H).

^{13}C NMR : δ 179.52, 178.93, 157.12, 134.59, 133.72, 133.40, 132.53, 130.53, 130.33, 128.63, 124.03, 112.67, 78.28, 38.79, 33.48, 31.80, 27.58, 20.92, 20.07, 19.84.

Dihydronaphthopyrandiones 14 and 15

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,4-dimethyl-1,3-pentadiene (0.288 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded **14** as a yellow crystalline solid (0.152 g, 54%) and **15** as a red semisolid (0.113 g, 40%).

2,3-Dihydro-2-methyl-2-(2-methylpropenyl)-4H-naphtho[2,3-b]pyran-5,10-dione 14

Recrystallized from CH_2Cl_2-hexane, mp. 95-97°C.

IR (KBr) $\nu_{(max)}$: 1678, 1642, 1612, 1381, 1337, 1306, 1297, 1202, 1101, 959 cm^{-1}.

^{1}H NMR : δ 8.08-8.04 (m, 2H), 7.68-7.65 (m, 2H), 5.10 (s, 1H), 2.72-2.62 (m, 1H), 2.55-2.44 (m, 1H), 2.05-1.97 (m, 1H), 1.81 (s, 3H), 1.76-1.70 (m, 1H), 1.68 (s, 3H), 1.60 (s, 3H).

^{13}C NMR : δ 184.11, 179.47, 154.39, 137.59, 133.60, 132.70, 132.14, 131.15, 126.70, 126.16, 125.90, 121.17, 79.47, 32.10, 27.15, 26.98, 18.86, 16.80.

HRMS calcd. for $C_{18}H_{18}O_3$: 282.1255. Found: 282.1246.

3,4-Dihydro-2-methyl-2-(2-methylpropenyl)-2H-naptho[1,2-b]pyran-5,6-dione 15

IR (neat) $\nu_{(max)}$: 1698, 1644, 1603, 1572, 1450, 1389, 1306, 1327, 1179, 1074 cm^{-1}.

^{1}H NMR : δ 8.06 (d, J = 7.3 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.3 Hz, 1H), 5.21 (s, 1H), 2.63-2.58 (m,

1H), 2.53-2.47 (m, 1H), 2.04-2.01 (m, 1H), 1.88-1.85 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.63 (s, 3H).

^{13}C NMR : δ 179.64, 178.42, 161.68, 137.50, 134.65, 130.52, 129.04, 128.76, 127.14, 123.91, 113.81, 80.69, 32.52, 31.66, 27.19, 26.97, 22.72.

Dihydronaphthopyrandiones 17 and 18

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 1-phenyl-1,3-butadiene (0.260 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded the product **17** as a yellow solid (0.133 g, 42%) and **18** as a red semisolid (0.073 g, 23%).

2,3-Dihydro-2-(2-phenylvinyl)-4H-naphtho[2,3-b]pyran-5,10-dione 17

Recrystallized from CH_2Cl_2-hexane, mp. 135-137 °C.

IR (KBr) $\nu_{(max)}$: 1672, 1647, 1616, 1578, 1390, 1342, 1300, 1261, 1203, 1150, 1066 cm^{-1}.

^{1}H NMR : δ 8.08-8.05 (m, 2H), 7.70-7.66 (m, 2H), 7.41-7.28 (m, 5H), 6.75 (d, J = 15.9 Hz, 1H), 6.31 (dd, J = 15.9, 6.2 Hz, 1H), 4.93-4.87 (m, 1H), 2.77-2.59 (m, 2H), 2.23-2.18 (m, 1H), 1.99-1.92 (m, 1H).

^{13}C NMR : δ 184.23, 179.61, 154.97, 135.96, 133.97, 133.08, 132.03, 131.06, 128.64, 128.23, 126.73, 126.37, 126.30, 126.08, 121.44, 77.80, 26.01, 17.75.

3,4-Dihydro-2-(2-phenylvinyl)-2H-naphtho[1,2-b]pyran-5,6-dione 18

IR (KBr) $\nu_{(max)}$: 1694, 1651, 1574, 1494, 1450, 1263, 1204 cm^{-1}.

^{1}H NMR : δ 8.08 (d, J = 7.0 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.43-7.28 (m, 5H), 6.75 (d, J = 15.8 Hz, 1H), 6.34 (dd, J = 15.9, 6.6 Hz, 1H), 4.93-4.91 (m, 1H), 2.77-2.69 (m, 1H), 2.61-2.44 (m, 1H), 2.27-2.22 (m, 1H), 2.02-1.90 (m, 1H).

^{13}C NMR : δ 179.23, 178.51, 162.25, 136.57, 135.76, 134.78, 133.39, 130.77, 130.20, 128.85, 128.78, 128.51, 126.77, 126.30, 124.09, 113.96, 78.90, 29.77, 18.01.

HRMS calcd. for $C_{21}H_{16}O_3$: 316.1099. Found: 316.1090.

2,3-Dihydro-2-methyl-2-propenyl-4H-naphtho[2,3-b]pyran-5,10-dione 20

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2-methyl-1,3-pentadiene (0.246 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded the product **20** as a yellow solid (0.209 g, 78%). It was recrystallized from CH_2Cl_2-hexane, mp. 83-85 °C.

IR (KBr) $\nu_{(max)}$: 1671, 1643, 1619, 1592, 1456, 1383, 1335, 1304, 1264, 1203, 1156, 1123, 1085 cm^{-1}.

^{1}H NMR : δ 8.10-8.04 (m, 2H), 7.71-7.65 (m, 2H), 5.67-5.60 (m, 1H), 5.47 (dd, J = 15.5, 1.1 Hz, 1H), 2.70-2.60 (m, 1H), 2.48-2.37 (m, 1H), 2.00-1.92 (m, 1H), 1.82-1.72 (m, 1H), 1.68 (dd, J = 6.3, 1.1 Hz, 3H), 1.51 (s, 3H).

^{13}C NMR : δ 184.14, 179.60, 154.48, 135.89, 134.53, 133.74, 132.85, 132.71, 127.91, 126.33, 126.02, 125.55, 121.93, 79.53, 35.52, 30.75, 17.62, 16.79.

2,3-Dihydro-2,3-dimethyl-2-(4-methyl-1,3-pentadienyl)-4H-naphtho[2,3-b]pyran-5,10-dione 22

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 2,6-dimethyl-2,4,6-octatriene (0.272 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded the product **22** as a yellow semisolid (0.094 g, 30%).

IR (neat) $\nu_{(max)}$: 1679, 1647, 1618, 1454, 1378, 1337, 1261, 1205, 1108, 967 cm^{-1}.

^{1}H NMR : δ 8.10-8.03 (m, 2H), 7.71-7.65 (m, 2H), 6.45 (dd, J = 13.7, 10.9 Hz, 1H), 5.78 (d, J = 10.5 Hz, 1H), 5.58 (d, J = 15.3 Hz, 1H), 2.69 (dd, J = 18.7, 5.5 Hz, 1H), 2.31 (dd, J = 18.7, 7.2 Hz, 1H), 2.02-1.93 (m, 1H), 1.76 (s, 3H), 1.72 (s, 3H), 1.42 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H).

^{13}C NMR : δ 184.16, 179.43, 154.04, 136.71, 133.69, 132.83, 132.48, 132.22, 131.26, 126.69, 126.30, 126.01, 124.29, 120.28, 82.69, 33.54, 26.07, 25.09, 20.53, 18.48, 15.66.

Dihydronaphthopyrandiones 24 and 25

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and ethyl vinyl ether (0.288 g, 4 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 4 h. The usual work-up followed by chromatographic purification afforded the product **24** as a yellow solid (0.129 g, 50%) and the 5,6 dione **25** as a red semisolid (0.077 g, 30%).

2,3-Dihydro-2-ethoxy-4H-naphtho[2,3-b]pyran-5,10-dione 24

Recrystallized from CH_2Cl_2-hexane, mp. 124-126 °C.

IR (KBr) $\nu_{(max)}$: 1676, 1620, 1340, 1191, 1041 cm^{-1}.

^{1}H NMR : δ 8.09-8.04 (m, 2H), 7.72-7.64 (m, 2H), 5.47 (s, 1H), 3.97-3.91 (m, 2H), 3.75-3.70 (m, 1H), 2.71-2.51 (m, 2H), 2.13-2.11 (m, 1H), 1.90-1.75 (m, 1H), 1.21 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 183.95, 179.50, 152.58, 133.77, 132.92, 131.98, 131.07, 126.23, 126.07, 122.65, 98.11, 64.80, 25.05, 15.05, 14.32.

Anal. calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.49. Found: C, 70.00; H, 5.46.

3,4-Dihydro-2-ethoxy-2H-naphtho[1,2-b]pyran-5,6-dione 25

IR (KBr) $\nu_{(max)}$: 1698, 1650, 1620, 1343, 1190, 1040 cm^{-1}.

^{1}H NMR : δ 8.06 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.4 Hz, 1H), 5.47 (s, 1H), 4.00-3.92 (m, 1H), 3.78-3.70 (m, 1H), 2.61-2.56 (m, 1H), 2.13-2.07 (m, 1H), 2.01-1.91 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H).

^{13}C NMR : δ 179.19, 178.45, 159.97, 134.76, 132.36, 130.62, 128.88, 123.71, 114.77, 99.75, 65.11, 25.66, 15.16, 14.47.

Dihydronaphthopyrandiones 27 and 28

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and β-methoxystyrene (0.268 g, 2 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 9 h. The usual work-up followed by chromatographic purification afforded the product **27** as a yellow solid (0.240 g, 75%) and the 5,6 dione **28** as a red semisolid (0.064 g, 20%).

2,3-Dihydro-2-methoxy-3-phenyl-4H-naphtho[2,3-b]pyran-5,10-dione 27

Recrystallized from CH_2Cl_2-hexane, mp. 160-162 °C.

IR (KBr) $\nu_{(max)}$: 1673, 1628, 1327, 1189, 1111, 1053 cm^{-1}.

^{1}H NMR : δ 8.11-8.07 (m, 2H), 7.71-7.68 (m, 2H), 7.31-7.20 (m, 5H), 5.39 (d, J = 3.1 Hz, 1H), 3.59 (s, 3H), 3.38-3.35 (m, 1H), 3.03 (dd, J = 18.9, 6.6 Hz, 1H), 2.94 (dd, J = 18.8, 4.2 Hz, 1H).

^{13}C NMR : δ 184.16, 179.27, 152.61, 139.12, 134.08, 133.15, 131.50, 130.25, 128.89, 127.40, 126.44, 126.26, 122.12, 103.08, 56.94, 40.01, 22.01.

Anal. calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.52; H, 5.06.

3,4-Dihydro-2-methoxy-3-phenyl-2H-naphtho[1,2-b]pyran-5,6-dione 28

IR (KBr) $\nu_{(max)}$: 1698, 1651, 1609, 1592, 1573, 1492, 1451, 1389, 1363, 1283, 1065 cm^{-1}.

^{1}H NMR : δ 8.09 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.36-7.19 (m, 5H), 5.40 (s, 1H), 3.50 (s, 3H), 3.19 (t, J = 9.3 Hz, 1H), 2.87 (d, J = 9.6 Hz, 2H).

^{13}C NMR : δ 179.09, 178.44, 159.12, 138.29, 134.94, 132.16, 130.77, 130.25, 129.08, 128.60, 128.49, 128.37, 127.57, 123.82, 115.51, 102.60, 57.00, 41.91, 20.46.

EIMS, m/z : 320 (M^+, 60), 289 (18), 231 (19), 158 (25), 134 (100), 102 (15), 91 (80), 76 (25).

2,3-Dihydro-2-methoxy-2-methyl-4H-naphtho[2,3-b]pyran-5,10-dione 30

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and methoxypropene (0.216 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 6 h. The usual work-up followed by chromatographic purification afforded the product **30** as a yellow solid (0.155 g, 60%). It was recrystallized from CH_2Cl_2-hexane solvent system, mp. 100-102 °C.

IR (KBr) $\nu_{(max)}$: 1673, 1644, 1620, 1591, 1383, 1342, 1303, 1266, 1211, 1197, 1169 cm^{-1}.

^1H NMR : δ 8.07-8.05 (m, 2H), 7.69-7.66 (m, 2H), 3.34 (s, 3H), 2.72-2.52 (m, 2H), 2.19-2.12 (m, 1H), 1.79-1.71 (m, 1H), 1.67 (s, 3H).

^{13}C NMR : δ 184.07, 179.36, 152.68, 133.63, 132.83, 131.96, 131.11, 126.15, 125.97, 122.88, 100.52, 49.63, 30.76, 24.41, 15.84.

Anal. calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.49. Found: C, 70.02; H, 5.50.

2,3-Dihydro-2-butoxy-4H-naphtho[2,3-b]pyran-5,10-dione 32

2-Hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and butyl vinyl ether (0.300 g, 3 mmol) were refluxed (100 °C) in dioxane (6 mL) under argon atmosphere for 3 h. The usual work-up followed by chromatographic purification afforded the product **32** as a yellow oil (0.143 g, 50%).

IR (neat) $\nu_{(max)}$: 1678, 1650, 1621, 1596, 1580, 1385, 1334, 1300, 1259, 1187, 1118, 1099, 1053 cm^{-1}.

^1H NMR : δ 8.10-8.05 (m, 2H), 7.71-7.64 (m, 2H), 5.46 (s, 1H), 3.92-3.84 (m, 1H), 3.68-3.61 (m, 1H), 2.69-2.57 (m, 2H), 2.14-2.10 (m, 1H), 1.88-1.82 (m, 1H), 1.59-1.50 (m, 2H), 1.35-1.26 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H).

^{13}C NMR : δ 184.01, 179.54, 152.65, 133.79, 132.94, 132.02, 131.12, 126.28, 126.12, 122.70, 98.30, 69.05, 31.52, 25.07, 19.17, 14.33, 13.79.

4.2. CAN MEDIATED OXIDATIVE ADDITION OF 2-HYDROXY-1,4-NAPHTHOQUINONE

4.2.1. INTRODUCTION

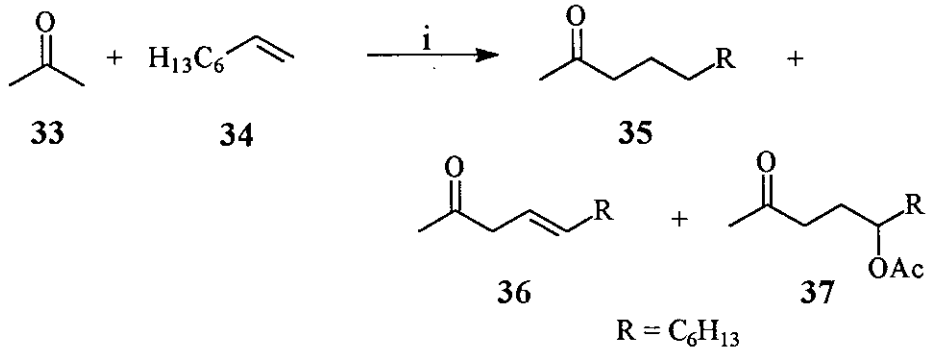
4.2.1.1. GENERAL

In the previous section, we have dealt with the synthesis of dihydropyran derivatives by the hetero Diels-Alder reactions of quinone methide derived from 2-hydroxy-1,4-naphthoquinone. As an extension of these studies we became interested in the synthesis of corresponding dihydrofuran derivatives by cerium(IV) ammonium nitrate (CAN) mediated oxidative addition of 2-hydroxy-1,4-naphthoquinone to dienes. The following passages provide an account of these investigations.

Since an extensive review of cerium(IV) ammonium nitrate (CAN) mediated reactions is beyond the scope of this chapter, only a very brief introduction to the CAN mediated oxidative addition reactions is given below.

4.2.1.2. OXIDATIVE ADDITION REACTIONS MEDIATED BY CAN

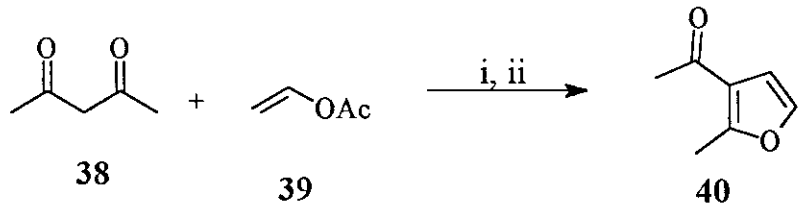
Cerium(IV) ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$, is a one electron oxidant, that has been utilized extensively for a variety of oxidative transformations.[13] The pioneering work of Heiba and Dessau has shown that electrophilic carbon centered radicals generated by Ce(IV) reagents undergo addition to alkenes.[14] The reaction between acetone and 1-octene is illustrative (Scheme 8).



i. $Ce(OAc)_4$, AcOH

Scheme 8

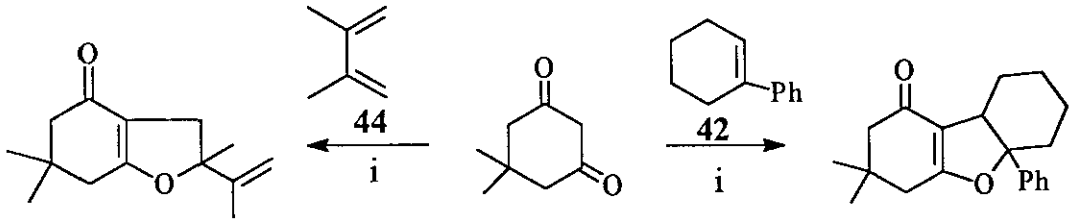
Subsequently Baciocchi *et al.* made significant advance in this area by showing that a number of synthetic transformations can be performed in methanol or acetonitrile using CAN. They have studied the CAN mediated oxidative addition of 1,3-dicarbonyl compounds to activated alkenes (Scheme 9).[15]



i. CAN; ii. PPTS

Scheme 9

Studies in our own laboratory have shown that CAN mediated oxidative addition of active methylene compounds such as dimedone, acetyl acetone and ethyl acetoacetate to alkenes provides an excellent route to dihydrofuran derivatives.[16] Similar reaction occurs with dienes also (Scheme 10).[17]

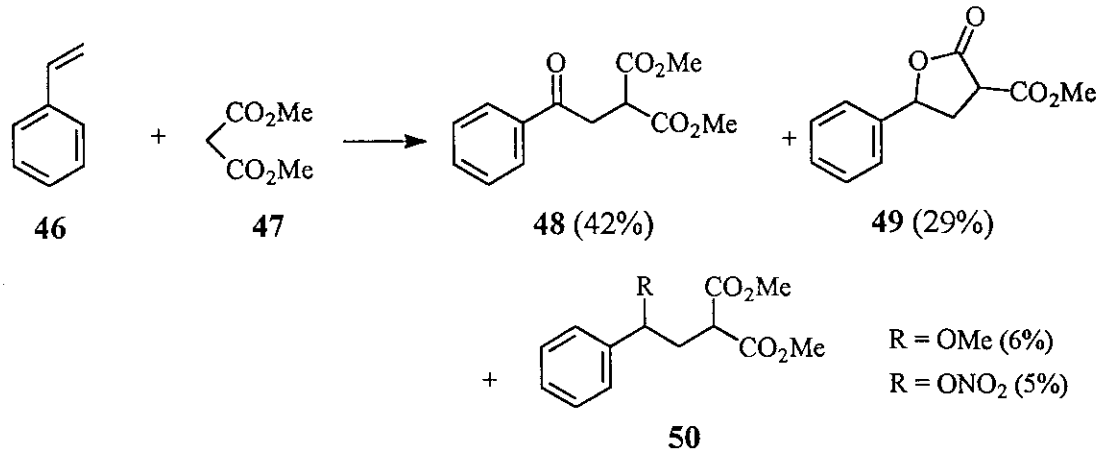


45 (70%) **41** **43** (98%)

i. CAN, MeOH, 0 °C

Scheme 10

An interesting and mechanistically fascinating reaction was observed in the oxidative addition of dimethyl malonate to styrene in the presence of CAN (Scheme 11).[18]



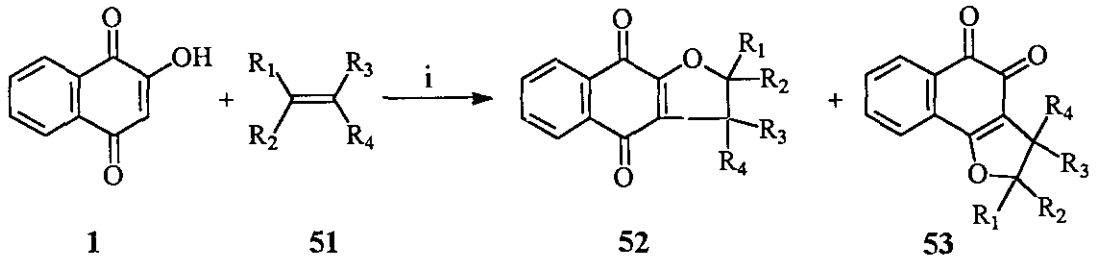
46 **47** **48** (42%) **49** (29%)

50

i. CAN, MeOH, 20 °C

Scheme 11

The CAN mediated radical addition of 2-hydroxy-1,4-naphthoquinone to alkenes was reported to result in the formation of *p*-furoquinones and the corresponding *o*-quinone derivatives (Scheme 12).[19]



1 **51** **52** **53**

i. CAN, CH_3CN, 0 °C, 30 min

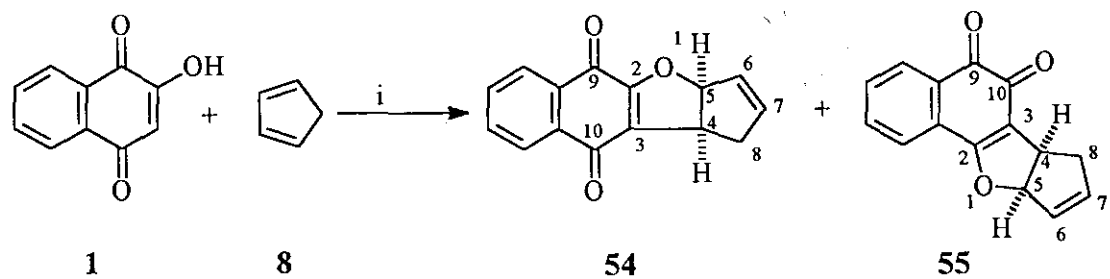
Scheme 12

Against this literature background and in the context of our general interest in the chemistry of quinonoid compounds,[9] we have studied the oxidative addition reaction of 2-hydroxy-1,4-naphthoquinone to dienes. The results of these investigations are delineated below.

4.2.2. RESULTS AND DISCUSSION

4.2.2.1. REACTION WITH CYCLIC DIENES

Our studies commenced with the reaction of 2-hydroxy-1,4-naphthoquinone **1** with cyclopentadiene. When a solution of **1** and cyclopentadiene in acetonitrile was treated with a solution of CAN in acetonitrile at 0 °C, two products **54** and **55** were obtained (Scheme 13).



1 **8** **54** **55**

i. CAN, CH_3CN, 0 °C, 80% (1:3)

Scheme 13

The structure of the products was assigned on the basis of spectroscopic analysis. The IR spectrum of **54** showed characteristic strong carbonyl absorption at 1676 cm^{-1}. In the ^{1}H NMR spectrum, the proton on C-4 resonated as double triplet at δ 4.18 (J = 2.2, 8.5 Hz) and that on C-5 at δ 5.95 as a multiplet. The olefinic proton on C-6 and C-7 appeared as a doublet at δ 6.10 (J = 8.9 Hz) and as a triplet at δ 6.19 (J = 2.6 Hz), respectively. The characteristic peaks corresponding to the carbonyl carbons were observed in the ^{13}C NMR spectrum at δ 182.43 (C-9) and 178.64 (C-10) and the signal due to the carbons C-2 and C-5 appeared at δ 158.51 and 96.09, respectively. The final proof for the structure was obtained from single crystal X-ray analysis (Figure 3).

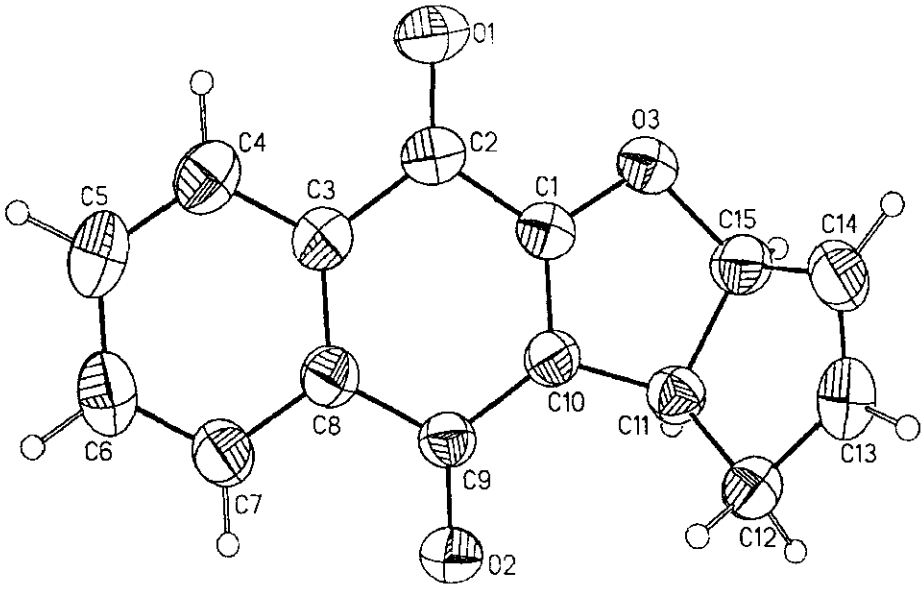
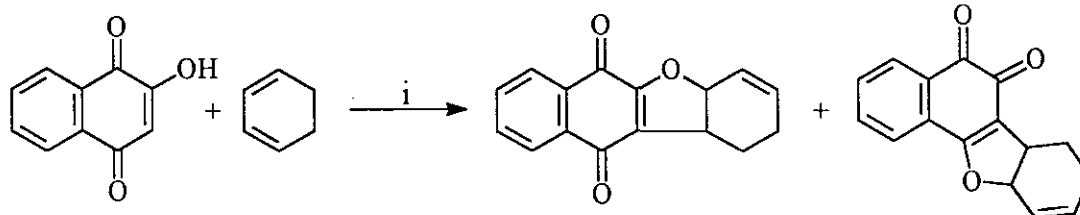


Figure 3. X-ray structure of **54**

The naphthofurandione **55** exhibited the carbonyl absorption peak at 1694 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum showed the proton on C-4 and C-5 as doublet of a triplet at δ 4.23 (J = 8.2, 2.2 Hz) and as a multiplet at δ 6.02, respectively. The signals due to the carbonyl carbons C-9 and C-10 were

observed in the ^{13}C NMR spectrum at δ 180.73 and 174.94, respectively. The signal due to C-2 appeared at δ 167.81 and C-5 showed a peak at δ 97.28.

Cyclohexadiene also showed similar reactivity towards 2-hydroxy-naphthoquinone in the presence of CAN (Scheme 14).



1 **56** **57** **58**

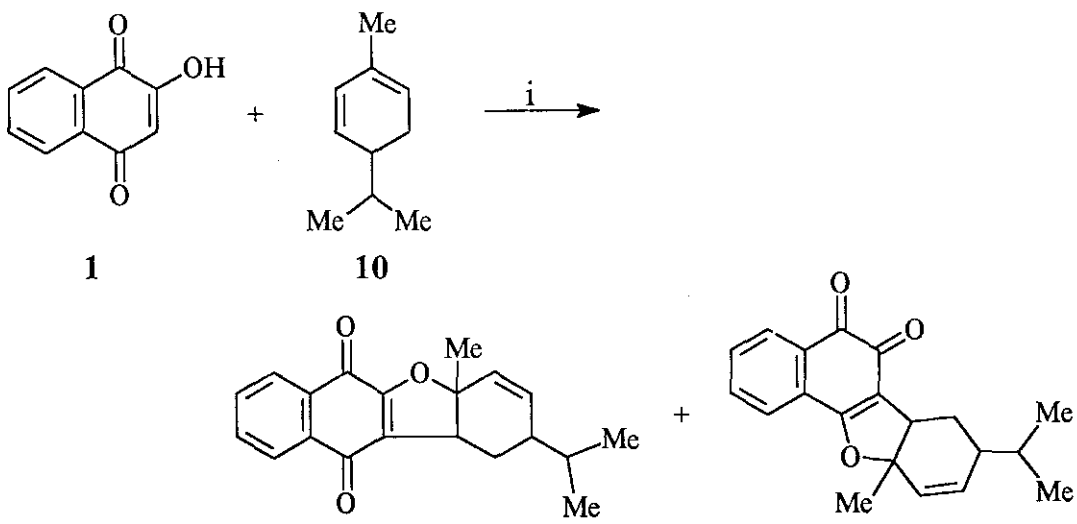
i. CAN, CH_3CN, 0 °C, 30 min, 95% (1:1)

Scheme 14

The dihydrofuran **57** exhibited the carbonyl absorption peak at 1677 cm^{-1}. In the ^1H NMR spectrum, the ring junction proton adjacent to the pyran oxygen appeared as a multiplet around δ 5.15. The olefinic protons displayed multiplets centered at δ 6.26 and 6.05. In the ^{13}C NMR spectrum, the signal due to the carbonyl groups were discernible at δ 182.42 and 178.40. Additional evidence for the regiochemistry of the products was drawn from the proton connectivity established by the 2D-COSY ^1H NMR of **57**. The ring junction proton at δ 5.15 (m) is connected to the olefinic proton at δ 6.05 (m) and the ring junction proton at δ 3.60 (m), which in turn is connected to the methylenic protons at δ 2.15 (m).

The IR spectrum of **58** displayed the carbonyl absorption band at 1697 cm^{-1}. The ^{13}C NMR signals due to carbonyl groups were seen at δ 181.25 and 175.42. All ^1H and ^{13}C NMR signals were in agreement with the assigned structure.

In another experiment, 2-hydroxy-1,4-naphthoquinone **1** was treated with α-phellandrene in the presence of CAN. The reaction afforded the adducts **59** and **60** (Scheme 15).



i. CAN, MeOH, 0 °C, 30 min, 76% (5:2)

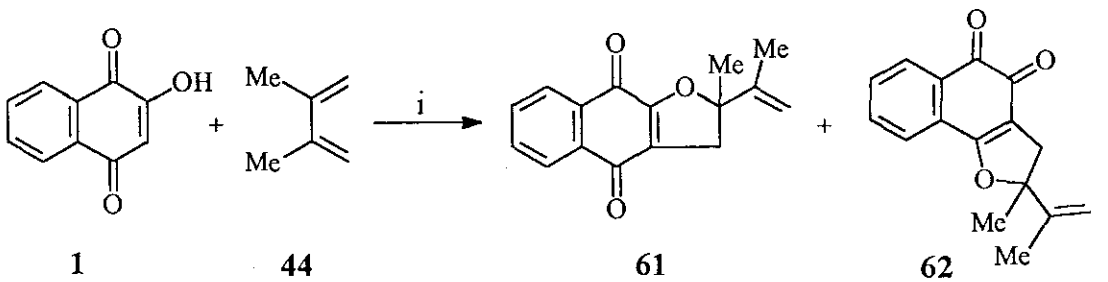
Scheme 15

The IR spectrum of **59** showed the carbonyl absorption peak at 1677 cm^{-1}. In the ^{13}C NMR spectrum, the signals due to the carbonyl groups were discernible at δ 182.77 and 178.37. The assigned structure was further confirmed by DEPT-135 spectrum. The DEPT-135 spectrum of **59** clearly established that the sp^3 carbon adjacent to the furan oxygen is a quaternary center, which cannot be true in the other possible regioisomer.

The carbonyl groups of **60** exhibited the characteristic IR absorption at 1697 cm^{-1}. The ^{13}C NMR spectrum displayed signals due to the carbonyl groups at δ 185.11 and 175.47.

4.2.2.2. REACTION WITH ACYCLIC DIENES

In the next phase of our investigations 2-hydroxy-1,4-naphthoquinone **1** was treated with 2,3-dimethylbutadiene. This reaction afforded the furan annulated naphthoquinone derivatives **61** and **62** (Scheme 16).



1 **44** **61** **62**

i. CAN, CH_3CN, 0 °C, 81% (1:3)

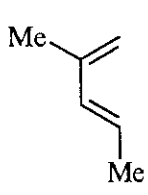
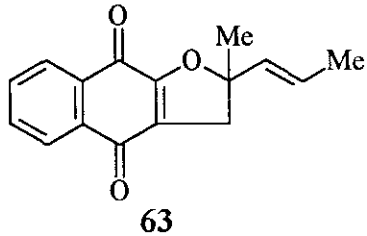
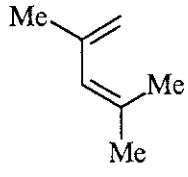
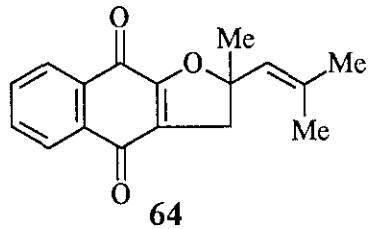
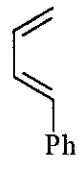
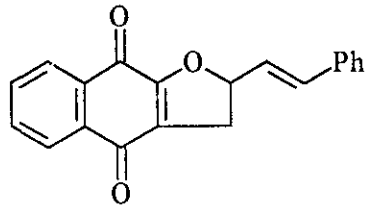
Scheme 16

As usual, the products were isolated by chromatography and characterized by spectroscopic analysis. The IR spectrum of the adduct **61** exhibited carbonyl absorption at 1680 cm^{-1}. The ^1H NMR spectrum displayed two singlets due to the olefinic protons at δ 5.12 and 4.92. The methylene protons of the furan ring appeared as doublets at δ 3.26 and 3.03 (J = 16.1 Hz).

The IR spectrum of **62** exhibited the carbonyl absorption peak at 1708 cm^{-1}. In the ^1H NMR spectrum, the olefinic protons displayed singlets at δ 5.11 and 4.95. The signals due to the carbonyl groups were discernible at δ 181.14 and 175.57 in the ^{13}C NMR spectrum.

Interestingly, when **1** was treated with other acyclic dienes, in each case the corresponding furan-4,9-dione was obtained as the only isolable product. Table 3 summarizes the results of these experiments.

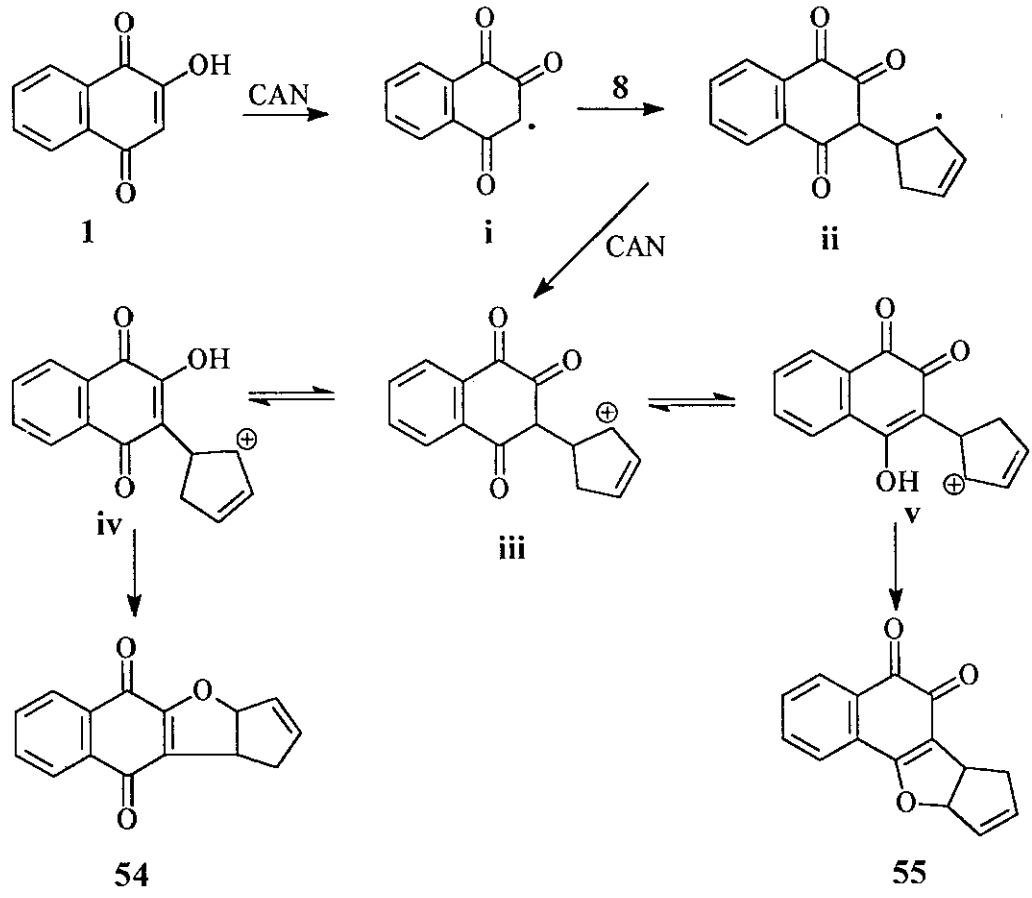
Table 3. Oxidative addition of 2-hydroxy-1,4-naphthoquinone **1** to dienes

Entry	Diene	Product	Yield (%)[a]
1	 **19**	 **63**	75
2	 **13**	 **64**	69
3	 **16**	 **65**	50

Reaction conditions: CAN, CH_3CN, 0 °C, 30 min; [a] Isolated yield

4.2.2.3. MECHANISTIC RATIONALIZATION

A mechanistic rationalization for the formation of the above products can be conceived as follows. Oxidation of **1** by CAN would lead to the radical **i**, which can be trapped by cyclopentadiene **8** to yield the reactive intermediate **ii**. The latter is further oxidized by CAN to the cation **iii**, which in turn undergoes tautomerisation yielding **iv** and **v**. The cyclization of **iv** leads to **54** and **v** affords **55** (Scheme 17).



Scheme 17

In conclusion, the present investigations offer a simple and rapid one step procedure for the synthesis of naphthofurandiones. It is noteworthy that there are a number of biologically active natural products, which contain both, linear and angular furanoquinone framework.[1,8] The present protocol may be applicable to the synthesis of such compounds.

4.2.3. EXPERIMENTAL DETAILS

For general information, see **Section 2.3.** of **Chapter 2**

General procedure for the reaction of hydroxyquinone with dienes in the presence of CAN

A solution of CAN (1.260 g, 2.3 mmol) in distilled acetonitrile (20 mL) was added dropwise to an ice-cooled solution of 2-hydroxy-1,4-naphthoquinone

1 (0.174 g, 1 mmol) and diene (2 mmol) in acetonitrile (15 mL). The reaction mixture was stirred for 30 minutes and then it was diluted with water (20 mL) and extracted with dichloromethane (4x15 mL). The solvent was evaporated off and the crude product was then purified by column chromatography on silica gel (100-200 mesh) using mixtures of ethyl acetate and hexane as eluents. All solid products were purified by recrystallization from dichloromethane-hexane solvent system.

Naphthofurandiones 54 and 55

A solution of CAN (1.260 g, 2.3 mmol) in acetonitrile (20 mL) was added dropwise to an ice-cooled solution of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and cyclopentadiene (0.132 g, 2 mmol) in acetonitrile (15 mL). The reaction mixture was stirred for 20 minutes and then it was diluted with water (20 mL) and extracted with dichloromethane (4x15 mL). The solvent was evaporated off and the residue on silica gel column chromatography using 5% ethyl acetate in hexane afforded **54** (0.054 g, 23%) as a yellow solid and **55** (0.136 g, 57%) as a red solid.

3a,10b-Dihydro-cyclopenta[2,3]naphtho[2,3-d]furan-5,10-dione 54

Recrystallized from CH_2Cl_2-hexane, mp. 191-193°C.

IR (KBr) $\nu_{(max)}$: 1676, 1639, 1613, 1587, 1449, 1385, 1365, 1244, 1195 cm^{-1}.

^1H NMR : δ 8.20-8.05 (m, 2H), 7.81-7.60 (m, 2H), 6.19 (t, J = 2.6 Hz, 1H), 6.10 (d, J = 8.9 Hz, 1H), 5.97-5.93 (m, 1H), 4.18 (dt, J = 8.5, 2.2 Hz, 1H), 2.99-2.89 (m, 2H).

^{13}C NMR : δ 182.43, 178.64, 158.51, 137.66, 134.23, 133.26, 132.99, 121.66, 127.84, 127,04, 126.31, 126.06, 96.09, 42.19, 38.32.

HRMS calcd. for $C_{15}H_{10}O_3$: 238.0632. Found: 238.0692.

X-RAY Crystal data: $C_{15}H_{10}O_3$. FW: 238.23. Crystal size: 0.40 x 0.40 x 0.20 mm^3, Monoclinic. Space group $P2_1/c$. Unit cell dimensions a = 8.1663(2) Å, α = 90°; b = 11.1884(2) Å, β = 105.473(1)°; c = 12.6039(2) Å, γ = 90°. R indices (all data) R1 = 0.0821, wR2 = 0.1261. Volume, Z = 1109.85(4) $Å^3$, 4. D calc =

1.426 mg/m^3. F (000) = 496. Absorption Coefficient = 0.100 mm^{-1}. Reflections collected = 2424. λ = 0.71073 Å. (Sheldrick, G. M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

6b,9a-Dihydrocyclopenta[8,9]naphtho[2,1-d]furan-5,6-dione 55

Recrystallized from CH_2Cl_2-hexane, mp. 144-146 °C.

IR (KBr) $\nu_{(max)}$: 1694, 1641, 1615, 1567, 1488, 1442, 1401, 1353, 1281, 1220, 1144, 1042 cm^{-1}.

^{1}H NMR : δ 8.10 (t, J = 9.0 Hz, 1H), 7.67-7.53 (m, 3H), 6.20-6.12 (m, 2H), 6.02 (m, 1H), 4.23 (dt, J = 8.2, 2.2 Hz, 1H), 2.94-2.83 (m, 1H), 2.74-2.64 (m, 1H).

^{13}C NMR : δ 180.73, 174.94, 167.81, 138.50, 134.51, 132.21, 131.30, 129.30, 127.52, 127.31, 124.53, 119.46, 97.28, 41.46, 38.37.

Anal. calcd. for $C_{15}H_{10}O_3$: C, 75.63; H, 4.20. Found: C, 75.53; H, 4.19.

Naphthofurandiones 57 and 58

A solution of CAN (1.260 g, 2.3 mmol) in acetonitrile (20 mL) was added dropwise to an ice-cooled solution of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and cyclohexadiene (0.160 g, 2 mmol) in acetonitrile. The aqueous work-up followed by chromatographic purification afforded **57** (0.123 g, 49%) as a yellow solid and **58** (0.116 g, 46%) as a red semisolid.

1,2,4a,10b-Tetrahydrobenzo[b]naphtho[2,3-d]-furan-5,10-dione 57

Recrystallized from CH_2Cl_2-hexane, mp. 145-147 °C.

IR (KBr) $\nu_{(max)}$: 1677, 1637, 1612, 1584, 1390, 1366, 1227, 1190, 963 cm^{-1}.

^{1}H NMR : δ 8.09-8.05 (m, 2H), 7.76-7.64 (m, 2H), 6.29-6.24 (m, 1H), 6.09-6.03 (m, 1H), 5.19-5.17 (m, 1H), 3.60 (m, 1H), 2.25-2.11 (m, 2H), 2.06-1.98 (m, 1H), 1.66-1.53 (m, 1H).

^{13}C NMR : δ 182.42, 178.40, 159.89, 135.24, 134.21, 133.24, 132.98, 131.60, 127.77, 126.33, 126.04, 122.63, 81.53, 38.84, 23.92, 22.76.

HRMS calcd. for $C_{16}H_{12}O_3$: 252.0786. Found: 252.0789.

6b,7,8,10a-Tetrahydrobenzo[c]naphtho[2,1-d]furan-5,6-dione 58

IR (neat) $\nu_{(max)}$: 1697, 1642, 1567, 1493, 1405, 1280, 1218, 1161, 1080 cm^{-1}.

^1H NMR : δ 8.05 (d, J = 7.1 Hz, 1H), 7.63-7.56 (m, 3H), 6.29 (brs, 1H), 6.06 (d, J = 9.9 Hz, 1H), 5.25 (d, J = 7.7 Hz, 1H), 3.55-3.47 (m, 1H), 2.20-2.14 (m, 2H), 1.99-1.93 (m, 1H), 1.60-1.53 (m, 1H).

^{13}C NMR : δ 181.25, 175.42, 169.71, 135.95, 134.47, 131.85, 130.50, 129.29, 128.29, 124.58, 122.45, 119.56, 82.86, 37.78, 23.76, 22.59.

EIMS, m/z : 253 (M^++1, 4), 252 (M^+, 15), 250 (25), 165 (28), 89 (25), 76 (45), 39 (44), 28 (80), 14 (100).

Naphthofurandiones 59 and 60

An ice cooled mixture of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and α-phellandrene (0.272 g, 2 mmol) in methanol (10 mL) was treated with CAN (1.260 g, 2 mmol) in methanol (10 mL) for 30 minutes. The aqueous work-up followed by chromatographic purification afforded the compound **59** (0.166 g, 54%) as a yellow semisolid and **60** (0.068 g, 22%) was obtained as a red oil.

1,2,4a,10b-Tetrahydro-4a-methyl-2-(1-methylethyl)-benzo[b]naphtho[2,3-d]furan-5,10-dione 59

IR (neat) $\nu_{(max)}$: 1677, 1649, 1614, 1595, 1387, 1367, 1270, 1206, 1085, 1040 cm^{-1}.

^1H NMR : δ 8.07-8.05 (m, 2H), 7.73-7.63 (m, 2H), 5.98 (d, J = 13.8 Hz, 1H), 5.72 (dd, J = 10.2, 1.5 Hz, 1H), 3.36-3.30 (m, 1H), 2.49-2.45 (m, 1H), 2.35-2.21 (m, 1H), 1.78 (m, 2H), 1.63 (s, 3H), 0.93 (d, J = 2.6 Hz, 6H).

^{13}C NMR : δ 182.71, 178.37, 159.75, 136.24, 134.06, 133.50, 132.78, 131.00, 128.16, 125.88, 125.10, 90.65, 45.33, 37.00, 31.43, 30.90, 26.35, 25.65, 19.60.

HRMS calcd. for $C_{20}H_{20}O_3$: 308.1412. Found: 308.1400

6b,7,8,10a-Tetrahydro-10a-methyl-8-(1-methylethyl)benzo[c]naphtho[2,1-d]furan-5,6-dione 60

IR (neat) $\nu_{(max)}$: 1697, 1661, 1613, 1371, 1222, 1054 cm^{-1}.

^1H NMR : δ 8.04 (d, J = 7.3 Hz, 1H), 7.60-7.51 (m, 3H), 5.96 (d, J = 10.2 Hz, 1H), 5.67 (dd, J = 10.1, 2.0 Hz, 1H), 3.50 (q, J = 4.4 Hz, 1H), 2.50-2.46 (m, 1H), 1.67 (s, 3H), 1.64-1.57 (s, 3H), 0.90 (d, J = 2.6 Hz, 3H), 0.88 (d, J = 2.5 Hz, 3H).

^{13}C NMR : δ 181.11, 175.47, 169.12, 136.97, 134.15, 131.66, 129.69, 128.06, 124.41, 117.29, 109.29, 104.70, 92.35, 83.94, 31.29, 26.41, 25.38, 19.50, 19.33.

HRMS calcd. for $C_{20}H_{20}O_3$: 308.1412. Found: 308.1398.

2,3-Dihydronaphthofurandiones 61 and 62

A solution of CAN (1.260 g, 2.3 mmol) in acetonitrile (20 mL) was added dropwise to an ice-cooled solution of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and 2,3-dimethyl butadiene (0.164 g, 2 mmol) in acetonitrile (15 mL). The aqueous work-up followed by chromatographic purification afforded **61** (0.051 g, 20%) as a yellow solid and **62** (0.155 g, 61%) as a red solid.

2,3-Dihydro-2-methyl-2-(1-methylvinyl) naphtho [2,3-b] furan-4,9-dione 61

Recrystallized from CH_2Cl_2-hexane, mp. 103 -105 °C.

IR (KBr) $\nu_{(max)}$: 1680, 1643, 1624, 1590, 1572, 1438, 1393, 1369, 1255, 1206, 1155 cm^{-1}.

^1H NMR : δ 8.08-8.05 (m, 2H), 7.72-7.67 (m, 2H), 5.12 (s, 1H), 4.92 (s, 1H), 3.26 (d, J = 16.1 Hz, 1H), 3.03 (d, J = 16.1 Hz, 1H), 1.85 (s, 3H), 1.66 (s, 3H).

^{13}C NMR : δ 182.45, 178.03, 158.92, 145.55, 134.11, 133.04, 132.92, 132.06, 126.30, 125.97, 123.37, 111.28, 94.57, 38.68, 26.23, 18.43.

HRMS calcd. for $C_{16}H_{14}O_3$: 254.0942. Found: 254.0949.

2,3-Dihydro-2-methyl-2-(1-methylvinyl)-naphtho[1,2-b]furan-4,5-dione 62

Recrystallized from CH_2Cl_2-hexane, mp. 112-114 °C.

IR (KBr) $\nu_{(max)}$: 1708, 1620, 1364, 1256 cm^{-1}.

^1H NMR : δ 8.10-8.08 (m, 1H), 7.69-7.59 (m, 3H), 5.11 (s, 1H), 4.95 (s, 1H), 3.16 (d, J = 15.4 Hz, 1H), 2.98 (d, J = 15.4 Hz, 1H), 1.85 (s, 3H), 1.68 (s, 3H).

^{13}C NMR : δ 181.14, 175.57, 168.70, 145.70, 134.58, 131.99, 130.85, 129.43, 127.69, 124.53, 114.88, 111.12, 96.24, 37.87, 26.28, 18.46.

HRMS calcd. for $C_{16}H_{14}O_3$: 254.0942. Found: 254.0949.

2,3-Dihydro-2-methyl-2-(2-methylpropenyl)naphtho[2,3-b]furan-4,9-dione 63

A solution of CAN (1.260 g, 2.3 mmol) in distilled acetonitrile (20 mL) was added dropwise to an ice-cooled solution of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and 2,4-dimethyl-1,3-pentadiene (0.192 g, 2 mmol) in acetonitrile. The aqueous work-up followed by chromatographic purification afforded the product **63** as a yellow solid (0.201 g, 75%). It was recrystallized from CH_2Cl_2-hexane, mp. 83-85 °C.

IR (KBr) $\nu_{(max)}$: 1682, 1651, 1620, 1370, 1264, 1201 cm^{-1}.

^1H NMR : δ 8.08-8.03 (m, 2H), 7.71-7.65 (m, 2H), 5.59 (s, 1H), 3.24 (d, J = 16.9 Hz, 1H), 3.18 (d, J = 16.9 Hz, 1H), 1.76 (s, 3H), 1.75 (s, 3H), 1.62 (s, 3H).

^{13}C NMR :δ 182.21, 177.90, 158.57, 136.44, 133.87, 133.15, 132.67, 131.64, 128.74, 126.18, 125.89, 123.22, 92.63, 41.17, 28.60, 26.52, 19.23.

HRMS calcd. for $C_{17}H_{16}O_3$: 268.1099. Found: 268.1094.

2,3-Dihydro-2-methyl-2-propenylnaphtho[2,3-b]furan-4,9-dione 64

An ice cooled mixture of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and 2-methyl-1,3-pentadiene (0.164 g, 2 mmol) in acetonitrile was

treated with a solution of CAN (1.260 g, 2.3 mmol) in the same solvent. The aqueous work-up followed by chromatographic purification yielded **64** as a yellow solid (0.175 g, 69 %). It was recrystallized from CH_2Cl_2-hexane, mp. 79-81 °C.

IR (KBr) $\nu_{(max)}$: 1681, 1634, 1384, 1249, 1202, 960 cm^{-1}.

^1H NMR : δ 8.06-8.02 (m, 2H), 7.71-7.63 (m, 2H), 5.78 (m, 2H), 3.19 (d, J = 17.0 Hz, 1H), 3.00 (d, J = 17.0 Hz, 1H), 1.71 (d, J = 5.4 Hz, 3H), 1.61 (s, 3H).

^{13}C NMR : δ 182.45, 178.15, 158.83, 134.07, 133.27, 132.85, 131.00, 126.26, 126.09, 125.95, 123.33, 92.50, 39.17, 26.79, 17.66.

Anal. calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.71; H, 5.76.

2,3-Dihydro-2-(2-phenylvinyl)naphtho[2,3-b]furan-4,9-dione 65

An ice cooled mixture of 2-hydroxy-1,4-naphthoquinone **1** (0.174 g, 1 mmol) and 1-phenyl-1,3-butadiene (0.260 g, 2 mmol) in acetonitrile was treated with a solution of CAN (1.260 g, 2.3 mmol) in the same solvent. The aqueous work-up followed by chromatographic purification yielded **65** as a yellow solid (0.152 g, 50%). It was recrystallized from CH_2Cl_2-hexane, mp. 145-147 °C.

IR (KBr) $\nu_{(max)}$: 1672, 1650, 1624, 1592, 1452, 1392, 1373, 1232, 1195 cm^{-1}.

^1H NMR : δ 8.08 (brs, 2H), 7.75-7.65 (m, 2H), 7.40-7.30 (m, 5H), 6.74 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.7, 7.2 Hz, 1H), 5.61 (dd, J = 17.3, 7.9 Hz, 1H), 3.47 (dd, J = 17.3, 7.9 Hz, 1H).

^{13}C NMR : δ 182.05, 177.62, 159.81, 135.56, 134.11, 133.13, 132.96, 131.65, 128.73, 128.59, 126.90, 126.38, 126.11, 125.95, 123.87, 86.35, 33.53.

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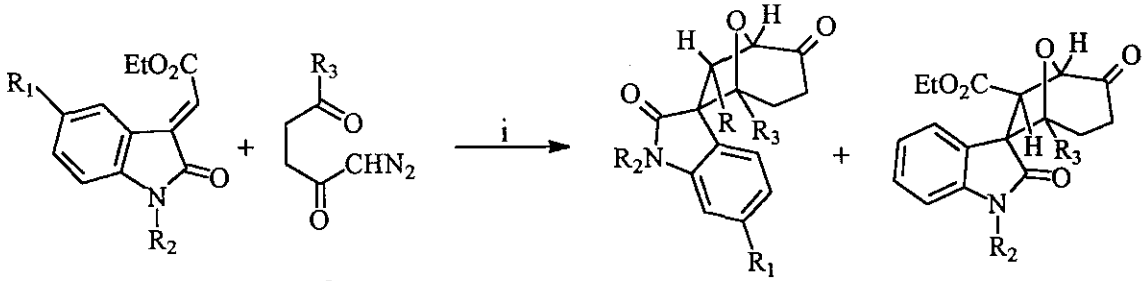
SUMMARY

The thesis entitled **"Novel Cycloaddition Reactions of *o*-Quinone Methides and Related Chemistry"** embodies the results of a series of investigations on the cycloaddition reactions of some heterocyclic and carbocyclic quinone methides.

The thesis is divided into four chapters and the contents of these chapters are summarized in the following pages.

Chapter 1 presents a general introduction to the chemistry of *o*-quinone methides with special emphasis on their cycloaddition reactions. A definition of the problem is also given.

The results of the investigations on dipolar cycloaddition reactions of carbonyl ylides to oxoindolinylidenes are delineated in the second chapter. A series of oxoindolinylidenes, when treated with six membered carbonyl ylides generated *in situ* by the rhodium catalyzed decomposition of α-diazoketones, underwent regioselective 1,3-dipolar cycloaddition to afford the corresponding cycloadducts in good yields (Scheme 1).



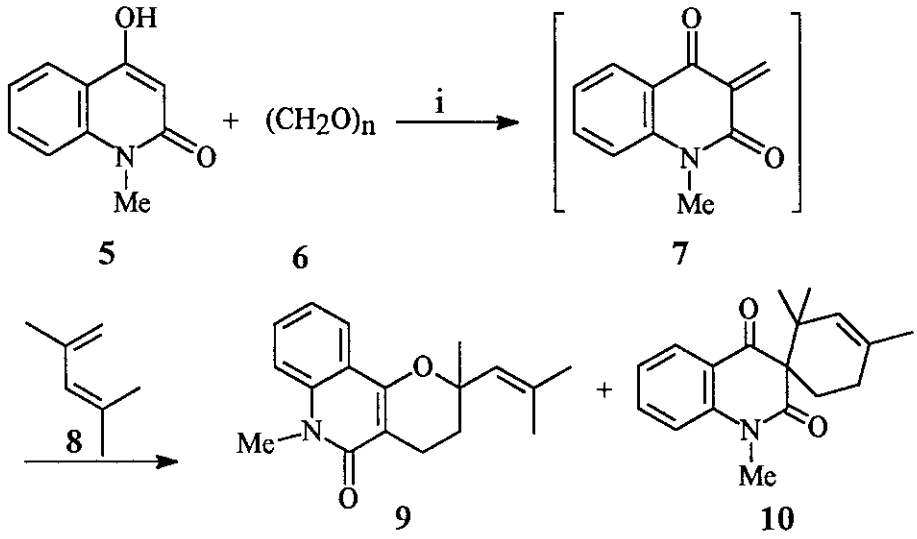
i. $Rh_2(OAc)_4$, Toluene, Argon, RT, 0.5-2 h, 70-98%

Scheme 1

Five membered carbonyl ylide also participated in facile 1,3-dipolar cycloaddition with oxoindolinylidenes. To explain the observed reactivity

theoretical calculations were carried out by the PM3 method using TITAN software (version 1).

The third chapter deals with the Diels-Alder trapping of quinolinone quinone methide using dienes and vinyl ethers which afforded corresponding pyranoquinolinones and/or spiroquinolinonediones. The reaction of 2,4-dimethyl-1,3-pentadiene yielding both the products is presented as an example (Scheme 2).



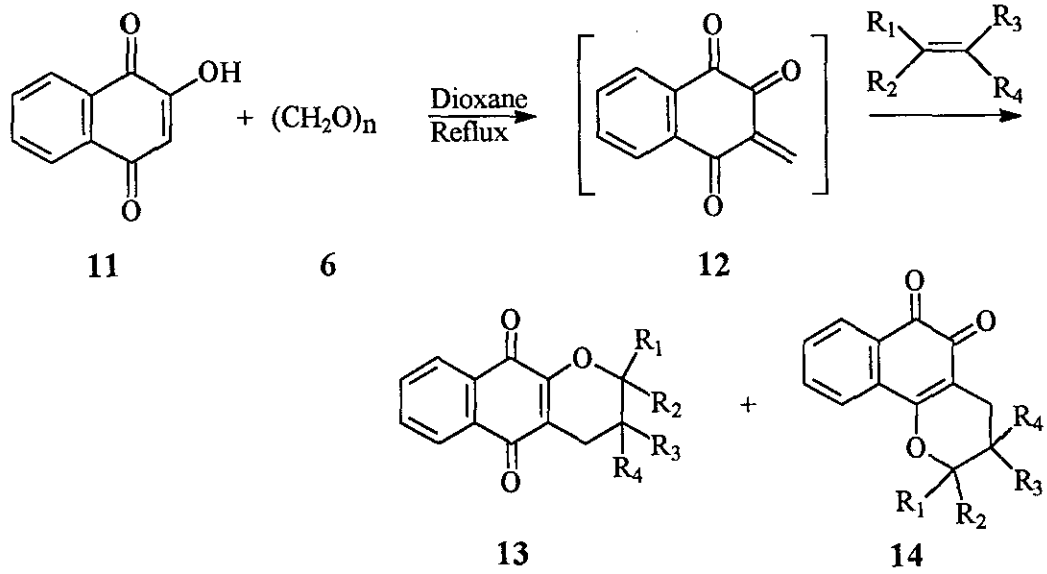
i. Dioxane, 100 °C, 3 h, 70% (1:2)

Scheme 2

Theoretical calculations performed on the methide and the reactants showed that the methide 7 is taking part in normal Diels-Alder reaction and inverse electron demand hetero Diels-Alder reaction depending on the Diels-Alder partner. Theoretical rationalization for the difference in reactivity of the methide towards different dienes has been obtained by calculating heats of formation of the corresponding products.

The final chapter of the thesis is divided into two sections. The results of our investigation on the synthesis of dihydronaphthopyrandiones by the cycloaddition

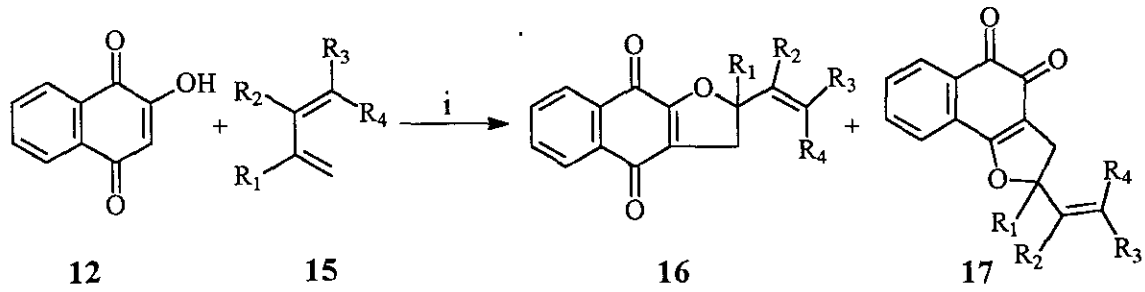
reactions of *in situ* generated quinone methide **12** with various cyclic and acyclic dienes and vinyl ethers form the subject matter of the first section (Scheme 3).



11 **6** **12** **13** **14**

Scheme 3

The second part deals with the synthesis of naphthofurandiones by CAN mediated oxidative addition of 2-hydroxynaphthoquinone to dienes (Scheme 4).



12 **15** **16** **17**

i. CAN, CH_3CN, 0 °C, 30 min

Scheme 4

In conclusion, we have developed simple and facile methods for the construction of a variety of heterocyclic compounds. It is conceivable that these compounds may undergo a number of useful and interesting transformations.

List of Publications

1. [4+2] Cycloaddition reactions of *o*-benzoquinones with styrenes: a facile synthesis of bicyclo[2.2.2]octenediones. Nair, V.; Maliakal, D.; **Treesa, P. M.**; Rath, N. P.; Eigendorf, G. K. *Synthesis* **2000**, 850.
2. Boron trifluoride-etherate induced rearrangement of bicyclo[2.2.2]octene-diones: An efficient synthesis of bicyclo[3.2.1]octenediones. Nair, V.; Maliakal, D.; **Treesa, P. M.**; Anilkumar, G. Vairamani, M.; Prabhakar, S.; Rath, N. P. *Tetrahedron* **2000**, *56*, 3735.
3. Novel heterocyclic construction *via* dipolar cycloadditions to 1,2-dicarbonyl compounds. Nair, V.; Sheela, K. C.; Vinod, A. U.; Nair, J. S.; Radhakrishnan, K. V.; Rajesh, C.; **Treesa, P. M.** *J. Heterocycl. Chem.* **2000**, *37*, 659.
4. Novel cycloaddition reactions of *o*-benzoquinones and related chemistry. Nair, V.; Kumar, S.; Anilkumar, G.; Radhakrishnan, K. V.; Nair, J. S.; Maliakal, D.; Sheela, K. C.; Mathew, B.; **Treesa,. P. M.**; Vinod, A. U.; Prabhakaran, J.; Sheeba, V.; Thomas, A. *Proc. Ind. Acad. Sc. (Chem. Sc.)*, **1998**, 110.
5. CAN mediated oxidative addition of 2-hydroxynaphthoquinone to dienes: A facile synthesis of naphthofurandiones. Nair, V.; **Treesa, P. M.**; Maliakal D.; Rath, N. P.; Vairamani, M.; Prabhakar, S. (to be communicated).
6. Dipolar cycloaddition reaction of carbonyl ylides to oxoindolinylidenes: A facile approach towards the synthesis of highly functionalized spiroindolenins. Nair, V.; **Treesa, P. M.** (to be communicated).
7. Diels-Alder trapping of 3-methylenequinolin-2,4-dione: Facile synthesis of pyranoquinolinones and spiroquinolindiones. Nair, V.; **Treesa, P. M.**; Jayan, C. N. (to be communicated).
8. Novel synthesis of α and β-lapachone derivatives *via* hetero Diels-Alder reactions of 3-methylene naphthalenetrione. Nair, V.; **Treesa, P. M.** (to be communicated).

Posters Presented at Symposia

1. Nair, J. S.; Radhakrishnan, K. V.; Maliakal, D.; **Treesa, P. M.**; Vinod, A. U.; Mathew, B.; Sheela, K. C.; Nair, V. "Novel cycloaddition reactions of *o*-Benzoquinones" presented in National Symposium on Emerging Trends in Organic Chemistry held at Trivandrum, Nov.18-19, 1996, Poster #P 21.